アクテムラ点滴静注用80mg，同200mg，同400mg
に関する資料

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アクテムラ点滴静注用80 mg，同200 mg，同400 mg
（トシリズマブ（遺伝子組換え））

［サイトカイン放出症候群］

第1部　（モジュール1）：

申請書等行政情報及び添付文書に関する情報

1.5 起原又は発見の経緯及び開発の経緯

中外製薬株式会社

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1.5 起原又は発見の経緯及び開発の経緯

1.5.1 起原又は発見の経緯

「アクテムラ点滴静注用80 mg，同点滴静注用200 mg 及び同点滴静注用400 mg（以下，本剤）」並びに「アクテムラ皮下注162 mg シリンジ及び同皮下注162 mg オートインジェクター」の有効成分であるトシリズマブ（遺伝子組換え）（以下，トシリズマブ）は，IgG_1サブクラスのヒト化抗ヒトインターロイキン6（IL-6）レセプターモノクローナル抗体である。トシリズマブは，マウスで作成された抗ヒト IL-6レセプターモノクローナル抗体をもとに，遺伝子組換え技術によりチャイニーズハムスター卵巣（CHO）細胞を用いて産生される。IL-6は，B 細胞を抗体産生細胞に分化誘導する因子として発見されたサイトカインであり，炎症反応，種々の細胞の分化誘導や増殖，免疫反応の調節，血小板増多等の生理作用を有することが明らかにされている。トシリズマブは，IL-6の生物学的作用を阻害することによりその薬効を示すことが期待され，IL-6が関与する疾患に対する治療薬として開発が進められてきた。

現在本邦では，本剤は以下の効能・効果で承認されている。

○ 既存治療で効果不十分な下記疾患
関節リウマチ（関節の構造的損傷の防止を含む），多関節に活動性を有する若年性特発性関節炎，全身型若年性特発性関節炎
○ キャッスルマン病に伴う諸症状及び検査所見（C 反応性タンパク高値，フィブリノーゲン高値，赤血球沈降速度亢進，ヘモグロビン低値，アルブミン低値，全身倦怠感）の改善。ただし，リンパ節の摘除が適応とならない患者に限る。

1.5.2 サイトカイン放出症候群に対する開発の経緯

1.5.2.1 海外における開発経緯・承認状況

米国では FDA より，トシリズマブのサイトカイン放出症候群（以下，CRS）を適応とした[redacted]を受けて，開発の検討を開始し，2016年9月に Type C 会議を行った。20[redacted]年[redacted]月に FDA より，本剤の CRS 適応審査のために，[redacted]要請を受けた。また，FDA は，ノバルティス社（スイス）及びギリアド・サイエンシズ社（米国）のそれぞれから許可を受けて，両社の提出したキメラ抗原受容体遺伝子導入 T 細胞製剤のための申請データを用いて，本剤の CRS 適応審査のための解析を自らが行うこととした。この要請に従い，20[redacted]年[redacted]月に承認申請を行い，Priority Review とオーファン指定を受けた。2017年8月に上述の申請資料に基づき，「ACTEMRA® (tocilizumab) is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients 2 years of age and older.（成人患者及び2歳以上の小児患者における CAR-T 細胞療法に伴う重度又は生命を脅かす CRS の治療）」を適応として承認を取得した。

EU においても，米国と同一の適応症が2018年8月に承認された。

表 1.5.2.1-1　米国における申請・承認の経緯

03/24/2016	FDA enquired about whether the Sponsor had any registration plans for a CRS indication, given the off-label use occurring which would be relevant to several oncology immunotherapies.
09/09/2016	Type C meeting held under pre-Investigational New Drug Application - FDA recommended that a submission based on literature would not be sufficient for a marketing application and that a prospective trial would be needed for a BLA supplement for treatment of CRS. FDA indicated support for ongoing discussions as the retrospective and prospective

	protocols are developed and recommended that the Sponsor request formal meetings with brief background material and specific questions for complicated or critical protocol design issues.
04/19/2017	Type A meeting held under PIND 125952: - FDA enquired about the Sponsor's ongoing discussions with Kite Pharma and potentially leveraging the available data from their CAR T-cell therapy, KTE-C19, for the purposes of updating the tocilizumab label for CRS and recommended that the Sponsor pursue a letter of authorization granting FDA access to analyze the KTE-C19 data under review for tocilizumab in CRS. - FDA also enquired as to whether the Sponsor has had any discussions with Novartis regarding their CAR T-cell therapy, CTL019, as the data is also under review at FDA and encouraged the Sponsor to discuss a potential letter of authorization for FDA to analyze the CTL019 data under review for tocilizumab in CRS. - FDA suggested the high-level proposal for a streamlined license application based on a comprehensive literature review and publications supporting the use of tocilizumab for the treatment of severe or life-threatening CRS, in addition to the potential letters of authorization from Kite Pharma and Novartis allowing FDA to analyze the data generated in the trials of their CAR T-cell therapies and presented in the respective BLAs for this purpose.
05/12/2017	Submission of an application for Orphan Drug Designation for tocilizumab in the treatment of patients with severe or life-threatening CRS to the FDA's Office for Orphan Products Development.
06/01/2017	This BLA 125276 supplement (S-114) was received in Electronic Common Technical Document (eCTD) format. The submission was found to be technically complete for review.
08/01/2017	FDA designated tocilizumab as Orphan Drug for the treatment of chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome.
08/30/2017	Approval

（BLA Multidisciplinary Review and Evaluation, BLA 125276 S-114より引用）

1.5.2.2　国内における開発・承認申請の経緯

ノバルティス ファーマ株式会社（以下，ノバルティス株式会社）が予定していた，キメラ抗原受容体遺伝子導入 T 細胞製剤（以下，CTL019）の承認申請にあたり，CTL019による CRS 管理のために，CRS 治療薬としてトシリズマブに効能を追加する承認事項一部変更承認申請が必要との医薬品医療機器総合機構（以下，PMDA）の意見を踏まえ，開発の検討を開始した。

申請者とノバルティス株式会社は，20[redacted]年[redacted]月[redacted]日実施した[redacted]面談で，[redacted]を相談した。[redacted]面談の結果，CRS 治療として本剤の CRS 治療の効能追加承認申請は可能であるとの PMDA 見解を得た。更に，20[redacted]年[redacted]月[redacted]日の[redacted]面談において，[redacted]について助言を得た。

今回，CTL019の臨床試験において，キメラ抗原受容体遺伝子導入 T 細胞製剤に特徴的な副

作用であるサイトカイン放出症候群の治療に，本剤が使用され，その有用性が示唆された。更に，CTL019又は他の CAR 遺伝子導入 T 細胞療法以外に，二重特異性 T 細胞誘導抗体治療，抗 PD-1抗体治療及び T 細胞受容体遺伝子導入 T 細胞（TCR-T）療法に伴う CRS に対してもトシリズマブを投与し，CRS が回復したことが報告されている。いずれも CTL019のように，T 細胞の増殖，活性化，細胞傷害活性の増強等の作用を有する抗悪性腫瘍療法であり，これらの療法に伴う CRS に対しても，トシリズマブ投与は有用であると考えられた。

以上を踏まえ，効能・効果，用法・用量を追加するための医薬品製造販売承認事項一部変更承認申請を行う。

本申請に係る効能・効果，用法・用量は以下のとおりである。

表 1.5.2.2-1　本申請に係る効能・効果及び用法・用量

効能・効果	用法・用量
抗悪性腫瘍療法に伴う T 細胞誘発性サイトカイン放出症候群	通常、トシリズマブ（遺伝子組換え）として、体重30 kg 以上は1回8 mg/kg、体重30 kg 未満は1回12 mg/kg を点滴静注する。

1.5.2.3　非臨床開発の経緯

本申請にあたり，新たな試験は実施していない。

1.5.3　申請製剤，申請効能以外の開発の概略

本剤は「成人発症スチル病」を予定される効能・効果として2018年5月に承認事項一部変更承認申請を行っている。

また，全身性強皮症は開発中であり、希少疾病用医薬品として指定されている。（指定番号（28薬）第378号）

アクテムラ点滴静注用80 mg，同200 mg，同400 mg（トシリズマブ（遺伝子組換え））

［サイトカイン放出症候群］

第1部　（モジュール1）：

申請書等行政情報及び添付文書に関する情報

1.6 外国における使用状況等に関する資料

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1.6　外国における使用状況等に関する資料

1.6.1　外国における承認状況

トシリズマブ製剤は，点滴静注用製剤が関節リウマチの治療薬として，米国においては2010年1月8日，EU では中央審査方式により2009年1月16日に承認された。

2018年3月現在において，点滴静注用製剤は米国，EU をはじめ世界100以上の国で承認されており，また，その他の効能では「全身型若年性特発性関節炎」及び「多関節に活動性を有する若年性特発性関節炎」の治療薬として米国では2011年4月15日及び2013年4月29日，EU では2011年8月1日及び2013年5月30日にそれぞれ承認されている。さらに「成人患者及び2歳以上の小児患者におけるキメラ抗原受容体（CAR）発現 T 細胞療法に伴う重度又は生命を脅かすサイトカイン放出症候群」の治療薬として米国では2017年8月30日に，EU では2018年8月23日に，スイスでは2018年10月3日に承認されている。

なお，皮下注製剤は，関節リウマチの治療薬として，米国では2013年10月21日，EU では2014年4月23日に承認された。また，巨細胞性動脈炎の治療薬として米国では2017年5月22日，EU では中央審査方式により2017年9月20日に承認された。

表 1.6.1-1　主要国におけるトシリズマブ製剤承認状況

国名 販売名 剤型・含量	承認内容（効能・効果及び承認年月日）	
米国 ACTEMRA [バイアル] ・80 mg/4 mL ・200 mg/10 mL ・400 mg /20 mL	【効能・効果】 1 種類以上の疾患修飾性抗リウマチ薬（DMARDs）が効果不十分であった中等度・重度の活動性関節リウマチ成人患者の治療を適応とする。	2010年1月8日 2012年10月11日* （*TNF 阻害薬療法を DMARDs に変更）
	【臨床成績】 関節リウマチに伴う関節の構造的損傷の防止と遅延，身体機能の改善	2011年1月4日** （**臨床成績の結果追加）
	【効能・効果】 2歳以上の患者における活動性を有する全身型若年性特発性関節炎の治療を適応とする。	2011年4月15日
	【効能・効果】 2歳以上の患者における活動性を有する多関節型若年性特発性関節炎の治療を適応とする。	2013年4月29日
米国 ACTEMRA [皮下投与用プレフィルドシリンジ・オートインジェクター] ・162mg/0.9mL	【効能・効果】 1 種類以上の疾患修飾性抗リウマチ薬（DMARDs）が効果不十分であった中等度・重度の活動性関節リウマチ成人患者の治療を適応とする。	2013年10月21日
	【効能・効果】 成人患者における巨細胞性動脈炎の治療を適応とする。	2017年5月22日
	【効能・効果】 2歳以上の患者における活動性を有する多関節型若年性特発性関節炎の治療を適応とする。	2018年5月12日

	【効能・効果】 2歳以上の患者における活動性を有する全身型若年性特発性関節炎の治療を適応とする。	2018年5月12日
米国 ACTEMRA [バイアル] ・80 mg/4 mL ・200 mg/10 mL ・400 mg /20 mL	【効能・効果】 成人患者及び2歳以上の小児患者におけるキメラ抗原受容体（CAR）発現 T 細胞療法に伴う重度又は生命を脅かすサイトカイン放出症候群の治療	2017年8月30日
EU（中央審査方式） RoActemra [バイアル] ・80 mg/4 mL ・200 mg/10 mL ・400 mg /20 mL	【効能・効果】 RoActemra［メトトレキサート（MTX）との併用］は，以下を適応とする。 • MTX 投与歴のない重度で活動性かつ進行性の関節リウマチ（RA）成人患者の治療 • 1 種類以上の疾患修飾抗リウマチ薬（DMARDs）又は腫瘍壊死因子（TNF）阻害薬による前治療が効果不十分であったか忍容性が不良であった中等度・重度の活動性 RA 成人患者の治療 これらの患者では，RoActemra を単剤療法として使用することも可能である（MTX に対する忍容性が不良である場合，又は MTX の継続投与が不適である場合）。 RoActemra をメトトレキサートと併用したところ，X 線スコアを指標とする関節破壊の進展率が低下し，身体機能が改善したことが示されている。	2009年1月16日 2010年6月4日*** （***関節破壊の抑制と身体機能の改善） 2014年9月1日**** （****MTX 投与歴のない重度で活動性かつ進行性の RA 成人患者）
	【効能・効果】 RoActemra は，NSAIDs 及び全身副腎皮質ステロイド薬による前治療が効果不十分であった2歳以上の患者における活動性を有する全身型若年性特発性関節炎（sJIA）の治療を適応とする。 RoActemra は，単剤療法として使用することも（MTX に対する忍容性が不良である場合，又は MTX の投与が不適である場合），MTX と併用することもできる。	2011年8月1日
	【効能・効果】 RoActemra［メトトレキサート（MTX）との併用］は， MTX による前治療が効果不十分であった2歳以上の患者における若年性特発性多発関節炎（pJIA，リウマチ因子陽性又は陰性，及び進展型少関節炎）の治療を適応とする。 RoActemra は，単剤療法として使用することも可能である（MTX に対する忍容性が不良である場合，又は MTX の継続投与が不適である場合）。	2013年5月30日

	【効能・効果】 成人患者及び2歳以上の小児患者におけるキメラ抗原受容体（CAR）発現 T 細胞療法に伴う重度又は生命を脅かすサイトカイン放出症候群の治療	2018年8月23日
EU（中央審査方式） RoActemra [皮下投与用プレフィルドシリンジ] ・162mg/0.9mL [皮下投与用プレフィルドペン] ・162mg/0.9mL	【効能・効果】 RoActemra［メトトレキサート（MTX）との併用］は，以下を適応とする。 • MTX 投与歴のない重度で活動性かつ進行性の関節リウマチ（RA）成人患者の治療 • 1 種類以上の疾患修飾抗リウマチ薬（DMARDs）又は腫瘍壊死因子（TNF）阻害薬による前治療が効果不十分であったか忍容性が不良であった中等度・重度の活動性 RA 成人患者の治療 これらの患者では，RoActemra を単剤療法として使用することも可能である（MTX に対する忍容性が不良である場合，又は MTX の継続投与が不適である場合）。 RoActemra をメトトレキサートと併用したところ，X 線スコアを指標とする関節破壊の進展率が低下し，身体機能が改善したことが示されている。	2014年4月23日 2016年7月29日***** （*****MTX 投与歴のない重度で活動性かつ進行性の RA 成人患者） 2018 年 3 月 21 日****** （******皮下投与用プレフィルドペン）
	【効能・効果】 成人患者における巨細胞性動脈炎の治療を適応とする。	2017年9月20日 2018 年 3 月 21 日****** （******皮下投与用プレフィルドペン）
	RoActemra［メトトレキサート（MTX）との併用］は，MTX による前治療が効果不十分であった2歳以上の患者における若年性特発性多発関節炎（pJIA，リウマチ因子陽性又は陰性，及び進展型少関節炎）の治療を適応とする。RoActemra は，単剤療法として使用することも可能である（MTX に対する忍容性が不良である場合，又は MTX の継続投与が不適である場合）。	2018年4月12日
	RoActemra は，NSAIDs 及び全身副腎皮質ステロイド薬による前治療が効果不十分であった1歳以上の患者における活動性を有する全身型若年性特発性関節炎（sJIA）の治療を適応とする。RoActemra は，単剤療法として使用することも（MTX に対する忍容性が不良である場合，又は MTX の投与が不適である場合），MTX と併用することもできる。	2018年10月29日

1.6.2　米国及び EU の添付文書の概要

米国添付文書（2018年11月改訂）の概要を表 1.6.2-1に示し，EU 添付文書（2019年1月改訂）の点滴静注用製剤の概要を表 1.6.2-2に，皮下注製剤の概要を表 1.6.2-3に示す。また，それぞれの原文を1.6.3，1.6.4に，企業中核データシート（CDS）を1.6.5に添付する。

表 1.6.2-1　米国における添付文書の概要

販売名	ACTEMRA
剤型・含量	静脈内投与用 ACTEMRA（20 mg/mL）1回用バイアル： • 80 mg/4 mL • 200 mg/10 mL • 400 mg/20 mL 皮下投与用プレフィルドシリンジ： • 0.9 mL で ACTEMRA 162 mg が投与される1回用プレフィルドシリンジ
効能・効果	＜関節リウマチ（RA）＞ ACTEMRA（トシリズマブ） は，1種類以上の疾患修飾性抗リウマチ薬（DMARDs）が効果不十分であった中等度・重度の活動性関節リウマチ成人患者の治療を適応とする。 ＜巨細胞性動脈炎（GCA）＞ ACTEMRA（トシリズマブ）は，成人患者における巨細胞性動脈炎（GCA）の治療を適応とする。 ＜多関節型若年性特発性関節炎（pJIA）＞ ACTEMRA（トシリズマブ） は，2歳以上の患者における活動性を有する多関節型若年性特発性関節炎の治療を適応とする。 ＜全身型若年性特発性関節炎（sJIA）＞ ACTEMRA（トシリズマブ） は，2歳以上の患者における活動性を有する全身型若年性特発性関節炎の治療を適応とする。 ＜サイトカイン放出症候群（CRS）＞ ACTEMRA（トシリズマブ）は，成人患者及び 2 歳以上の小児患者におけるキメラ抗原受容体（CAR）発現 T 細胞療法に伴う重度又は生命を脅かすサイトカイン放出症候群（CRS）の治療を適応とする。
用法・用量	＜関節リウマチ＞ 単剤療法として，又はメトトレキサートやその他の生物学的製剤でない DMARDs との併用で，点滴静脈内投与又は皮下注射により使用できる。 推奨される静脈内投与レジメン： 成人患者に60分かけて単剤点滴静注する場合の推奨用量は4 mg/kg の4週間隔での投与であり，その後，臨床的反応に基づいて8 mg/kg の4週間隔での投与に増量する。 • 特定の用量相関的な臨床検査値変化（肝酵素増加，好中球減少症，血小板減少症など）を管理するには，8 mg/kg から4 mg/kg に減量することが推奨される［「用法・用量」，「警告及び使用上の注意」，及び「副作用」を参

照］。
- RA 患者では，注入1回あたり800 mg を超える用量は推奨されない［「臨床薬理」を参照］。

推奨される皮下投与レジメン：

体重100 kg 未満の患者	162 mg を 2 週間隔で皮下投与した後，臨床的反応に基づいて 1 週間に 1 回投与に増量
体重100 kg 以上の患者	162 mg を 1 週間に 1 回皮下投与

静脈内投与から皮下投与に移行するときには，次回投与予定時に，静脈内投与の代わりに最初の皮下投与を行う。
特定の用量相関的な臨床検査値変化（肝酵素増加，好中球減少症，血小板減少症など）を管理するには，皮下投与を中断するか，又は投与頻度を1週間に1回から2週間に1回に減らすことが推奨される［「用法・用量」，「警告及び使用上の注意」，及び「副作用」を参照］。

＜巨細胞性動脈炎＞
成人 GCA 患者に対する ACTEMRA の推奨用量としては，糖質コルチコイドの用量を漸減しながら，本剤 162 mg を週 1 回皮下注射により投与する。

臨床判断に基づき，糖質コルチコイドの用量を漸減しながら 162 mg を 2 週に 1 回皮下注射により投与しても差し支えない。

ACTEMRA は，糖質コルチコイド投与中止後も単独投与可能である。

- 投与関連性の臨床検査異常（肝酵素増加，好中球減少症，血小板減少症等）を管理するため投与中断が必要となることがある [「用法・用量」を参照]。
- GCA に対する静脈内投与は承認されていない。

＜多関節型若年性特発性関節炎＞
単剤療法として使用することも，メトトレキサートと併用することもできる。体重は変動する可能性があるため，1回の来院の体重測定のみに基づいて用量を変更しないこと。

推奨される静脈内投与レジメン：
pJIA 患者に4週間隔で60分かけて単剤点滴静注する場合の推奨用量は次のとおりである。

pJIA 患者に静脈内投与する場合の推奨用量（4週間隔投与）	
体重30 kg 未満の患者	10 mg/kg
体重30 kg 以上の患者	8 mg/kg

推奨される皮下投与レジメン：

体重30 kg 未満の患者	162 mg を 3 週間に 1 回皮下投与
体重30 kg 以上の患者	162 mg を 2 週間に 1 回皮下投与

静脈内投与から皮下投与に移行するときには，次回投与予定時に，静脈内投与の

代わりに最初の皮下投与を行う。

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- 用量相関的な臨床検査値異常（肝酵素増加，好中球減少症，血小板減少症など）の管理のため，投与の中断が必要となる場合がある［「用法・用量」を参照］。

＜全身型若年性特発性関節炎＞
点滴静脈内投与又は皮下注射により，単剤療法として使用することも，メトトレキサートと併用することもできる。体重は変動する可能性があるため，1回の来院の体重測定のみに基づいて用量を変更しないこと。

推奨される静脈内投与レジメン：
sJIA 患者に2週間隔で60分かけて単剤点滴静注する場合の推奨用量は次のとおりである。

sJIA 患者の推奨用量（2週間隔投与）	
体重30 kg 未満の患者	12 mg/kg
体重30 kg 以上の患者	8 mg/kg

推奨される皮下投与レジメン：

体重30 kg 未満の患者	162 mg を 2 週間に 1 回皮下投与
体重30 kg 以上の患者	162 mg を 1 週間に 1 回皮下投与

静脈内投与から皮下投与に移行するときには，次回投与予定時に，静脈内投与の代わりに最初の皮下投与を行う。

- 用量相関的な臨床検査値異常（肝酵素増加，好中球減少症，血小板減少症など）の管理のため，投与の中断が必要となる場合がある［「用法・用量」を参照］。

＜サイトカイン放出症候群>
CRS の治療には静脈内投与のみを用いる。CRS の治療では，以下の推奨用量の ACTEMRA を60分かけて点滴静脈内投与する。

CRS に対して推奨される静脈内投与用量	
体重30 kg 未満の患者	12 mg/kg
体重30 kg 以上の患者	8 mg/kg
単独又は副腎皮質ステロイドと併用	

- 初回投与後に CRS の徴候・症状の臨床的改善が認められない場合，ACTEMRA を 3 回まで追加投与できる。投与間は少なくとも 8 時間空けること。
- CRS 患者に対する 1 回 800 mg を超える投与は推奨されない。
- CRS に対する皮下投与は承認されていない。

■　重篤な感染症や臨床検査値異常による用法・用量の変更

重篤な感染症があらわれた場合は，その感染症がコントロールされるまで ACTEMRA の投与を中断すること。

＜関節リウマチ及び巨細胞性動脈炎＞

肝酵素異常［「警告及び使用上の注意」を参照］：	
臨床検査値	推奨
正常上限値を超え，正常上限値の3倍以下	必要に応じ，併用している DMARDs 又は免疫調整薬の用量を調節する。 この範囲の高値が持続する場合： • ACTEMRA を静脈内投与している患者の場合，用量を4 mg/kg に減量するか，ALT 又は AST が正常値に復するまで ACTEMRA の投与を中断する。 • ACTEMRA を皮下投与している患者の場合，注射頻度を2週間隔に減らすか，ALT 又は AST が正常値に復するまで投与を中断する。投与再開は2週間隔で行い，臨床的に妥当と判断されれば投与頻度を週1回に増やす。
正常上限値の3倍を超え，正常上限値の5倍以下（再検査により確認）	正常上限値の3倍を下回るまで ACTEMRA の投与を中断し，上記の「正常上限値を超え，正常上限値の3倍以下」の推奨に従う。 正常上限値の3倍を超える状態が持続した場合は，ACTEMRA を中止する。
正常上限値の5倍を超える	ACTEMRA を中止する。

絶対好中球数（ANC）減少 ［「警告及び使用上の注意」を参照］：	
臨床検査値（1 mm^3あたりの血球数）	推奨
ANC が1000を超える	用量を維持する。
ANC が 500 ～ 1000	ACTEMRA の投与を中断する。 ANC が1000/mm^3を上回った段階で， • ACTEMRA を静脈内投与している患者の場合，4 mg/kg の用量で投与を再開し，臨床的に妥当と判断されれば8 mg/kg に増量する。 • ACTEMRA を皮下投与している患者の場合，2週間隔で投与を再開し，臨床的に妥当と判断されれば投与頻度を週1回に増やす。
ANC が500未満	ACTEMRA を中止する。

血小板数減少［「警告及び使用上の注意」を参照］：	
臨床検査値（1 mm^3あたりの血球数）	推奨

	<table><tr><td>50,000～100,000</td><td>ACTEMRA の投与を中断する。 血小板数が100,000/mm^{3}を上回った段階で， • ACTEMRA を静脈内投与している患者の場合，4 mg/kg の用量で投与を再開し，臨床的に妥当と判断されれば8 mg/kg に増量する。 • ACTEMRA を皮下投与している患者の場合，2週間隔で投与を再開し，臨床的に妥当と判断されれば投与頻度を週1回に増やす。</td></tr><tr><td>50,000未満</td><td>ACTEMRA を中止する。</td></tr></table> ＜多関節型及び全身型若年性特発性関節炎＞ pJIA 及び sJIA 集団では ACTEMRA の減量についての検討が行われていない。pJIA 及び sJIA 患者において，上記の RA 患者の項で示した値と同程度の肝酵素異常，好中球数減少，及び血小板数減少が認められた場合は，ACTEMRA の投与を中断することが望ましい。必要に応じ，併用しているメトトレキサート又は他の医薬品の用量を調節するか投与を停止するとともに，臨床状況の評価が行われるまで ACTEMRA の投与を中断する。pJIA 及び sJIA の場合，臨床検査値異常による ACTEMRA 投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。
投与に関する一般的注意事項	• ACTEMRA と生物学的 DMARDs（TNF 阻害薬，IL-1R 拮抗薬，抗 CD20モノクローナル抗体，選択的共刺激調節薬など）との併用については，免疫抑制を増強して感染リスクを高めるおそれがあるため未検討である。ACTEMRA と生物学的 DMARDs の併用は避けること。 • 絶対好中球数（ANC）が2000/mm^{3}を下回る患者，血小板数が100,000/mm^{3}を下回る患者，又は ALT 又は AST が正常上限値（ULN）の1.5倍を超える患者では，ACTEMRA の投与を開始しないことが望ましい。 - 重度又は生命を脅かす CRS を有する患者は、リンパ球枯渇化学療法または CRS のために、しばしば血球減少症または ALT 又は AST 上昇が認められる。 CRS を治療する潜在的利益と ACTEMRA を用いる短期治療のリスクとを考慮し，ACTEMRA の投与を決定すること。
警告	重篤な感染症のリスク ACTEMRA の投与を受ける患者は，入院又は死亡に至る可能性のある重篤な感染症の発生リスクが高い［「警告及び使用上の注意」，「副作用」を参照］。これらの感染症があらわれた患者の大部分は，免疫抑制薬（メトトレキサートなど）又は副腎皮質ステロイド薬を併用していた。 重篤な感染症があらわれた場合は，その感染症がコントロールされるまで ACTEMRA の投与を中断すること。 これまでに下記のような感染症が報告されている。 • 活動性結核（肺結核や肺外結核として発現することがある）。ACTEMRA の使用開始前及び ACTEMRA 療法中には潜在性結核感染の検査を行うこと。ACTEMRA の使用を開始する前に，不顕性感染の治療を行うこと。 • 侵襲性真菌感染症（カンジダ症，アスペルギルス症，ニューモシスティス症などを含む）。侵襲性真菌感染症の患者は，限局性疾患ではなく播種性疾患で受診する可能性がある。 • 細菌感染症，ウイルス感染症，及び日和見病原体に起因するその他の感染症

	慢性又は再発性感染症の患者については，ACTEMRA の投与を開始する前に，治療上の危険性と有益性を十分に考慮すること。 ACTEMRA による治療中及び治療後は，治療開始前に潜在性結核感染検査が陰性であった患者に結核が発現する可能性を含め，感染の徴候・症状があらわれていないか注意深く観察すること。［「警告及び使用上の注意」を参照］
禁忌	ACTEMRA は，本剤に対し過敏症の既往歴のある患者を禁忌とする［「警告及び使用上の注意」を参照］。
警告及び使用上の注意	重篤な感染症 免疫抑制剤（ACTEMRA も含む）を投与している患者では，細菌，マイコバクテリア，侵襲性真菌，ウイルス，原虫，又はその他の日和見病原体による重篤な感染症があらわれることがあり，場合によっては致命的な経過をたどることが報告されている。最も多く報告されている重篤な感染症は，肺炎，尿路感染，蜂巣炎，帯状疱疹，胃腸炎，憩室炎，敗血症及び細菌性関節炎などである［「副作用」を参照］。日和見感染の中で ACTEMRA に関連して報告があるものとしては，結核，クリプトコッカス症，アスペルギルス症，カンジダ症及びニューモシスティス症がある。上記以外の，臨床試験では報告されていない重篤な感染症があらわれる可能性もある（ヒストプラスマ症，コクシジオイデス症，リステリア症など）。限局性疾患ではなく播種性疾患の受診例もあり，そのような患者は，関節リウマチに加え易感染性の状態にもさせる可能性のある免疫抑制薬（メトトレキサートなど）や副腎皮質ステロイド薬を併用していることが多かった。 ACTEMRA は，活動性感染症（限局性感染を含む）の患者には投与しないこと。次の患者については，ACTEMRA の投与を開始する前に，治療上の危険性と有益性を十分に考慮すること。 • 慢性又は再発性感染症の患者 • 結核患者との接触歴を有する患者 • 重篤な感染又は日和見感染の既往歴のある患者 • 結核又は真菌症が流行している地域に居住又は旅行したことのある患者 • 易感染性の状態となる可能性のある基礎疾患を有する患者 急性期反応物質が抑制されることにより急性炎症の徴候・症状が減弱する可能性があるため，ACTEMRA による治療中及び治療後は感染の徴候・症状があらわれていないか注意深く観察する必要がある［「用法・用量」，「副作用」，及び「患者への情報提供」を参照］。 重篤な感染症，日和見感染，又は敗血症があらわれた場合には，ACTEMRA の投与を中断すること。ACTEMRA による治療中に新規の感染があらわれた場合は，免疫機能が低下した患者に適した完全な診断検査を迅速に実施したうえで，適切な抗生物質療法を開始し，患者の状態を十分に観察すること。 結核 ACTEMRA の使用を開始する前に，各患者の結核の危険因子を評価するとともに，不顕性感染の有無を検査する。 潜在性結核又は活動性結核の既往歴があるが適切な治療コースが確定できない患者，及び潜在性結核の検査結果は陰性であるが結核感染の危険因子を有する患者については，ACTEMRA の使用を開始する前に抗結核療法の実施についても考慮すること。個々の患者の抗結核療法開始の適否を判断する一助とするため，結核

	治療についての専門知識を有する医師に相談することが望ましい。 治療開始前に潜在性結核感染症の検査結果が陰性であった患者も含め，結核の徴候・症状があらわれていないか注意深く観察する必要がある。 ACTEMRA の使用を開始する前に，潜在性結核感染症について患者をスクリーニングすることが望ましい。グローバルの臨床開発プログラムでは，結核の発現頻度は0.1%である。潜在性結核の患者は，ACTEMRA の投与を開始する前に，標準的な抗マイコバクテリア療法による治療を行うこと。 ウイルス再活性化 免疫抑制作用のある生物学的療法を行った患者でウイルス再活性化が報告されており，ACTEMRA の臨床試験では帯状疱疹が増悪した例が認められている。治験では，B 型肝炎が再燃した例は認められていないものの，肝炎のスクリーニング検査で陽性であった患者は除外していた。 消化管穿孔 臨床試験では消化管穿孔の事象が報告されている（主に RA 患者の憩室炎の合併症として）。消化管穿孔のリスクが高い可能性のある患者では，ACTEMRA を慎重に投与すること。新たな腹部症状があらわれたため受診した患者については，消化管穿孔の早期特定のため速やかに評価を行うこと［「副作用」を参照］。 臨床検査値 ＜関節リウマチ及び巨細胞性動脈炎＞ 好中球減少症 ACTEMRA の投与に関連して，好中球減少症の発現頻度の上昇が認められている。長期投与試験及び市販後の使用経験においては，本剤投与に関連した好中球減少症により感染症が発現した症例はまれであった。 - 好中球数が減少している患者［絶対好中球数（ANC）が2000/mm^{3}未満］の患者が ACTEMRA の投与を開始することは推奨されない。絶対好中球数が500/mm^{3}未満となった患者では，ACTEMRA による治療は推奨されない。 - 好中球数は，治療開始4～8週後及び以後3ヵ月ごとに観察すること［「臨床薬理」を参照］。ANC の結果に基づく推奨用量調節については，「用法・用量」を参照のこと。 血小板減少症 ACTEMRA の投与に関連して，血小板数の減少が認められている。臨床試験では，投与に関連した血小板数減少による重篤な出血事象は認められていない［「副作用」を参照］。 - 血小板数が100,000/mm^{3}未満の患者が ACTEMRA の投与を開始することは望ましくない。血小板数が50,000/mm^{3}未満の患者では，ACTEMRA による治療は推奨されない。 - 血小板を，治療開始4～8週後及び以後3ヵ月ごとに観察すること。血小板数に基づく推奨用量調節については，「用法・用量」を参照のこと。 肝酵素増加 ACTEMRA の投与に関連して，トランスアミナーゼ値上昇の発現頻度の上昇が認められている。臨床試験では，トランスアミナーゼ値上昇により明らかな持続的な肝障害や臨床的に明白な肝障害に至った例はなかった［「副作用」を参照］。

	肝障害を起こす可能性のある薬剤（MTX など）を ACTEMRA と併用した際に，トランスアミナーゼ上昇の発現頻度及び重症度の上昇が認められている。 トランスアミナーゼ値上昇のない患者1例において，ACTEMRA 8 mg/kg の単剤療法により正常上限値の10倍を超える AST 上昇が認められた。この患者が，MTX を ACTEMRA と併用しはじめたところ，ALT 上昇は正常上限値の16倍を上回った。両剤の投与を中断したところ，トランスアミナーゼは正常値に復したが，MTX と ACTEMRA の用量を減量したうえで投与を再開すると再び上昇した。MTX 及び ACTEMRA の投与を中止したところ，検査値の上昇は消失した。 - トランスアミナーゼ（ALT 又は AST）が正常上限値の1.5倍を超える患者が ACTEMRA の投与を開始することは望ましくない。ALT 又は AST が正常上限値の5倍を超える患者では，ACTEMRA による治療は推奨されない。 - ALT 及び AST を治療開始4～8週後及び以後3ヵ月ごとに観察すること。臨床上必要である場合は，他の肝機能検査（ビリルビンなど）の実施を考慮すること。トランスアミナーゼに基づく推奨用量調節については，「用法・用量」を参照のこと。 脂質異常 ACTEMRA の投与に関連して，総コレステロール，中性脂肪，LDL コレステロール，HDL コレステロールなどの脂質検査項目に上昇が認められている［「副作用」を参照］。 - ACTEMRA 療法の開始から約4～8週後に脂質検査項目の評価を行い，その後は約24週間隔で行うこと。 - 高脂血症の管理に関する臨床ガイドライン［National Cholesterol Educational Program（NCEP）など］に従って患者を管理すること。 ＜多関節型及び全身型若年性特発性関節炎＞ pJIA 及び sJIA 集団では，ACTEMRA の投与に関連して，類似したパターンの肝酵素上昇，好中球数減少，血小板数減少及び脂質増加が認められている。好中球，血小板，ALT 及び AST を2回目の投与時に観察し，その後 pJIA の場合は4～8週ごと，sJIA の場合は2～4週ごとに観察すること。脂質については，上記の RA の項で記載した内容に従って観察すること［「用法・用量」を参照］。 免疫抑制 ACTEMRA の投与が悪性腫瘍の発生に及ぼす影響についてはわかっていないが，臨床試験では悪性腫瘍が認められている［「副作用」を参照］。ACTEMRA は免疫抑制薬であり，免疫抑制薬の投与は悪性腫瘍のリスクを高めるおそれがある。 過敏症反応（アナフィラキシーを含む） ACTEMRA に関連して過敏症反応（アナフィラキシーを含む）が報告されており［「副作用」を参照］，ACTEMRA の静脈内注入に関連してアナフィラキシー事象と致命的転帰が報告されている。投与中止が必要となったアナフィラキシー及びその他の過敏症反応が報告されたのは，静脈内投与用 ACTEMRA の6ヵ月間の比較対照試験では患者の0.1%（2644例中3例），本剤を静脈内投与した RA 集団全体（intravenous all-exposure RA population）では患者の0.2%（4009例中8例），皮下投与した6ヵ月間の比較対照 RA 試験では0.7%（1068例中8例），皮下投与した集団全体では患者の0.7%（1465例中10例）であった。また，静脈内投与用

	ACTEMRA の sJIA 比較対照試験では，112例中1例（0.9%）に投与中止が必要となった過敏症反応があらわれた。静脈内投与用 ACTEMRA の pJIA 比較対照試験では，投与中止が必要となった過敏症反応があらわれたのは ACTEMRA を投与した集団全体の188例中0例（0%）であった。投与中止が必要となった反応としては，全身紅斑，発疹，蕁麻疹などがあった。注射部位反応はさらに分類した［「副作用」を参照］。 市販後では，静脈内投与用 ACTEMRA のさまざまな用量において過敏症反応（アナフィラキシーを含む）が発現しており，死亡に至った症例も報告されている。これらの症例は関節炎治療薬の併用有無にかかわらず報告された。事象は，プレメディケーションが行われた患者で発現している。過敏症（アナフィラキシーを含む）は，過敏症反応の既往を有する患者，並びに同事象の既往を有さない患者においても認められ，早期（ACTEMRA 初回注入時）にみられた［「副作用」を参照］。静脈内投与用 ACTEMRA の投与は，アナフィラキシーを管理できるだけの十分な医療支援体制が整っている医療従事者のみが行うこと。ACTEMRA 皮下注射については，患者に対し，過敏症反応の症状を経験した場合には直ちに医師の診察を受けるよう指導すること。アナフィラキシー又はその他の過敏症反応があらわれた場合は，ACTEMRA の投与を直ちに停止するとともに，ACTEMRA による治療を永続的に中止すること。ACTEMRA は，本剤に対し過敏症の既往歴のある患者には投与しないこと［「禁忌」及び「副作用」を参照］。 脱髄疾患 ACTEMRA の投与が脱髄疾患に及ぼす影響については不明であるが，RA の臨床試験では多発性硬化症及び慢性炎症性脱髄性多発ニューロパチーの報告がまれにあった。脱髄疾患を示唆する可能性のある徴候・症状について患者を観察すること。脱髄疾患の基礎疾患のある患者及び脱髄疾患が最近あらわれた患者については，処方者は ACTEMRA の投与の可否を慎重に検討すること。 活動性肝疾患及び肝障害 活動性肝疾患又は肝障害のある患者には，ACTEMRA を投与しないことが望ましい［「副作用」，及び「特殊な集団における使用」を参照］。 ワクチン接種 臨床での安全性が確立されていないため，ACTEMRA 投与と同時に生ワクチンを接種することは避けること。生ワクチン接種を受けた人から ACTEMRA 投与を受けた人への二次感染伝播については入手可能なデータがない。 ACTEMRA の投与を受けた患者におけるワクチン接種の有効性については，データが得られていない。IL-6が阻害されると，新たな抗原に対する正常な免疫応答が妨げられるおそれがあるため，可能であれば，いずれの患者も（特に pJIA 及び sJIA 患者），ACTEMRA 療法の開始までに現行の予防接種ガイドラインに従ってすべての予防接種を済ませておくことが望ましい。生ワクチン接種から ACTEMRA 療法開始までの期間は，免疫抑制剤に関する現行のワクチン接種ガイドラインに準拠すること。

相互作用	成人の適応治療のための併用薬 RA 患者では，母集団薬物動態解析において，トシリズマブのクリアランスに対するメトトレキサート（MTX），非ステロイド抗炎症薬及び副腎皮質ステロイドの影響は認められなかった。ACTEMRA 10 mg/kg 単回静脈内投与と MTX 10～25 mg 週 1 回投与の併用は，MTX の曝露量に対する臨床的に有意な影響をもたらさなかった。生物学的製剤に属する DMARDs（TNF 拮抗薬等）と ACTEMRA の併用は検討されていない[「用法・用量」を参照]。 GCA 患者では，トシリズマブの曝露量に対する副腎皮質ステロイド併用の影響は認められなかった。 CYP450基質との相互作用 肝臓内のチトクローム P450は，感染刺激や炎症刺激（IL-6などのサイトカインを含む）によってダウンレギュレーションされる。RA 患者にトシリズマブを投与することで IL-6を介したシグナル伝達が阻害されると，トシリズマブを投与しない場合を上回るレベルにまで CYP450の活性が回復し，CYP450の基質となる薬剤の代謝の亢進をまねく可能性がある。In vitro 試験では，トシリズマブが複数の CYP 酵素（CYP1A2，CYP2B6，CYP2C9，CYP2C19，CYP2D6，CYP3A4など）の発現に影響を及ぼす可能性があることが示されている。トシリズマブが CYP2C8やトランスポーターに影響を及ぼすか否かはわかっていない。In vivo 試験において，ACTEMRA 単回投与の1週間後にオメプラゾール（CYP2C19及び CYP3A4により代謝される）及びシンバスタチン（CYP3A4により代謝される）を投与したところ，曝露量はそれぞれ28%及び57%低下した。CYP450の基質となり，かつ用量を個別に調整するような治療域が狭い薬剤にとって，トシリズマブが CYP 酵素に与える影響は，臨床上重大なものとなる可能性がある。このようなタイプの薬剤を投与している患者が ACTEMRA 療法を開始又は中止する際には，作用（ワルファリンなど）又は薬剤濃度（シクロスポリン，テオフィリンなど）についての治療モニタリングを実施し，必要に応じて個々の薬剤用量を調整すること。CYP3A4の基質となる薬剤で，かつ有効性の低下が望ましくないもの（経口避妊薬，ロバスタチン，アトルバスタチンなど）を ACTEMRA と併用する場合は，処方者は慎重に行うこと。トシリズマブが CYP450の酵素活性に及ぼす影響は，トシリズマブ療法の停止後も数週間にわたって持続する可能性がある［「臨床薬理」を参照］。 生ワクチン 生ワクチンを ACTEMRA と同時に使用することは避けること［「警告及び使用上の注意」を参照］。
特殊な集団における使用	妊婦 妊娠曝露登録 ACTEMRA に曝露された妊婦の転帰をモニタリングするため，妊娠曝露登録が設けられている。医師に対して患者を登録するよう奨励するとともに，妊婦に対しても 1-877-311-8972 に電話して自身を登録するよう奨励している。 リスクの概要 ACTEMRA について妊婦で得られているデータは限られているため，薬物関連性の著明な先天障害や流産のリスクがあるかどうかを判断するには，データが十分ではない。トシリズマブのようなモノクローナル抗体は妊娠第 3 三半期において経胎盤的に能動輸送され，子宮内で曝露された出生児の免疫反応に影響を及ぼす

	可能性がある［「臨床において考慮すべき事項」を参照］。動物を用いた生殖試験では，トシリズマブを器官形成期のカニクイザルに静脈内投与したとき，ヒトに対する最高推奨用量（8 mg/kg を 2～4 週間隔で静脈内投与）の 1.25 倍以上の用量において，流産／胚・胎児死亡がもたらされた。動物実験の文献で，IL-6 によるシグナル伝達の阻害が子宮頸管の熟化と拡張及び子宮筋層の収縮活動を妨げ，分娩の遅れにつながる可能性があることが示唆されている［「データ」を参照］。このような動物データから，胎児に対する潜在的な危険性が生じる可能性がある。 適応となる集団における著明な先天障害と流産の背景リスクは不明である。どのような妊娠にも，先天障害，妊娠損失その他有害な転帰の背景リスクがある。米国一般人口において，臨床的に認知された妊娠における著明な先天障害と流産の背景リスクは，それぞれ 2～4%及び 15～20%と推定される。 臨床において考慮すべき事項 胎児／新生児における副作用 モノクローナル抗体は経胎盤的に輸送され，移行量は妊娠の進行に伴って増加し，第 3 三半期が最大となる。子宮内で ACTEMRA に曝露された乳児に対して生ワクチンや弱毒ワクチンを投与するときには，事前にリスクとベネフィットを考慮すること［「警告及び使用上の注意」を参照］。 データ 動物データ 胚・胎児発生毒性試験が行われており，妊娠カニクイザルにトシリズマブが 2，10 又は 50 mg/kg の 1 日投与量で器官形成期［妊娠 20～50 日（GD 20～50）］に静脈内投与された。いずれの用量でも，催奇形性／異常形態形成作用を示す証拠は認められなかったが，母体に 10 mg/kg 及び 50 mg/kg のトシリズマブを静脈内投与することによる 1.25 倍以上の MRHD において，流産／胚・胎児死亡の頻度が上昇した。トシリズマブのマウス型アナログ抗体をマウスで検討する試験において，着床（GD 6）から分娩 21 日後（離乳）まで 3 日間隔で 50 mg/kg を静脈内投与したところ，出生前及び出生後の発生期間中に出生児に対し害を及ぼすことを示す証拠は認められなかった。出生児の発達・行動，学習能，免疫能及び受胎能の機能的障害を示す証拠も認められなかった。 分娩時には，子宮頸管と子宮筋層の IL-6 が著明に増加する。文献データで，IL-6 によるシグナル伝達の阻害が子宮頸管の熟化と拡張及び子宮筋層の収縮活動を妨げ，分娩の遅れにつながる可能性があることが示唆されている。IL-6 欠損マウス（$Il6^{-/-}$ヌルマウス）では分娩が野生型（$Il6^{+/+}$）マウスよりも遅れ，$Il6^{-/-}$ヌルマウスに組み換え IL-6 を投与したところ，正常な分娩時期が回復した。 授乳婦 リスクの概要 トシリズマブのヒト乳汁中への移行，乳児に対する影響及び泌乳への影響については，知見が得られていない。母体の免疫グロブリン G（IgG）はヒト乳汁中に移行する。トシリズマブがヒト乳汁中に移行した場合に，乳児の消化管における局所曝露や限定的な全身曝露の可能性がどのような影響をもたらすかはわかっていない。授乳中の臨床データがないため，授乳中の乳児に対する ACTEMRA のリスクを明確に判断することはできない。従って，発育及び健康面に対する授乳の有益性と，母体における ACTEMRA の臨床的必要性，及びトシリズマブ又は母体の基礎疾患が授乳中の乳児に悪影響を及ぼす可能性を併せて考慮すること。

小児への投与
ACTEMRA の静脈内投与は，以下の小児患者の治療を適応とする。
- 2歳以上の患者における活動性を有する全身型若年性特発性関節炎
- 2歳以上の患者における活動性を有する多関節型若年性特発性関節炎
- 2 歳以上の患者における CAR T 細胞療法に伴う重度又は生命を脅かすサイトカイン放出症候群（CRS）

ACTEMRA の皮下投与は，以下の小児患者の治療を適応とする。
- 2歳以上の患者における活動性を有する全身型若年性特発性関節炎
- 2歳以上の患者における活動性を有する多関節型若年性特発性関節炎

pJIA，sJIA 及び CRS 以外の小児患者における ACTEMRA の安全性及び有効性は確立されていない。また，pJIA，sJIA 及び CRS の2歳未満の小児患者における安全性及び有効性は確立されていない。小児患者におけるオートインジェクターを用いた自己注射の実施能力は検討されていない。

全身型若年性特発性関節炎 – 静脈内投与のみ
2歳未満の sJIA 患者（N=11）を対象とした，多施設共同非盲検単群試験が行われ，12週間にわたる Actemra の PK，安全性及び探索的 PD 及び有効性が検討された。患者は ACTEMRA 12 mg/kg の2週間隔の静脈内投与を受けた。コルチコステロイド，MTX，および／または非ステロイド系炎症薬による安定したバックグラウンド治療の併用が許容された。
12週間の期間を終了した患者は，延長期間（合計52週間または患者が2歳となるまでのいずれか長い方）まで継続することができた。
ACTEMRA の定常状態における PK の主要評価項目（Cmax，Cmin および2週間 AUC）は，2歳から17歳の sJIA 患者で観察されたこれらのパラメータの範囲内で合った。
2歳未満の sJIA 患者に対する ACTEMRA の安全性及び免疫原性を記述的に評価した。SAE，AE による中止，及び感染症関連 AE は，それぞれ27.3 %，36.4 %及び81.8 %の患者に認められた。6例（54.5 %）において，ACTEMRA に関連すると考えられる投与中，又は24時間以内に起こるすべての有害事象として定義される過敏反応を経験した。これらの患者のうち3例は，過敏反応を示し，中断された。過敏症反応を示した3例（うち，重篤な過敏反応2名を含む）が，治療後に抗トシリズマブ抗体が誘発されていた。プロトコル基準に基づく重篤な MAS の症例は認められなかったが，Revelli 基準に基づく MAS 疑いの2例が認められた。

サイトカイン放出症候群 – 静脈内投与のみ

CAR T 細胞療法により誘発された CRS に対して ACTEMRA が投与された患者に関する併合アウトカムデータのレトロスペクティブな解析において，25例が小児（2歳～12歳），17例が青年（12歳～18歳）であった。安全性と有効性に小児患者と成人患者で差はなかった。

高齢者への投与
試験 I～V［「臨床試験」を参照］で ACTEMRA の投与を受けた2644例の患者のうち，計435例の関節リウマチ患者が65歳以上であり，うち50例は75歳以上であった。SC-I 及び SC-II 試験で ACTEMRA-SC の投与を受けた1069例の患者のうち，295例が65歳以上であり，うち41例は75歳以上であった。65歳以上の ACTEMRA 投与例では，重篤な感染症の報告頻度が65歳未満の投与例に比べて高かった。高齢者集団は一般に感染の発現頻度が高いことから，高齢者に投与する場合は慎重

	を期すること。 CRS に対する ACTEMRA の投与が含まれた臨床試験には十分な数の 65 歳以上の患者が含まれていなかったため，65 歳以上の患者が 65 歳未満の患者と異なる反応を示すかどうかは判断できない。 肝障害 肝障害のある患者（血清学的検査で HBV 及び HCV 陽性の患者を含む）における ACTEMRA の安全性及び有効性については未検討である［「警告及び使用上の注意」を参照］。 腎障害 軽度腎障害のある患者で用量調節を行う必要はない。中等度・重度の腎障害のある患者での ACTEMRA の検討は行われていない［「臨床薬理」を参照］。
薬物乱用及び依存性	ACTEMRA が依存性を引き起こす可能性について検討した試験はない。しかし，得られているデータからは，ACTEMRA 投与が依存性を引き起こすことを示す証拠は認められない。
過量投与	ACTEMRA の過量投与に関しては，限られたデータしか得られていない。静脈内投与用 ACTEMRA について，偶発的過量投与が1例（40 mg/kg を単回投与した多発性骨髄腫患者）報告されている。副作用は認められなかった。健康被験者に単回投与した場合，28 mg/kg の用量まで重篤な副作用は認められていない。ただし，28 mg/kg（最高用量）を投与した5例全例において，用量制限につながる好中球減少症が認められた。 過量投与が生じた場合には，副作用の徴候・症状があらわれないか観察することが望ましい。副作用があらわれた患者には適切な対症的治療を行うこと。

表 1.6.2-2　EU における添付文書の概要（点滴静注用製剤）

<table>
<tr><td>販売名</td><td>RoActemra</td></tr>
<tr><td>剤型・含量</td><td>剤型：バイアル
含量：80 mg/4 mL，200 mg/10 mL，400 mg /20 mL</td></tr>
<tr><td>効能・効果</td><td>RoActemra［メトトレキサート（MTX）との併用］は，以下を適応とする。
• MTX 投与歴のない重度で活動性かつ進行性の関節リウマチ（RA）成人患者の治療
• 1種類以上の疾患修飾抗リウマチ薬（DMARDs）又は腫瘍壊死因子（TNF）阻害薬による前治療が効果不十分であったか忍容性が不良であった中等度・重度の活動性 RA 成人患者の治療
これらの患者では，RoActemra を単剤療法として使用することも可能である（MTX に対する忍容性が不良である場合，又は MTX の継続投与が不適である場合）。
RoActemra をメトトレキサートと併用したところ，X 線スコアを指標とする関節破壊の進展率が低下し，身体機能が改善したことが示されている。

RoActemra は，NSAIDs 及び全身副腎皮質ステロイド薬による前治療が効果不十分であった2歳以上の患者における活動性を有する全身型若年性特発性関節炎（sJIA）の治療を適応とする。RoActemra は，単剤療法として使用することも（MTX に対する忍容性が不良である場合，又は MTX の投与が不適である場合），MTX と併用することもできる。

RoActemra［メトトレキサート（MTX）との併用］は， MTX による前治療が効果不十分であった2歳以上の患者における若年性特発性多発関節炎（pJIA，リウマチ因子陽性又は陰性，及び進展型少関節炎）の治療を適応とする。 RoActemra は，単剤療法として使用することも可能である（MTX に対する忍容性が不良である場合，又は MTX の継続投与が不適である場合）。

RoActemra は，成人患者及び2歳以上の小児患者におけるキメラ抗原受容体（CAR）発現 T 細胞療法に伴う重度又は生命を脅かすサイトカイン放出症候群（CRS）の治療を適応とする。</td></tr>
<tr><td>用法・用量</td><td>投与は，RA，sJIA，pJIA 又は CRS の診断・治療の経験をもつ医療従事者が開始すること。
RoActemra の投与を受けるすべての患者に Patient Alert Card を配布すること。

RA 患者
推奨される用量は，8 mg/kg の4週間隔の投与である。
体重が100 kg を超える患者では，注入1回あたり800 mg を超える用量は推奨されない。
1.2 g を超える用量については，臨床試験による評価が行われていない。

臨床検査値異常による用量調節
肝酵素異常
<table>
<tr><th>臨床検査値</th><th>措置</th></tr>
<tr><td>正常上限値（ULN）を超</td><td>必要に応じ，併用している MTX の用量を調節する。
この範囲の高値が持続する場合，RoActemra の用量を4</td></tr>
</table>
</td></tr>
</table>

え，正常上限値の3倍以下	mg/kg に減量するか，アラニン・アミノトランスフェラーゼ（ALT）又はアスパラギン酸アミノトランスフェラーゼ（AST）が正常値に復するまで RoActemra の投与を中断する。 臨床的に妥当と判断されれば4 mg/kg 又は8 mg/kg で投与再開する。
正常上限値の3倍を超え，正常上限値の5倍以下	正常上限値の3倍を下回るまで RoActemra の投与を中断し，上記の「正常上限値を超え，正常上限値の3倍以下」の推奨に従う。 正常上限値の3倍を超える状態が持続した場合は，RoActemra を中止する。
正常上限値の5倍を超える	RoActemra を中止する。

絶対好中球数（ANC）減少

RoActemra による治療歴がない患者の場合，絶対好中球数（ANC）が2×10^9/L 未満であれば RoActemra 療法を開始しないことが望ましい。

臨床検査値（$\times10^9$/L）	措置
ANC が1を超える	用量を維持する。
ANC が0.5～1	RoActemra の投与を中断する。 ANC が1×10^9/L を上回った段階で，4 mg/kg の用量で投与を再開し，臨床的に妥当と判断されれば8 mg/kg に増量する。
ANC が0.5未満	RoActemra を中止する。

血小板数減少

臨床検査値（$\times10^3$/μl）	措置
50～100	RoActemra の投与を中断する。 血小板数が100×10^3/μl を上回った段階で，4 mg/kg の用量で投与を再開し，臨床的に妥当と判断されれば8 mg/kg に増量する。
50未満	RoActemra を中止する。

サイトカイン放出症候群（CRS）（成人及び小児）

CRS の治療において60分かけて点滴静脈内投与する場合の推奨用量は，体重30 kg 未満の患者に対して12 mg/kg，又は体重30 kg 以上の患者対して8 mg/kg である。RoActemra は単独又は副腎皮質ステロイドと併用できる。

初回投与後に CRS の徴候・症状の臨床的改善が認められない場合，RoActemra を3回まで追加投与できる。投与間は少なくとも8時間空けること。CRS 患者に対する1回800 mg を超える投与は推奨されない。

重度又は生命を脅かす CRS を有する患者は，リンパ球枯渇化学療法または CRS のために，しばしば血球減少症または ALT 又は AST 上昇が認められる。

特別な母集団

小児患者：

sJIA 患者：
2歳を超える患者に推奨される用量は，体重30 kg 以上の患者が8 mg/kg の2週間隔投与，体重30 kg 未満の患者が12 mg/kg の2週間隔投与である。用量は，各投与時の患者の体重に基づいて算出する。患者の体重に経時的に一貫性のある変化が見られた場合にのみ，用量を変更すること。

2歳未満の患者における RoActemra 点滴静注用製剤の安全性及び有効性は確立されていない。

sJIA 患者の場合，下表の臨床検査値異常が認められたときはトシリズマブの投与を中断することが望ましい。必要に応じ，併用している MTX 又は他の医薬品の用量を調節するか投与を停止するとともに，臨床状況の評価が行われるまでトシリズマブの投与を中断する。sJIA には，臨床検査値に影響を及ぼす可能性のある合併症が数多く存在するため，臨床検査値異常によるトシリズマブ投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。

肝酵素異常

臨床検査値	措置
正常上限値を超え，正常上限値の3倍以下	併用している MTX の用量を適宜調節する。 この範囲の高値が持続する場合，ALT／AST が正常値に復するまで RoActemra の投与を中断する。
正常上限値の3倍を超え，正常上限値の5倍以下	併用している MTX の用量を適宜調節する。 正常上限値の3倍を下回るまで RoActemra の投与を中断し，上記の「正常上限値を超え，正常上限値の3倍以下」の推奨に従う。
正常上限値の5倍を超える	RoActemra を中止する。 sJIA の場合，臨床検査値異常による RoActemra 投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。

絶対好中球数（ANC）減少

臨床検査値（$\times 10^9$/L）	措置
ANC が1を超える	用量を維持する。
ANC が0.5～1	RoActemra の投与を中断する。 ANC が1×10^9/L を上回った段階で，RoActemra の投与を再開する。
ANC が 0.5 未満	RoActemra を中止する。 sJIA の場合，臨床検査値異常による RoActemra 投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。

血小板数減少

臨床検査値（$\times 10^3$/μl）	措置

50～100	併用している MTX の用量を適宜調節する。 RoActemra の投与を中断する。 血小板数が$100\times10^3/\mu l$ を上回った段階で，RoActemra の投与を再開する。
50未満	RoActemra を中止する。 sJIA の場合，臨床検査値異常による RoActemra 投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。

sJIA 患者では，臨床検査値異常によるトシリズマブ減量についての検討は行われていない。

得られているデータからは，RoActemra 投与開始後6週間以内に臨床的改善が認められることが示唆されている。この期間内に改善が見られない患者については，治療継続の可否を慎重に検討すること。

pJIA 患者：
2歳を超える患者に推奨される用量は，体重30 kg 以上の患者が8 mg/kg の4週間隔投与，体重30 kg 未満の患者が10 mg/kg の4週間隔投与である。用量は，各投与時の患者の体重に基づいて算出する。患者の体重に経時的に一貫性のある変化が見られた場合にのみ，用量を変更すること。

2歳未満の患者における RoActemra 点滴静注用製剤の安全性及び有効性は確立されていない。参照可能なデータはない。

pJIA 患者の場合，下表の臨床検査値異常が認められたときはトシリズマブの投与を中断することが望ましい。必要に応じ，併用している MTX 又は他の医薬品の用量を調節するか投与を停止するとともに，臨床状況の評価が行われるまでトシリズマブの投与を中断する。pJIA には，臨床検査値に影響を及ぼす可能性のある合併症が数多く存在するため，臨床検査値異常によるトシリズマブ投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。

肝酵素異常

臨床検査値	措置
正常上限値を超え，正常上限値の3倍以下	併用している MTX の用量を適宜調節する。 この範囲の高値が持続する場合，ALT／AST が正常値に復するまで RoActemra の投与を中断する。
正常上限値の3倍を超え，正常上限値の5倍以下	併用している MTX の用量を適宜調節する。 正常上限値の3倍を下回るまで RoActemra の投与を中断し，上記の「正常上限値を超え，正常上限値の3倍以下」の推奨に従う。
正常上限値の5倍を超える	RoActemra を中止する。 pJIA の場合，臨床検査値異常による RoActemra 投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。

絶対好中球数（ANC）減少

	臨床検査値（$\times 10^9$/L）：措置 ANC が1を超える：用量を維持する。 ANC が0.5～1：RoActemra の投与を中断する。ANC が1×10^9/L を上回った段階で，RoActemra の投与を再開する。 ANC が 0.5 未満：RoActemra を中止する。pJIA の場合，臨床検査値異常による RoActemra 投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。 血小板数減少 臨床検査値（$\times 10^3$/μl）：措置 50～100：併用している MTX の用量を適宜調節する。RoActemra の投与を中断する。血小板数が100×10^3/μl を上回った段階で，RoActemra の投与を再開する。 50未満：RoActemra を中止する。pJIA の場合，臨床検査値異常による RoActemra 投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。 pJIA 患者では，臨床検査値異常によるトシリズマブ減量についての検討は行われていない。 得られているデータからは，RoActemra 投与開始後12週間以内に臨床的改善が認められることが示唆されている。この期間内に改善が見られない患者については，治療継続の可否を慎重に検討すること。 高齢者：65歳以上の患者で用量調節を行う必要はない。 腎障害： 軽度腎障害のある患者で用量調節を行う必要はない。中等度・重度の腎障害のある患者での RoActemra の検討は行われていない。これらの患者では，腎機能を慎重に観察すること。 肝障害：肝障害のある患者では，RoActemra の検討は行われていない。したがって，用量に関する推奨を行うことはできない。
禁忌	本剤の有効成分又は添加物に対し過敏症の既往歴のある患者。 重度の活動性感染症のある患者。
特別な警告及び使用上の注意	トレーサビリティ 生物学的製剤のトレーサビリティを改善するため，投与した製品の商品名を患者ファイルに明確に記録すること。 感染症 免疫抑制剤（RoActemra を含む）を投与している患者では，重篤な感染症があらわれることがあり，場合によっては致命的な経過をたどることが報告されてい

	る。活動性感染症の患者では RoActemra による治療を開始しないこと。重篤な感染症があらわれた場合は，その感染症がコントロールされるまで RoActemra の投与を中断する。再発性又は慢性感染症の既往歴のある患者や易感染性の状態となる可能性のある基礎疾患（憩室炎，糖尿病，間質性肺疾患など）を有する患者で RoActemra の使用を検討する場合には，医療従事者は慎重を期すること。 中等度・重度の RA，sJIA 又は pJIA の治療のため生物学的製剤の投与を受けている患者では，急性期反応の抑制に伴って急性炎症の徴候・症状が減弱する可能性があるため，重篤な感染症を適時に検出することができるよう監視することが望ましい。感染症があらわれる可能性のある患者を評価する際は，トシリズマブが C 反応性蛋白（CRP），好中球及び感染の徴候・症状に及ぼす影響を考慮すること。迅速な評価と適切な治療を可能とするため，感染症の発症を示唆する症状があらわれた場合は直ちに担当の医療従事者に連絡を取るよう患者（自身の症状について伝達する能力がやや劣る年少の sJIA・pJIA 患者を含む）及び sJIA・pJIA 患者の親／後見人を指導すること。 結核 他の生物学的製剤による治療でも推奨されているとおり，RA 患者，sJIA 患者及び pJIA 患者については，RoActemra 療法を開始する前に潜在性結核（TB）感染の有無をスクリーニングする必要がある。潜在性結核の患者は，RoActemra の投与を開始する前に，標準的な抗マイコバクテリア療法による治療を行うこと。医師は，特に重症な症例や，免疫が低下している症例では，ツベルクリン反応やインターフェロンガンマ TB 血液テストの結果が陰性に出るリスクを考慮すること。 患者に対し，本剤による治療中もしくは治療した後に，咳の持続，体重の減少，微熱など結核の感染を示唆するような徴候・症状が起こった場合には，医学的な助言を受けることを指示しなければならない。 ウイルス再活性化 RA に対し生物学的療法を行った患者において，ウイルス再活性化（B 型肝炎ウイルスなど）が報告されている。トシリズマブの臨床試験では，肝炎のスクリーニング検査が陽性であった患者は除外した。 憩室炎の合併症 RA 患者では，RoActemra を投与した場合にまれに憩室穿孔の事象が報告されている（憩室炎の合併症として）。RoActemra は，腸管潰瘍形成又は憩室炎の既往歴のある患者には慎重に投与すること。憩室炎の合併症を示唆する可能性のある症状（腹痛，出血，発熱を伴う原因不明の排便習慣変化など）を発現した患者については，消化管穿孔を伴う可能性のある憩室炎を早期に特定するため，速やかに評価を行うこと。 過敏症反応 RoActemra の注入に関連して重篤な過敏症反応が報告されている。前回の注入時に過敏症反応があらわれた患者では，たとえステロイド薬及び抗ヒスタミン薬の前投与を受けていても，そのような反応はさらに重症化する可能性があり，場合によっては致命的な経過をたどるおそれもある。RoActemra の投与中は，アナフィラキシー反応があらわれた場合には適切な治療が速やかに受けられるようにしておくこと。アナフィラキシー反応又はその他の重篤な過敏症／重篤な注入に伴

	う反応があらわれた場合は，RoActemra の投与を直ちに停止するとともに，RoActemra による治療を永続的に中止すること。 活動性肝疾患及び肝障害 RoActemra の投与に伴って（特に MTX と併用する場合），肝トランスアミナーゼ値が上昇することがある。したがって，活動性肝疾患又は肝障害のある患者への投与を検討する場合には慎重を期すること。 肝トランスアミナーゼ値上昇 臨床試験では，RoActemra 投与後に一過性又は間欠的な軽度・中等度の肝トランスアミナーゼ値上昇が高い頻度で報告されているが，肝障害に進行した例はない。肝障害を起こす可能性のある薬剤（MTX など）を RoActemra と併用した際に，トランスアミナーゼ上昇の発現頻度の上昇が認められている。臨床上必要である場合は，他の肝機能検査（ビリルビンなど）の実施を考慮すること。 正常上限値の1.5倍を超える ALT 上昇又は AST 上昇が認められる患者においてRoActemra の投与開始を検討する場合には慎重を期すること。ベースラインのALT 又は AST が正常上限値の5倍を超える患者には投与しないことが望ましい。 RA 患者では，ALT 及び AST を投与開始後6ヵ月間は4～8週ごとに観察し，その後は12週ごとに観察すること。トランスアミナーゼに基づく推奨用量調節については，「用法・用量」を参照のこと。正常上限値の3倍超～5倍以下の ALT 上昇又は AST 上昇が，再検査により確認された場合は，RoActemra の投与を中断すること。 sJIA 及び pJIA の患者では，ALT 及び AST を2回目の注入時に観察し，その後は医薬品の臨床試験の実施の基準に準拠して観察すること。 血液学的異常 トシリズマブ8 mg/kg を MTX と併用した際に好中球数及び血小板数の減少が認められている。TNF 阻害薬による治療歴のある患者は，好中球減少症のリスクが高い可能性がある。 RoActemra による治療歴のない患者の場合，絶対好中球数（ANC）が2×10^9/L 未満であれば RoActemra 療法を開始しないことが望ましい。血小板数減少（血小板数が100×10^3/ μl 未満）のある患者で RoActemra の投与開始を検討する場合は，慎重を期すること。ANC が0.5×10^9/L 未満又は血小板数が50×10^3/ μl 未満となった患者では，投与の継続は推奨されない。 重度の好中球減少症は重篤な感染症の発現リスクを高める可能性がある。ただし，RoActemra の臨床試験では，好中球数減少と重篤な感染症の発生との間にこれまでのところ明確な関連性は認められていない。 RA 患者では，RoActemra 療法の開始から4～8週後に好中球数及び血小板数を観察し，その後は標準的な臨床診療に準拠して観察すること。ANC 及び血小板数に基づく推奨用量調節については，「用法・用量」を参照のこと。

	sJIA 及び pJIA の患者では，好中球及び血小板を2回目の注入時に観察し，その後は医薬品の臨床試験の実施の基準に準拠して観察すること。 脂質検査項目 トシリズマブを投与した患者において，総コレステロール，低比重リポ蛋白質（LDL），高比重リポ蛋白（HDL），中性脂肪などの脂質検査項目に上昇が認められている。大部分の患者では，動脈硬化指数（Atherogenic index）の上昇は認められず，総コレステロール値の上昇は脂質低下剤による治療に反応した。 sJIA，pJIA 及び RA の患者では，RoActemra 療法の開始から4～8週後に脂質検査項目の評価を行うこと。高脂血症の管理に関する現地の臨床ガイドラインに従って患者を管理すること。 神経学的障害 医師は，中枢神経脱髄疾患の新規発生を示唆する可能性のある症状があらわれていないか監視すること。RoActemra 投与により中枢神経脱髄が生じる可能性については現時点では不明である。 悪性腫瘍 RA 患者は悪性腫瘍の発現リスクが高い。免疫調節薬は悪性腫瘍のリスクを高める可能性がある。 ワクチン接種 臨床での安全性が確立されていないため，RoActemra 投与中は生ワクチンや弱毒生ワクチンを接種しないこと。ある無作為化オープンラベル試験において，RoActemura と MTX を投与された成人 RA 患者は，23価肺炎球菌多糖体ワクチンと破傷風トキソイドワクチンいずれに対しても，MTX のみが投与された患者と同等の有効な反応を示すことができた。いずれの患者も（特に sJIA 及び pJIA の患者），RoActemra 療法の開始までに現行の予防接種ガイドラインに従ってすべての予防接種を済ませておくことが望ましい。生ワクチン接種から RoActemra 療法開始までの期間は，免疫抑制剤に関する現行のワクチン接種ガイドラインに準拠すること。 心血管リスク RA 患者は心血管障害の発現リスクが高いため，日常の標準治療の一環として危険因子（高血圧，高脂血症など）の管理を行うこと。 TNF 阻害薬との併用 RA，sJIA 又は pJIA の患者において RoActemra を TNF 阻害薬又は他の生物学的製剤と併用した経験はない。RoActemra を他の生物学的製剤と併用することは推奨されない。 ナトリウム 本剤の最高用量（1200 mg）には，ナトリウムが1.17 mmol（26.55 mg）含まれるので，ナトリウム制限食で管理されている患者はこのことを考慮すること。本剤投与量が1025 mg 未満の場合，ナトリウム含有量は1 mmol（23 mg）未満であり，本剤は実質的に「ナトリウム不含」である。

	小児患者 sJIA 患者 マクロファージ活性化症候群（MAS）は，sJIA 患者にあらわれる可能性のある生命を脅かす重篤な疾患である。臨床試験では，活動性 MAS のエピソード中の患者を対象とするトシリズマブの試験は行われていない。
薬物-薬物相互作用及びその他の相互作用	相互作用試験は成人のみで行われた。 トシリズマブ（10 mg/kg，単回投与）と MTX（10～25 mg，週1回投与）の併用は，MTX の曝露量に対して，臨床的に問題となる影響を及ぼさなかった。 MTX，非ステロイド性抗炎症薬（NSAIDs）及び副腎皮質ステロイド薬がトシリズマブのクリアランスに影響を及ぼすとの知見は母集団薬物動態解析では検出されなかった。 肝酵素 CYP450の発現は，慢性炎症を促進させるサイトカイン（IL-6など）によって抑制される。したがって，トシリズマブなどの強力なサイトカイン阻害療法を導入することによって CYP450の発現が回復する可能性がある。 培養ヒト肝細胞を用いた *in vitro* 試験では，IL-6が CYP1A2，CYP2C9，CYP2C19，及び CYP3A4の発現量を減少させることが示されている。トシリズマブは，これらの酵素の発現量を正常に戻す。 RA 患者を対象とした試験では，トシリズマブ単回投与の1週間後にシンバスタチン（CYP3A4により代謝される）を投与したところ，シンバスタチンの濃度は57%低下した。この低下した濃度は健康被験者での値と同程度かわずかに上回る値である。 トシリズマブ療法を開始又は停止する際に，患者が個別に用量が調整される薬剤で，かつ CYP450 3A4，1A2又は2C9によって代謝される薬剤（アトルバスタチン，カルシウム拮抗薬，テオフィリン，ワルファリン，フェンプロクモン，フェニトイン，シクロスポリン，ベンゾジアゼピン系薬剤など）を服用している場合，治療効果維持のため用量を増量する必要が生じる可能性があるため，患者を観察する必要がある。トシリズマブは消失半減期（$t_{1/2}$）が長いため，トシリズマブが CYP450の酵素活性に及ぼす影響は，治療停止後も数週間にわたって持続する可能性がある。
受胎能，妊婦及び授乳婦への投与	妊娠可能な女性 妊娠する可能性がある婦人は，投与中及び投与3ヵ月後まで効果的な避妊を行わなければならない。 妊婦 妊婦におけるトシリズマブの使用については，十分なデータが得られていない。 動物試験では，高用量で自然流産／胚・胎児死亡のリスク上昇が認められている。ヒトに対する潜在的な危険性は不明である。 妊娠中の婦人には，明らかな必要性がある場合にのみ RoActemra を投与すること。 授乳 トシリズマブがヒトの乳汁中に移行するかどうかはわかっていない。トシリズマブの乳汁中への移行については，動物を用いた試験が行われていない。授乳することで乳児が得る利益と RoActemra 療法を行うことで母体が得る利益を検討したうえで，授乳の継続／中止及び RoActemra 投与の継続／中止の可否を判断すること 。

	受胎能 これまでに得られている非臨床データでは，トシリズマブ投与の受胎能への影響は示唆されていない。
自転車運転及び機械操作に対する影響	RoActemra は，自動車運転及び機械操作能力に対する軽微な影響を有する。
過量投与	RoActemra の過量投与に関しては，限られたデータしか得られていない。偶発的過量投与が1例（40 mg/kg を単回投与した多発性骨髄腫患者）報告されている。副作用は認められなかった。 健康被験者に単回投与した場合，28 mg/kg の用量まで重篤な副作用は認められていない。ただし，用量制限につながる好中球減少症が認められた。

表 1.6.2-3　EU における添付文書の概要（皮下注製剤）

販売名	RoActemra
剤型・含量	剤型：プレフィルドシリンジ入り注射液，プレフィルドペン入り注射剤 含量：162 mg/0.9 ml
効能・効果	RoActemra［メトトレキサート（MTX）との併用］は，以下を適応とする。 • MTX 投与歴のない重度で活動性かつ進行性の関節リウマチ（RA）成人患者の治療 • 1種類以上の疾患修飾抗リウマチ薬（DMARDs）又は腫瘍壊死因子（TNF）阻害薬による前治療が効果不十分であったか忍容性が不良であった中等度・重度の活動性 RA 成人患者の治療 これらの患者では，RoActemra を単剤療法として使用することも可能である（MTX に対する忍容性が不良である場合，又は MTX の継続投与が不適である場合）。 RoActemra をメトトレキサートと併用したところ，X 線スコアを指標とする関節破壊の進展率が低下し，身体機能が改善したことが示されている。 RoActemra は，NSAIDs 及び全身副腎皮質ステロイド薬による前治療が効果不十分であった1歳以上の患者における活動性を有する全身型若年性特発性関節炎（sJIA）の治療を適応とする。RoActemra は，単剤療法として使用することも（MTX に対する忍容性が不良である場合，又は MTX の投与が不適である場合），MTX と併用することもできる。 RoActemra［メトトレキサート（MTX）との併用］は， MTX による前治療が効果不十分であった2歳以上の患者における若年性特発性多発関節炎（pJIA，リウマチ因子陽性又は陰性，及び進展型少関節炎）の治療を適応とする。 MTX に対する忍容性が不良である場合，又は MTX の継続投与が不適である場合，RoActemra は単剤療法として使用することも可能である。 RoActemra は，成人巨細胞性動脈炎（GCA）患者の治療を適応とする。
用法・用量	トシリズマブ皮下注製剤は単回使用の PFS+NSD とともに用いること。本剤の投与は，RA，sJIA，pJIA 及び/又は GCA 診断・治療の経験をもつ医療従事者が開始すること。最初の皮下投与は、適切な資格を有する医療従事者監督のもとで行うこと。医師がその妥当性を検討し、患者または患者の親／後見人が必要に応じて医学的フォローアップを行うことに同意し、また適切な投与方法が訓練されている場合に限り、患者または患者の親／後見人は RoActemra を自己投与することができる。 静脈内投与用製剤から皮下投与用製剤に移行する患者は，最初の皮下投与を，次に予定された静脈内投与の代わりに，適切な資格を有する医療従事者監督のもとで行う。 RoActemra の投与を受けるすべての患者に Patient Alert Card を配布すること。 患者または患者の親／後見人が自宅での皮下投与に適しているかどうかを評価し，アレルギー反応の症状を経験した場合は次回投与前に医療従事者に連絡するよう，患者または患者の親／後見人を指導する。重篤なアレルギー反応の症状が発現した場合は，直ちに医師の診察を受けること。

<RA>
推奨される用量は，162 mg の1週間に1回皮下投与である。
RoActemra 静脈内投与用製剤から RoActemra 皮下投与用固定用量製剤への患者切り替えについては，限られた知見しか得られていない。1週間に1回という投与間隔を遵守すること。
静脈内投与用製剤から皮下投与用製剤に移行する患者は，最初の皮下投与を，次に予定された静脈内投与の代わりに，適切な資格を有する医療従事者監督のもとで行う。

<GCA>
推奨用量として，糖質コルチコイドの用量を漸減しながら，本剤162 mgを週1回皮下投与する。RoActemraは糖質コルチコイド投与中止後も単独投与可能である。
RoActemra単独療法を，急性再発の治療に用いることはできない。

GCAは慢性疾患であるので，52週を超える投与については疾患活動性，医師の判断及び患者選択を参考に判断すること。

＜RA 及び GCA>

臨床検査値異常による用量調節
肝酵素異常

臨床検査値	措置
正常上限値（ULN）を超え，正常上限値の3倍以下	適宜，併用している DMARD（RA）又は免疫修飾薬（GCA）の用量を調節する。 この範囲の高値が持続する場合，RoActemra の投与頻度を 2 週間に 1 回の注射に減らすか，アラニン・アミノトランスフェラーゼ（ALT）又はアスパラギン酸アミノトランスフェラーゼ（AST）が正常値に回復するまで RoActemra の投与を中断する。 臨床的に妥当と判断されれば，1週間に1回又は2週間に1回の注射間隔で投与再開する。
正常上限値の3倍を超え，正常上限値の5倍以下	正常上限値の3倍を下回るまで RoActemra の投与を中断し，上記の「正常上限値を超え，正常上限値の3倍以下」の推奨に従う。 正常上限値の3倍を超える状態が持続した場合（再検査により確認），RoActemra を中止する。
正常上限値の5倍を超える	RoActemra を中止する。

絶対好中球数（ANC）減少

RoActemra による治療歴がない患者の場合，絶対好中球数（ANC）が2×10^9/L 未満であれば RoActemra 療法を開始しないことが望ましい。

臨床検査値（$\times10^9$/L）	措置
ANC が 1 を超える	用量を維持する。
ANC が0.5～1	RoActemra の投与を中断する。 ANC が1×10^9/L を上回った段階で，2週間に1回の間隔で投与を再開し，臨床的に妥当と判断されれば1週間に1回の注射に増量する。
ANC が0.5未満	RoActemra を中止する。

血小板数減少

臨床検査値（$\times10^3$/μl）	措置
50～100	RoActemra の投与を中断する。 血小板数が100×10^3/μl を上回った段階で，2週間に1回の間隔で投与を再開し，臨床的に妥当と判断されれば1週間に1回の注射に増量する。
50未満	RoActemra を中止する。

＜RA 及び GCA>

<u>投与を忘れた場合</u>

患者が RoActemra の1週間に1回の皮下注射を投与予定日から7日以内に行わなかった場合，忘れた分の投与を次回予定日に投与するよう指導する。患者が RoActemra の2週間に1回の皮下注射を投与予定日から7日以内に行わなかった場合は，忘れた分の投与を直ちに行い，次回投与を次回予定日に行うよう指導する。

特別な母集団

高齢者：

65歳以上の患者で用量調節を行う必要はない。

腎障害：

軽度腎障害のある患者で用量調節を行う必要はない。中等度・重度の腎障害のある患者での RoActemra の検討は行われていない。これらの患者では，腎機能を慎重に観察すること。

肝障害：

肝障害のある患者では，RoActemra の検討は行われていない。したがって，用量に関する推奨を行うことはできない。

小児患者：

新生児から1歳未満の小児における RoActemra 皮下投与用製剤の安全性と有効性は確立されていない。データはない。

患者の体重に継時的に一貫性のある変化が見られた場合にのみ，用量を変更すること。

RoActemra は単剤療法として使用することも，MTX と併用することもできる。

sJIA 患者：
1歳以上の患者に推奨される用量は，体重30 kg 以上の患者が162 mg の1週間に1回皮下投与，体重30 mg 未満の患者が162 mg の2週間に1回皮下投与である。RoActemra の皮下投与する場合は，患者の体重は10 kg 以上必要である。

pJIA 患者：
2歳以上の患者に推奨される用量は，体重30 kg 以上の患者が162 mg の2週間に1回皮下投与，体重30 mg 未満の患者が162 mg の3週間に1回皮下投与である。

臨床検査値異常による用量調節（sJIA 及び pJIA）
臨床検査値異常が認められたときは，必要に応じて，併用している MTX 又は他の医薬品の用量を調整するか中断し，またトシリズマブの投与を，臨床状態が評価されるまで中断することが望ましい。sJIA 又は pJIA には，臨床検査値に異常を及ぼす可能性のある合併症が数多く存在するため，臨床検査値異常によるトシリズマブ投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。

肝酵素異常

臨床検査値	措置
正常上限値（ULN）を超え，正常上限値の3倍以下	適宜，併用している MTX の用量を調節する。 この範囲の高値が持続する場合，ALT／AST が正常値に回復するまで RoActemra の投与を中断する。
正常上限値の3倍を超え，正常上限値の5倍以下	適宜，併用している MTX の用量を調節する。 正常上限値の3倍を下回るまで RoActemra の投与を中断し，上記の「正常上限値を超え，正常上限値の3倍以下」の推奨に従う。
正常上限値の5倍を超える	RoActemra を中止する。 sJIA 又は pJIA の場合，臨床検査値異常による RoActemra 投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。

絶対好中球数（ANC）減少

臨床検査値（$\times 10^9$/L）	措置
ANC が1を超える	用量を維持する。
ANC が0.5～1	RoActemra の投与を中断する。 ANC が1×10^9/L を上回った段階で，RoActemra を再開する
ANC が0.5未満	RoActemra を中止する。 sJIA 又は pJIA の場合，臨床検査値異常による RoActemra 投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。

血小板数減少

臨床検査値	措置

	<table><tr><td>（$\times 10^3/\mu l$）</td><td></td></tr><tr><td>50～100</td><td>適宜，併用している MTX の用量を調節する。 RoActemra の投与を中断する。 血小板数が$100\times 10^3/\mu l$ を上回った段階で，RoActemra を再開する。</td></tr><tr><td>50未満</td><td>RoActemra を中止する。 sJIA 又は pJIA の場合，臨床検査値異常による RoActemra 投与中止の判断は，個々の患者の医学的評価に基づいて行うこと。</td></tr></table> sJIA および pJIA 患者では，臨床検査値異常によるトシリズマブ減量についての検討は行われていない。 sJIA または pJIA 患者以外の小児における RoActemra 皮下注投与用製剤の安全性と有効性は確立されていない。 点滴静注用製剤で得られているデータからは，RoActemra 投与開始後12週間以内に臨床的改善が認められることが示唆されている。この期間内に改善がみられない患者については，治療継続の可否を慎重に検討すること。 投与を忘れた場合 sJIA の患者が RoActemra の1週間に1回の皮下注射を投与予定日から7日以内に行わなかった場合，忘れた分の投与を次回予定日に投与するよう指導する。患者が RoActemra の2週間に1回の皮下注射を投与予定日から7日以内に行わなかった場合は，忘れた分の投与を直ちに行い，次回投与を次回予定日に行うよう指導する。 pJIA の患者が RoActemra の皮下注射を投与予定日から7日以内に行わなかった場合，忘れた分の投与を直ちに行い，また，次回予定日にも投与するよう指導する。患者が RoActemra の皮下注射を投与予定日から7日を超えて行わなかった場合，又は投与したか不明な場合は，医師または薬剤師に電話する。 投与方法 RoActemra は皮下投与用製剤である。 担当医が妥当と判断した患者であれば，注射手技について適切な訓練を行った上で，患者が RoActemra を自己注射して差し支えない。プレフィルドシリンジに充填されている全量（0.9 ml）を，皮下注射により投与する。推奨される注射部位（腹部，大腿及び上腕）は注射ごとに替え，ほくろやあざ，瘢痕の内部や，圧痛・内出血・発赤又は硬化がみられる皮膚，及び傷のある部位には注射しないこと。 プレフィルドシリンジは振らないこと。 RoActemra プレフィルドシリンジ投与のための総合的な説明は，添付文書に示されている。
禁忌	本剤の有効成分又は添加物に対し過敏症の既往歴のある患者。 重度の活動性感染症のある患者。
特別な警告及び使用上の注意	皮下注製剤の静脈内投与は承認されていない。 体重10 kg 未満の sJIA 小児患者に対する皮下投与は承認されていない。 トレーサビリティ

	生物学的製剤のトレーサビリティを改善するため，投与した製品の商品名を患者ファイルに明確に記録すること。 感染症 免疫抑制剤（RoActemra を含む）を投与している患者では，重篤な感染症があらわれることがあり，場合によっては致命的な経過をたどることが報告されている。活動性感染症の患者では RoActemra による治療を開始しないこと。重篤な感染症があらわれた場合は，その感染症がコントロールされるまで RoActemra の投与を中断する。再発性又は慢性感染症の既往歴のある患者や易感染性の状態となる可能性のある基礎疾患（憩室炎，糖尿病，間質性肺疾患など）を有する患者で RoActemra の使用を検討する場合には，医療従事者は慎重を期すること。 生物学的製剤の投与を受けている患者では，急性期反応物質の抑制に伴って急性炎症の徴候・症状が減弱する可能性があるため，重篤な感染症を適時に検出することができるよう監視することが望ましい。感染症があらわれる可能性のある患者を評価する際は，トシリズマブが C 反応性蛋白（CRP），好中球及び感染の徴候・症状に及ぼす影響を考慮すること。迅速な評価と適切な治療を可能とするため，感染症の発症を示唆する症状があらわれた場合は直ちに担当の医療従事者に連絡を取るよう患者（自身の症状について伝達する能力がやや劣る年少の sJIA・pJIA 患者を含む）及び sJIA・pJIA 患者の親／後見人を指導すること。 結核 他の生物学的製剤による治療でも推奨されているとおり，RA 患者については，RoActemra 療法を開始する前に潜在性結核（TB）感染の有無をスクリーニングする必要がある。潜在性結核の患者は，RoActemra の投与を開始する前に，標準的な抗マイコバクテリア療法による治療を行うこと。医師は，特に重症な症例や，免疫が低下している症例では，ツベルクリン反応やインターフェロンガンマ TB 血液テストの結果が陰性に出るリスクを考慮すること。 患者に対し，本剤による治療中もしくは治療した後に，咳の持続，体重の減少，微熱など結核の感染を示唆するような徴候・症状が起こった場合には，医学的な助言を受けることを指導しなければならない。 ウイルス再活性化 RA に対し生物学的療法を行った患者において，ウイルス再活性化（B 型肝炎ウイルスなど）が報告されている。トシリズマブの臨床試験では，肝炎のスクリーニング検査が陽性であった患者は除外した。 憩室炎の合併症 RA 患者では，RoActemra を投与した場合にまれに憩室穿孔の事象が報告されている（憩室炎の合併症として）。RoActemra は，腸管潰瘍形成又は憩室炎の既往歴のある患者には慎重に投与すること。憩室炎の合併症を示唆する可能性のある症状（腹痛，出血，発熱を伴う原因不明の排便習慣変化など）を発現した患者については，消化管穿孔を伴う可能性のある憩室炎を早期に特定するため，速やかに評価を行うこと。 過敏症反応 RoActemra に関連して重篤な過敏症反応（アナフィラキシーを含む）が報告されている。前回のトシリズマブ投与時に過敏症反応があらわれた患者では，たとえ

	ステロイド薬及び抗ヒスタミン薬の前投与を受けていても，そのような反応はさらに重症化する可能性があり，場合によっては致命的な経過をたどるおそれもある。アナフィラキシー反応又はその他の重篤な過敏症反応があらわれた場合は，RoActemra の投与を直ちに停止するとともに適切な治療を開始し，トシリズマブによる治療を永続的に中止すること。 活動性肝疾患及び肝障害 RoActemra の投与に伴って（特に MTX と併用する場合），肝トランスアミナーゼ値が上昇することがある。したがって，活動性肝疾患又は肝障害のある患者への投与を検討する場合には慎重を期すること。 肝トランスアミナーゼ値上昇 臨床試験では，RoActemra 投与後に一過性又は間欠的な軽度・中等度の肝トランスアミナーゼ値上昇が高い頻度で報告されているが，肝障害に進行した例はない。肝障害を起こす可能性のある薬剤（MTX など）を RoActemra と併用した際に，トランスアミナーゼ上昇の発現頻度の上昇が認められている。臨床上必要である場合は，他の肝機能検査（ビリルビンなど）の実施を考慮すること。 正常上限値の1.5倍を超える ALT 上昇又は AST 上昇が認められる患者においてRoActemra の投与開始を検討する場合には慎重を期すること。ベースラインのALT 又は AST が正常上限値の5倍を超える患者には投与しないことが望ましい。 RA 及び GCA 患者では，ALT 及び AST を投与開始後6ヵ月間は4～8週ごとに観察し，その後は12週ごとに観察すること。トランスアミナーゼに基づく推奨用量調節については，「用法・用量」を参照のこと。正常上限値の3倍超～5倍以下のALT 上昇又は AST 上昇の場合は，RoActemra の投与を中断すること。 sJIA 及び pJIA の患者では，ALT 及び AST を2回目の投与時に観察し，その後は医薬品の臨床試験の実施の基準に準拠して観察すること。 血液学的異常 トシリズマブ8 mg/kg を MTX と併用した際に好中球数及び血小板数の減少が認められている。TNF 阻害薬による治療歴のある患者は，好中球減少症のリスクが高い可能性がある。 RoActemra による治療歴のない患者の場合，絶対好中球数（ANC）が2×10^9/L 未満であれば RoActemra 療法を開始しないことが望ましい。血小板数減少（血小板数が100×10^3/μl 未満）のある患者で RoActemra の投与開始を検討する場合は，慎重を期すること。ANC が0.5×10^9/L 未満又は血小板数が50×10^3/μl 未満となった患者では，投与の継続は推奨されない。 重度の好中球減少症は重篤な感染症の発現リスクを高める可能性がある。ただし，RoActemra の臨床試験では，好中球数減少と重篤な感染症の発生との間にこれまでのところ明確な関連性は認められていない。 RA 及び GCA 患者では，RoActemra 療法の開始から4～8週後に好中球数及び血小板数を観察し，その後は標準的な臨床診療に準拠して観察すること。ANC 及び血小板数に基づく推奨用量調節については，「用法・用量」を参照のこと。 sJIA 及び pJIA の患者では，好中球及び血小板を2回目の投与時に観察し，その後は医薬品の臨床試験の実施の基準に準拠して観察すること。

	脂質検査項目 トシリズマブを投与した患者において，総コレステロール，低比重リポ蛋白質（LDL），高比重リポ蛋白（HDL），中性脂肪などの脂質検査項目に上昇が認められている。大部分の患者では，動脈硬化指数（Atherogenic index）の上昇は認められず，総コレステロール値の上昇は脂質低下剤による治療に反応した。 全ての患者では，RoActemra 療法の開始から4～8週後に脂質検査項目の評価を行うこと。高脂血症の管理に関する現地の臨床ガイドラインに従って患者を管理すること。 神経学的障害 医師は，中枢神経脱髄疾患の新規発生を示唆する可能性のある症状があらわれていないか監視すること。RoActemra 投与により中枢神経脱髄が生じる可能性については現時点では不明である。 悪性腫瘍 RA 患者は悪性腫瘍の発現リスクが高い。免疫調節薬は悪性腫瘍のリスクを高める可能性がある。 ワクチン接種 臨床での安全性が確立されていないため，RoActemra 投与中は生ワクチンや弱毒生ワクチンを接種しないこと。ある無作為化オープンラベル試験において，RoActemura と MTX を投与された成人 RA 患者は，23価肺炎球菌多糖体ワクチンと破傷風トキソイドワクチンいずれに対しても，MTX のみが投与された患者と同等の有効な反応を示すことができた。いずれの患者（特に小児患者または高齢患者）も，RoActemra 療法の開始までに現行の予防接種ガイドラインに従ってすべての予防接種を済ませておくことが望ましい。生ワクチン接種から RoActemra 療法開始までの期間は，免疫抑制剤に関する現行のワクチン接種ガイドラインに準拠すること。 心血管リスク RA 患者は心血管障害の発現リスクが高いため，日常の標準治療の一環として危険因子（高血圧，高脂血症など）の管理を行うこと。 TNF 阻害薬との併用 RA 患者において RoActemra を TNF 阻害薬又は他の生物学的製剤と併用した経験はない。RoActemra を他の生物学的製剤と併用することは推奨されない。 GCA RoActemra 単独療法を急性再発の治療に用いないこと（急性再発に対する有効性は確立されていない）。医学的判断と診療ガイドラインに従い，糖質コルチコイドを投与する。 sJIA マクロファージ活性化症候群（MAS）は，sJIA 患者にあらわれる可能性のある生命を脅かす重篤な疾患である。臨床試験では，活動性 MAS のエピソード中の患者を対象とする RoActemra の試験は行われていない。

薬物-薬物相互作用及びその他の相互作用	相互作用試験は成人のみで行われた。 トシリズマブ（10 mg/kg，単回投与）と MTX（10～25 mg，週1回投与）の併用は，MTX の曝露量に対して，臨床的に問題となる影響を及ぼさなかった。 MTX，非ステロイド性抗炎症薬（NSAIDs）及び副腎皮質ステロイド薬がトシリズマブのクリアランスに影響を及ぼすとの知見は母集団薬物動態解析では検出されなかった。 肝酵素 CYP450の発現は，慢性炎症を促進させるサイトカイン（IL-6など）によって抑制される。したがって，トシリズマブなどの強力なサイトカイン阻害療法を導入することによって CYP450の発現が回復する可能性がある。 培養ヒト肝細胞を用いた *in vitro* 試験では，IL-6が CYP1A2，CYP2C9，CYP2C19，及び CYP3A4の発現量を減少させることが示されている。トシリズマブは，これらの酵素の発現量を正常に戻す。 RA 患者を対象とした試験では，トシリズマブ単回投与の1週間後にシンバスタチン（CYP3A4により代謝される）を投与したところ，シンバスタチンの濃度は57%低下した。この低下した濃度は健康被験者での値と同程度かわずかに上回る値である。 トシリズマブ療法を開始又は停止する際に，患者が個別に用量が調整される薬剤で，かつ CYP450 3A4，1A2又は2C9によって代謝される薬剤（アトルバスタチン，カルシウム拮抗薬，テオフィリン，ワルファリン，フェンプロクモン，フェニトイン，シクロスポリン，ベンゾジアゼピン系薬剤など）を服用している場合，治療効果維持のため用量を増量する必要が生じる可能性があるため，患者を観察する必要がある。トシリズマブは消失半減期（$t_{1/2}$）が長いため，トシリズマブが CYP450の酵素活性に及ぼす影響は，治療停止後も数週間にわたって持続する可能性がある。
受胎能，妊婦及び授乳婦への投与	妊娠可能な女性 妊娠する可能性がある婦人は，投与中及び投与3ヵ月後まで効果的な避妊を行わなければならない。 妊婦 妊婦におけるトシリズマブの使用については，十分なデータが得られていない。動物試験では，高用量で自然流産／胚・胎児死亡のリスク上昇が認められている。ヒトに対する潜在的な危険性は不明である。 妊娠中の婦人には，明らかな必要性がある場合にのみ RoActemra を投与すること。 授乳 トシリズマブがヒトの乳汁中に移行するかどうかはわかっていない。トシリズマブの乳汁中への移行については，動物を用いた試験が行われていない。授乳することで乳児が得る利益と RoActemra 療法を行うことで母体が得る利益を検討したうえで，授乳の継続／中止及び RoActemra 投与の継続／中止の可否を判断すること 。 受胎能 これまでに得られている非臨床データでは，トシリズマブ投与の受胎能への影響は示唆されていない。
自転車運転及	RoActemra は，自動車運転及び機械操作能力に対する軽微な影響を有する。

び機械操作に対する影響	
過量投与	RoActemra の過量投与に関しては，限られたデータしか得られていない。偶発的過量投与が1例（40 mg/kg を単回投与した多発性骨髄腫患者）報告されている。副作用は認められなかった。 健康被験者に単回投与した場合，28 mg/kg の用量まで重篤な副作用は認められていない。ただし，用量制限につながる好中球減少症が認められた。

1.6.3　米国における添付文書

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACTEMRA safely and effectively. See full prescribing information for ACTEMRA.

ACTEMRA® (tocilizumab) injection, for intravenous or subcutaneous use
Initial U.S. Approval: 2010

WARNING: RISK OF SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.
- **Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA. (5.1)**
- **If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting ACTEMRA. (5.1)**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.3, 2.8)	05/2018
Dosage and Administration (2.4, 2.8)	09/2018
Dosage and Administration (2.8)	11/2018

---------- INDICATIONS AND USAGE----------
ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of:

Rheumatoid Arthritis (RA) (1.1)
- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

Giant Cell Arteritis (GCA) (1.2)
- Adult patients with giant cell arteritis.

Polyarticular Juvenile Idiopathic Arthritis (PJIA) (1.3)
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.

Systemic Juvenile Idiopathic Arthritis (SJIA) (1.4)
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

Cytokine Release Syndrome (CRS) (1.5)
- Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

----------DOSAGE AND ADMINISTRATION----------
For RA, pJIA and sJIA, ACTEMRA may be used alone or in combination with methotrexate: and in RA, other DMARDs may be used. (2)

Rheumatoid Arthritis (2.1)
Recommended Adult Intravenous Dosage:
When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

Recommended Adult Subcutaneous Dosage:

Patients less than 100 kg weight	162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response
Patients at or above 100 kg weight	162 mg administered subcutaneously every week

Giant Cell Arteritis (2.2)
Recommended Adult Subcutaneous Dosage:
The recommended dose of ACTEMRA for adult patients with GCA is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids.

A dose of 162 mg given once every other week as a subcutaneous injection, in combination with a tapering course of glucocorticoids, may be prescribed based on clinical considerations.

ACTEMRA can be used alone following discontinuation of glucocorticoids.

ACTEMRA subcutaneous formulation is not intended for intravenous administration.

Polyarticular Juvenile Idiopathic Arthritis (2.3)

Recommended Intravenous PJIA Dosage Every 4 Weeks	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous PJIA Dosage	
Patients less than 30 kg weight	162 mg once every three weeks
Patients at or above 30 kg weight	162 mg once every two weeks

Systemic Juvenile Idiopathic Arthritis (2.4)

Recommended Intravenous SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous SJIA Dosage	
Patients less than 30 kg weight	162 mg every two weeks
Patients at or above 30 kg weight	162 mg every week

Cytokine Release Syndrome (2.5)

Recommended Intravenous CRS Dosage	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg
Alone or in combination with corticosteroids.	

General Dosing Information (2.6)
- It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm^3, platelet count below 100,000 per mm^3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN). (2.1, 5.3)
- ACTEMRA doses exceeding 800 mg per infusion are not recommended in RA or CRS patients. (2.1, 2.5, 12.3)

Administration of Intravenous formulation (2.7)
- For adults with RA, CRS, PJIA and SJIA patients at or above 30 kg, dilute to 100 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- For PJIA, SJIA and CRS patients less than 30 kg, dilute to 50 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- Administer as a single intravenous drip infusion over 1 hour; do not administer as bolus or push.

Administration of Subcutaneous formulation (2.8)
- Follow the Instructions for Use for prefilled syringe

Dose Modifications (2.9)
- Recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia.

---------- DOSAGE FORMS AND STRENGTHS----------
Intravenous Infusion
Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion (3)
Subcutaneous Injection
Injection: 162 mg/0.9 mL in a single-dose prefilled syringe or single-dose prefilled autoinjector (ACTPen™) (3)

----------CONTRAINDICATIONS ----------
- ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA. (4)

---------- WARNINGS AND PRECAUTIONS----------
- Serious Infections – do not administer ACTEMRA during an active infection, including localized infections. If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)

- Gastrointestinal (GI) perforation—use with caution in patients who may be at increased risk. (5.2)
- Laboratory monitoring—recommended due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests. (2.8, 5.3)
- Hypersensitivity reactions, including anaphylaxis and death have occurred. (5.5)
- Live vaccines—Avoid use with ACTEMRA. (5.8, 7.3)

---------- **ADVERSE REACTIONS**----------

Most common adverse reactions (incidence of at least 5%): upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, injection site reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- **USE IN SPECIFIC POPULATIONS**----------

- **Pregnancy:** Based on animal data, may cause fetal harm. (8.1)
- **Lactation:** Discontinue drug or nursing taking into consideration importance of drug to mother. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS INFECTIONS

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2 DOSAGE AND ADMINISTRATION
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3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt ACTEMRA until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before ACTEMRA use and during therapy. Treatment for latent infection should be initiated prior to ACTEMRA use.**
- **Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with ACTEMRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis (RA)

ACTEMRA® (tocilizumab) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

1.2 Giant Cell Arteritis (GCA)

ACTEMRA® (tocilizumab) is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

1.3 Polyarticular Juvenile Idiopathic Arthritis (PJIA)

ACTEMRA® (tocilizumab) is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

1.4 Systemic Juvenile Idiopathic Arthritis (SJIA)

ACTEMRA® (tocilizumab) is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

1.5 Cytokine Release Syndrome (CRS)

ACTEMRA® (tocilizumab) is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients 2 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Rheumatoid Arthritis

ACTEMRA may be used as monotherapy or concomitantly with methotrexate or other non-biologic DMARDs as an intravenous infusion or as a subcutaneous injection.

Recommended Intravenous Dosage Regimen:

The recommended dosage of ACTEMRA for adult patients given as a 60-minute single intravenous drip infusion is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

- Reduction of dose from 8 mg per kg to 4 mg per kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.9), Warnings and Precautions (5.3), and Adverse Reactions (6.1)]*.
- Doses exceeding 800 mg per infusion are not recommended in RA patients *[see Clinical Pharmacology (12.3)]*.

Recommended Subcutaneous Dosage Regimen:

Patients less than 100 kg weight	162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response
Patients at or above 100 kg weight	162 mg administered subcutaneously every week

When transitioning from ACTEMRA intravenous therapy to subcutaneous administration administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Interruption of dose or reduction in frequency of administration of subcutaneous dose from every week to every other week dosing is recommended for management of certain dose-related laboratory changes including elevated

liver enzymes, neutropenia, and thrombocytopen*ia [see Dosage and Administration (2.9), Warnings and Precautions (5.3), and Adverse Reactions (6.2)]*.

2.2 Giant Cell Arteritis

The recommended dose of ACTEMRA for adult patients with GCA is 162 mg given once every week as a subcutaneous injection in combination with a tapering course of glucocorticoids.

A dose of 162 mg given once every other week as a subcutaneous injection in combination with a tapering course of glucocorticoids may be prescribed based on clinical considerations.

ACTEMRA can be used alone following discontinuation of glucocorticoids.

- Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.9)]*.
- Intravenous administration is not approved for GCA.

2.3 Polyarticular Juvenile Idiopathic Arthritis

ACTEMRA may be used alone or in combination with methotrexate. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate.

Recommended Intravenous Dosage Regimen:

The recommended dosage of ACTEMRA for PJIA patients given once every 4 weeks as a 60-minute single intravenous drip infusion is:

Recommended Intravenous PJIA Dosage Every 4 Weeks	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous Dosage Regimen:

Recommended Subcutaneous PJIA Dosage	
Patients less than 30 kg weight	162 mg once every 3 weeks
Patients at or above 30 kg weight	162 mg once every 2 weeks

When transitioning from ACTEMRA intravenous therapy to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.9)]*.

2.4 Systemic Juvenile Idiopathic Arthritis

ACTEMRA may be used as an intravenous infusion or as a subcutaneous injection alone or in combination with methotrexate. Do not change a dose based solely on a single visit body weight measurement, as weight may fluctuate.

Recommended Intravenous Dosage Regimen:

The recommended dose of ACTEMRA for SJIA patients given once every 2 weeks as a 60-minute single intravenous drip infusion is:

Recommended Intravenous SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous Dosage Regimen:

Recommended Subcutaneous SJIA Dosage	
Patients less than 30 kg weight	162 mg once every two weeks
Patients at or above 30 kg weight	162 mg once every week

When transitioning from ACTEMRA intravenous therapy to subcutaneous administration, administer the first subcutaneous dose when the next scheduled intravenous dose is due.

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.9)]*.

2.5 Cytokine Release Syndrome (CRS)

Use only the intravenous route for treatment of CRS. The recommended dose of ACTEMRA for treatment of CRS given as a 60-minute intravenous infusion is:

Recommended Intravenous CRS Dosage	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg
Alone or in combination with corticosteroids	

- If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of ACTEMRA may be administered. The interval between consecutive doses should be at least 8 hours.
- Doses exceeding 800 mg per infusion are not recommended in CRS patients.
- Subcutaneous administration is not approved for CRS

2.6 General Considerations for Administration

- ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators because of the possibility of increased immunosuppression and increased risk of infection. Avoid using ACTEMRA with biological DMARDs.
- It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm^3, platelet count below 100,000 per mm^3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN).
  - Patients with severe or life-threatening CRS frequently have cytopenias or elevated ALT or AST due to the lymphodepleting chemotherapy or the CRS. The decision to administer ACTEMRA should take into account the potential benefit of treating the CRS versus the risks of short-term treatment with ACTEMRA.

2.7 Preparation and Administration Instructions for Intravenous Infusion

ACTEMRA for intravenous infusion should be diluted by a healthcare professional using aseptic technique as follows:

- Patients **less than 30 kg**: use a **50 mL** infusion bag or bottle of 0.9% or 0.45% Sodium Chloride Injection, USP, and then follow steps 1 and 2 below.
- Patients **at or above 30 kg weight**: use a **100 mL** infusion bag or bottle, and then follow steps 1 and 2 below.

− Step 1. Withdraw a volume of 0.9% or 0.45% Sodium Chloride Injection, USP, equal to the volume of the ACTEMRA injection required for the patient's dose from the infusion bag or bottle *[see Dosage and Administration (2.1, 2.3, 2.4, 2.5)]*.

For Intravenous Use: Volume of ACTEMRA Injection per kg of Body Weight		
Dosage	Indication	Volume of ACTEMRA injection per kg of body weight
4 mg/kg	Adult RA	0.2mL/kg
8 mg/kg	Adult RA SJIA, PJIA and CRS (≥30 kg of body weight)	0.4mL/kg
10 mg/kg	PJIA (< 30 kg of body weight)	0.5 mL/kg
12 mg/kg	SJIA and CRS (< 30 kg of body weight)	0.6mL/kg

− Step 2. Withdraw the amount of ACTEMRA for intravenous infusion from the vial(s) and add slowly into the 0.9% or 0.45% Sodium Chloride Injection, USP infusion bag or bottle. To mix the solution, gently invert the bag to avoid foaming.

- The fully diluted ACTEMRA solutions for infusion using 0.9% Sodium Chloride Injection, USP may be stored at 2° to 8°C (36° to 46°F) or room temperature for up to 24 hours and should be protected from light.
- The fully diluted ACTEMRA solutions for infusion using 0.45% Sodium Chloride Injection, USP may be stored at 2° to 8°C (36° to 46°F) for up to 24 hours or room temperature for up to 4 hours and should be protected from light.
- ACTEMRA solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used.
- Allow the fully diluted ACTEMRA solution to reach room temperature prior to infusion.
- The infusion should be administered over 60 minutes, and must be administered with an infusion set. Do not administer as an intravenous push or bolus.
- ACTEMRA should not be infused concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of ACTEMRA with other drugs.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates and discolorations are noted, the product should not be used.
- Fully diluted ACTEMRA solutions are compatible with polypropylene, polyethylene and polyvinyl chloride infusion bags and polypropylene, polyethylene and glass infusion bottles.

2.8 Preparation and Administration Instructions for Subcutaneous Injection

- ACTEMRA for subcutaneous injection is not intended for intravenous drip infusion.
- Assess suitability of patient for subcutaneous home use and instruct patients to inform a healthcare professional before administering the next dose if they experience any symptoms of allergic reaction. Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions. ACTEMRA subcutaneous injection is intended for use under the guidance of a healthcare practitioner. After proper training in subcutaneous injection technique, a patient may self-inject ACTEMRA or the patient's caregiver may administer ACTEMRA if a healthcare practitioner determines that it is appropriate. PJIA and SJIA patients may self-inject with ACTEMRA prefilled syringe or the patient's caregiver may administer ACTEMRA if both the healthcare practitioner and the parent/legal guardian determines it is appropriate. The ability of pediatric patients to self-inject with the autoinjector has not been tested. Patients, or patient caregivers, should

be instructed to follow the directions provided in the Instructions for Use (IFU) for additional details on medication administration

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use ACTEMRA prefilled syringes (PFS) or autoinjectors (AI) exhibiting particulate matter, cloudiness, or discoloration. ACTEMRA for subcutaneous administration should be clear and colorless to pale yellow. Do not use if any part of the PFS or AI appears to be damaged.
- Patients using ACTEMRA for subcutaneous administration should be instructed to inject the full amount in the syringe (0.9 mL)) or full amount in the autoinjector (0.9 mL), which provides 162 mg of ACTEMRA, according to the directions provided in the IFU.
- Injection sites should be rotated with each injection and should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

2.9 Dosage Modifications due to Serious Infections or Laboratory Abnormalities

Hold ACTEMRA treatment if a patient develops a serious infection until the infection is controlled.

Rheumatoid Arthritis and Giant Cell Arteritis

Liver Enzyme Abnormalities *[see Warnings and Precautions (5.3)]:*	
Lab Value	**Recommendation**
Greater than 1 to 3x ULN	Dose modify concomitant DMARDs (RA) or immunomodulatory agents (GCA) if appropriate For persistent increases in this range: • For patients receiving intravenous ACTEMRA, reduce dose to 4 mg per kg or hold ACTEMRA until ALT or AST have normalized • For patients receiving subcutaneous ACTEMRA, reduce injection frequency to every other week or hold dosing until ALT or AST have normalized. Resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate.
Greater than 3 to 5x ULN (confirmed by repeat testing)	Hold ACTEMRA dosing until less than 3x ULN and follow recommendations above for greater than 1 to 3x ULN For persistent increases greater than 3x ULN, discontinue ACTEMRA
Greater than 5x ULN	Discontinue ACTEMRA

Low Absolute Neutrophil Count (ANC) ***[see Warnings and Precautions (5.3)]:***	
Lab Value (cells per mm^3)	**Recommendation**
ANC greater than 1000	Maintain dose
ANC 500 to 1000	Hold ACTEMRA dosing When ANC greater than 1000 cells per mm^3: • For patients receiving intravenous ACTEMRA, resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate • For patients receiving subcutaneous ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate
ANC less than 500	Discontinue ACTEMRA

Low Platelet Count ***[see Warnings and Precautions (5.3)]:***	
Lab Value (cells per mm^3)	**Recommendation**
50,000 to 100,000	Hold ACTEMRA dosing When platelet count is greater than 100,000 cells per mm^3: • For patients receiving intravenous ACTEMRA, resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate • For patients receiving subcutaneous ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate
Less than 50,000	Discontinue ACTEMRA

Polyarticular and Systemic Juvenile Idiopathic Arthritis:

Dose reduction of ACTEMRA has not been studied in the PJIA and SJIA populations. Dose interruptions of ACTEMRA are recommended for liver enzyme abnormalities, low neutrophil counts, and low platelet counts in patients with PJIA and SJIA at levels similar to what is outlined above for patients with RA. If appropriate, dose modify or stop concomitant methotrexate and/or other medications and hold ACTEMRA dosing until the clinical situation has been evaluated. In PJIA and SJIA the decision to discontinue ACTEMRA for a laboratory abnormality should be based upon the medical assessment of the individual patient.

3 DOSAGE FORMS AND STRENGTHS

Intravenous Infusion

Injection: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL as a clear, colorless to pale yellow solution in 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

Subcutaneous Injection
Injection: 162 mg/0.9 mL clear, colorless to slightly yellowish solution in a single-dose prefilled syringe or autoinjector.

4 CONTRAINDICATIONS

ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including ACTEMRA. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis *[see Adverse Reactions (6.1)]*. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with ACTEMRA. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, listeriosis). Patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids which in addition to rheumatoid arthritis may predispose them to infections.

Do not administer ACTEMRA in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating ACTEMRA in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of serious or an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with ACTEMRA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants *[see Dosage and Administration (2.6), Adverse Reactions (6.1), and Patient Counseling Information (17)]*.

Hold ACTEMRA if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with ACTEMRA should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, initiate appropriate antimicrobial therapy, and closely monitor the patient.

Tuberculosis

Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating ACTEMRA.

Consider anti-tuberculosis therapy prior to initiation of ACTEMRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Closely monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

It is recommended that patients be screened for latent tuberculosis infection prior to starting ACTEMRA. The incidence of tuberculosis in worldwide clinical development programs is 0.1%. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating ACTEMRA.

Viral Reactivation

Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with ACTEMRA. No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded.

5.2 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis in patients treated with ACTEMRA. Use ACTEMRA with caution in patients who may be at increased risk for gastrointestinal perforation. Promptly evaluate patients presenting with new onset abdominal symptoms for early identification of gastrointestinal perforation *[see Adverse Reactions (6.1)]*.

5.3 Laboratory Parameters

Rheumatoid Arthritis and Giant Cell Arteritis

Neutropenia

Treatment with ACTEMRA was associated with a higher incidence of neutropenia. Infections have been uncommonly reported in association with treatment-related neutropenia in long-term extension studies and postmarketing clinical experience.

– It is not recommended to initiate ACTEMRA treatment in patients with a low neutrophil count, i.e., absolute neutrophil count (ANC) less than 2000 per mm^3. In patients who develop an absolute neutrophil count less than 500 per mm^3 treatment is not recommended.

– Monitor neutrophils 4 to 8 weeks after start of therapy and every 3 months thereafter *[see Clinical Pharmacology (12.2)]*. For recommended modifications based on ANC results see *Dosage and Administration (2.9).*

Thrombocytopenia

Treatment with ACTEMRA was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials *[see Adverse Reactions (6.1, 6.2)]*.

– It is not recommended to initiate ACTEMRA treatment in patients with a platelet count below 100,000 per mm^3. In patients who develop a platelet count less than 50,000 per mm^3 treatment is not recommended.

– Monitor platelets 4 to 8 weeks after start of therapy and every 3 months thereafter. For recommended modifications based on platelet counts see *Dosage and Administration (2.9).*

Elevated Liver Enzymes

Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials *[see Adverse Reactions (6.1, 6.2)]*. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with ACTEMRA.

In one case, a patient who had received ACTEMRA 8 mg per kg monotherapy without elevations in transaminases experienced elevation in AST to above 10x ULN and elevation in ALT to above 16x ULN when MTX was initiated in combination with ACTEMRA. Transaminases normalized when both treatments were held, but elevations recurred when MTX and ACTEMRA were restarted at lower doses. Elevations resolved when MTX and ACTEMRA were discontinued.

– It is not recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST greater than 1.5x ULN. In patients who develop elevated ALT or AST greater than 5x ULN treatment is not recommended.

– Monitor ALT and AST levels 4 to 8 weeks after start of therapy and every 3 months thereafter. When clinically indicated, other liver function tests such as bilirubin should be considered. For recommended modifications based on transaminases *[see Dosage and Administration (2.9)]*.

Lipid Abnormalities

Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol *[see Adverse Reactions (6.1, 6.2)]*.

– Assess lipid parameters approximately 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately 24 week intervals.

– Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

Polyarticular and Systemic Juvenile Idiopathic Arthritis

A similar pattern of liver enzyme elevation, low neutrophil count, low platelet count and lipid elevations is noted with ACTEMRA treatment in the PJIA and SJIA populations. Monitor neutrophils, platelets, ALT and AST at the time of the second administration and thereafter every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA. Monitor lipids as above for approved adult indications *[see Dosage and Administration (2.9)]*.

5.4 Immunosuppression

The impact of treatment with ACTEMRA on the development of malignancies is not known but malignancies were observed in clinical studies *[see Adverse Reactions (6.1)]*. ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

5.5 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA *[see Adverse Reactions (6)]* and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of intravenous ACTEMRA, 0.2% (8 out of 4009) of patients in the intravenous all-exposure RA population, 0.7% (8 out of 1068) in the subcutaneous 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the subcutaneous all-exposure population. In the SJIA controlled trial with intravenous ACTEMRA, 1 out of 112 patients (0.9%) experienced hypersensitivity reactions that required treatment discontinuation. In the PJIA controlled trial with intravenous ACTEMRA, 0 out of 188 patients (0%) in the ACTEMRA all-exposure population experienced hypersensitivity reactions that required treatment discontinuation. Reactions that required treatment discontinuation included generalized erythema, rash, and urticaria. Injection site reactions were categorized separately [s*ee Adverse Reactions (6)*].

In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with or without concomitant therapies. Events have occurred in patients who received premedication. Hypersensitivity, including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA *[see Adverse Reactions (6.6)]*. ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA *[see Contraindications (4) and Adverse Reactions (6)]*.

5.6 Demyelinating Disorders

The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies. Monitor patients

for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

5.7 Active Hepatic Disease and Hepatic Impairment

Treatment with ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment *[see Adverse Reactions (6.1), Use in Specific Populations (8.6)]*.

5.8 Vaccinations

Avoid use of live vaccines concurrently with ACTEMRA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA.

No data are available on the effectiveness of vaccination in patients receiving ACTEMRA. Because IL-6 inhibition may interfere with the normal immune response to new antigens, it is recommended that all patients, particularly pediatric or elderly patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ACTEMRA therapy. The interval between live vaccinations and initiation of ACTEMRA therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Gastrointestinal Perforations *[see Warnings and Precautions (5.2)]*
- Laboratory Parameters *[see Warnings and Precautions (5.3)]*
- Immunosuppression *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions, Including Anaphylaxis *[see Warnings and Precautions (5.5)]*
- Demyelinating Disorders *[see Warnings and Precautions (5.6)]*
- Active Hepatic Disease and Hepatic Impairment *[see Warnings and Precautions (5.7)]*

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

6.1 Clinical Trials Experience in Rheumatoid Arthritis Patients Treated with Intravenous ACTEMRA (ACTEMRA-IV)

The ACTEMRA-IV data in rheumatoid arthritis (RA) includes 5 double-blind, controlled, multicenter studies. In these studies, patients received doses of ACTEMRA-IV 8 mg per kg monotherapy (288 patients), ACTEMRA-IV 8 mg per kg in combination with DMARDs (including methotrexate) (1582 patients), or ACTEMRA-IV 4 mg per kg in combination with methotrexate (774 patients).

The all exposure population includes all patients in registration studies who received at least one dose of ACTEMRA-IV. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3309 for at least one year; 2954 received treatment for at least 2 years and 2189 for 3 years.

All patients in these studies had moderately to severely active rheumatoid arthritis. The study population had a mean age of 52 years, 82% were female and 74% were Caucasian.

The most common serious adverse reactions were serious infections *[see Warnings and Precautions (5.1)]*. The most commonly reported adverse reactions in controlled studies up to 24 weeks (occurring in at least 5% of

patients treated with ACTEMRA-IV monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The proportion of patients who discontinued treatment due to any adverse reactions during the double-blind, placebo-controlled studies was 5% for patients taking ACTEMRA-IV and 3% for placebo-treated patients. The most common adverse reactions that required discontinuation of ACTEMRA-IV were increased hepatic transaminase values (per protocol requirement) and serious infections.

Overall Infections

In the 24 week, controlled clinical studies, the rate of infections in the ACTEMRA-IV monotherapy group was 119 events per 100 patient-years and was similar in the methotrexate monotherapy group. The rate of infections in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group was 133 and 127 events per 100 patient-years, respectively, compared to 112 events per 100 patient-years in the placebo plus DMARD group. The most commonly reported infections (5% to 8% of patients) were upper respiratory tract infections and nasopharyngitis.

The overall rate of infections with ACTEMRA-IV in the all exposure population remained consistent with rates in the controlled periods of the studies.

Serious Infections

In the 24 week, controlled clinical studies, the rate of serious infections in the ACTEMRA-IV monotherapy group was 3.6 per 100 patient-years compared to 1.5 per 100 patient-years in the methotrexate group. The rate of serious infections in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group was 4.4 and 5.3 events per 100 patient-years, respectively, compared to 3.9 events per 100 patient-years in the placebo plus DMARD group.

In the all-exposure population, the overall rate of serious infections remained consistent with rates in the controlled periods of the studies. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported *[see Warnings and Precautions (5.1)]*.

Gastrointestinal Perforations

During the 24 week, controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient-years with ACTEMRA-IV therapy.

In the all-exposure population, the overall rate of gastrointestinal perforation remained consistent with rates in the controlled periods of the studies. Reports of gastrointestinal perforation were primarily reported as complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, or methotrexate *[see Warnings and Precautions (5.2)]*. The relative contribution of these concomitant medications versus ACTEMRA-IV to the development of GI perforations is not known.

Infusion Reactions

In the 24 week, controlled clinical studies, adverse events associated with the infusion (occurring during or within 24 hours of the start of infusion) were reported in 8% and 7% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group, respectively, compared to 5% of patients in the placebo plus DMARD group. The most frequently reported event on the 4 mg per kg and 8 mg per kg dose during the infusion was hypertension (1% for both doses), while the most frequently reported event occurring within 24 hours of finishing an infusion were headache (1% for both doses) and skin reactions (1% for both doses), including rash, pruritus and urticaria. These events were not treatment limiting.

Anaphylaxis

Hypersensitivity reactions requiring treatment discontinuation, including anaphylaxis, associated with ACTEMRA-IV were reported in 0.1% (3 out of 2644) in the 24 week, controlled trials and in 0.2% (8 out of 4009) in the all-exposure population. These reactions were generally observed during the second to fourth infusion of

ACTEMRA-IV. Appropriate medical treatment should be available for immediate use in the event of a serious hypersensitivity reaction *[see Warnings and Precautions (5.5)]*.

Laboratory Abnormalities

Neutropenia

In the 24 week, controlled clinical studies, decreases in neutrophil counts below 1000 per mm^3 occurred in 1.8% and 3.4% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group, respectively, compared to 0.1% of patients in the placebo plus DMARD group. Approximately half of the instances of ANC below 1000 per mm^3 occurred within 8 weeks of starting therapy. Decreases in neutrophil counts below 500 per mm^3 occurred in 0.4% and 0.3% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD, respectively, compared to 0.1% of patients in the placebo plus DMARD group. There was no clear relationship between decreases in neutrophils below 1000 per mm^3 and the occurrence of serious infections.

In the all-exposure population, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 24 week controlled clinical studies *[see Warnings and Precautions (5.3)]*.

Thrombocytopenia

In the 24 week, controlled clinical studies, decreases in platelet counts below 100,000 per mm^3 occurred in 1.3% and 1.7% of patients on 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD, respectively, compared to 0.5% of patients on placebo plus DMARD, without associated bleeding events.

In the all-exposure population, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 24 week controlled clinical studies *[see Warnings and Precautions (5.3)]*.

Elevated Liver Enzymes

Liver enzyme abnormalities are summarized in **Table 1**. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of ACTEMRA-IV, or reduction in ACTEMRA-IV dose, resulted in decrease or normalization of liver enzymes *[see Dosage and Administration (2.6)]*. These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency *[see Warnings and Precautions (5.3)]*.

Table 1　Incidence of Liver Enzyme Abnormalities in the 24 Week Controlled Period of Studies I to V*

	ACTEMRA 8 mg per kg MONOTHERAPY N = 288 (%)	**Methotrexate N = 284 (%)**	**ACTEMRA 4 mg per kg + DMARDs N = 774 (%)**	**ACTEMRA 8 mg per kg + DMARDs N = 1582 (%)**	**Placebo + DMARDs N = 1170 (%)**
AST (U/L)					
> ULN to 3x ULN	22	26	34	41	17
> 3x ULN to 5x ULN	0.3	2	1	2	0.3
> 5x ULN	0.7	0.4	0.1	0.2	< 0.1
ALT (U/L)					
> ULN to 3x ULN	36	33	45	48	23
> 3x ULN to 5x ULN	1	4	5	5	1
> 5x ULN	0.7	1	1.3	1.5	0.3

ULN = Upper Limit of Normal

*For a description of these studies, see Section 14, Clinical Studies.

In the all-exposure population, the elevations in ALT and AST remained consistent with what was seen in the 24 week, controlled clinical trials

Lipids
Elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were first assessed at 6 weeks following initiation of ACTEMRA-IV in the controlled 24 week clinical trials. Increases were observed at this time point and remained stable thereafter. Increases in triglycerides to levels above 500 mg per dL were rarely observed. Changes in other lipid parameters from baseline to week 24 were evaluated and are summarized below:

– Mean LDL increased by 13 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 20 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 25 mg per dL in ACTEMRA 8 mg per kg monotherapy.

– Mean HDL increased by 3 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 5 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 4 mg per dL in ACTEMRA 8 mg per kg monotherapy.

– Mean LDL/HDL ratio increased by an average of 0.14 in the ACTEMRA 4 mg per kg+DMARD arm, 0.15 in the ACTEMRA 8 mg per kg+DMARD, and 0.26 in ACTEMRA 8 mg per kg monotherapy.

– ApoB/ApoA1 ratios were essentially unchanged in ACTEMRA-treated patients.

Elevated lipids responded to lipid lowering agents.

In the all-exposure population, the elevations in lipid parameters remained consistent with what was seen in the 24 week, controlled clinical trials.

Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to tocilizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the 24 week, controlled clinical studies, a total of 2876 patients have been tested for anti-tocilizumab antibodies. Forty-six patients (2%) developed positive anti-tocilizumab antibodies, of whom 5 had an associated, medically significant, hypersensitivity reaction leading to withdrawal. Thirty patients (1%) developed neutralizing antibodies.

Malignancies
During the 24 week, controlled period of the studies, 15 malignancies were diagnosed in patients receiving ACTEMRA-IV, compared to 8 malignancies in patients in the control groups. Exposure-adjusted incidence was similar in the ACTEMRA-IV groups (1.32 events per 100 patient-years) and in the placebo plus DMARD group (1.37 events per 100 patient-years).

In the all-exposure population, the rate of malignancies remained consistent with the rate observed in the 24 week, controlled period *[see Warnings and Precautions (5.4)]*.

Other Adverse Reactions
Adverse reactions occurring in 2% or more of patients on 4 or 8 mg per kg ACTEMRA-IV plus DMARD and at least 1% greater than that observed in patients on placebo plus DMARD are summarized in **Table 2.**

Table 2 Adverse Reactions Occurring in at Least 2% or More of Patients on 4 or 8 mg per kg ACTEMRA plus DMARD and at Least 1% Greater Than That Observed in Patients on Placebo plus DMARD

24 Week Phase 3 Controlled Study Population					
Preferred Term	**ACTEMRA**	**Methotrexate**	**ACTEMRA**	**ACTEMRA**	**Placebo + DMARDs**

	8 mg per kg MONOTHERAPY N = 288 (%)	N = 284 (%)	4 mg per kg + DMARDs N = 774 (%)	8 mg per kg + DMARDs N = 1582 (%)	N = 1170 (%)
Upper Respiratory Tract Infection	7	5	6	8	6
Nasopharyngitis	7	6	4	6	4
Headache	7	2	6	5	3
Hypertension	6	2	4	4	3
ALT increased	6	4	3	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1
Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2
Gastritis	1	2	1	2	1
Transaminase increased	1	5	2	2	1

Other infrequent and medically relevant adverse reactions occurring at an incidence less than 2% in rheumatoid arthritis patients treated with ACTEMRA-IV in controlled trials were:

Infections and Infestations: oral herpes simplex
Gastrointestinal disorders: stomatitis, gastric ulcer
Investigations: weight increased, total bilirubin increased
Blood and lymphatic system disorders: leukopenia
General disorders and administration site conditions: edema peripheral
Respiratory, thoracic, and mediastinal disorders: dyspnea, cough
Eye disorders: conjunctivitis
Renal disorders: nephrolithiasis
Endocrine disorders: hypothyroidism

6.2 Clinical Trials Experience in Rheumatoid Arthritis Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The ACTEMRA-SC data in rheumatoid arthritis (RA) includes 2 double-blind, controlled, multicenter studies. Study SC-I was a non-inferiority study that compared the efficacy and safety of tocilizumab 162 mg administered every week subcutaneously and 8 mg/kg intravenously every four weeks in 1262 adult subjects with rheumatoid arthritis. Study SC-II was a placebo controlled superiority study that evaluated the safety and efficacy of tocilizumab 162 mg administered every other week subcutaneously or placebo in 656 patients. All patients in both studies received background non-biologic DMARDs.

The safety observed for ACTEMRA-SC administered subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of injection site reactions (ISRs), which were more common with ACTEMRA-SC compared with placebo SC injections (IV arm).

Injection Site Reactions
In the 6-month control period, in SC-I, the frequency of ISRs was 10.1% (64/631) and 2.4% (15/631) for the weekly ACTEMRA-SC and placebo SC (IV-arm) groups, respectively. In SC-II, the frequency of ISRs was 7.1% (31/437) and 4.1% (9/218) for the every other week ACTEMRA-SC and placebo groups, respectively. These ISRs (including erythema, pruritus, pain and hematoma) were mild to moderate in severity. The majority resolved without any treatment and none necessitated drug discontinuation.

Immunogenicity
In the 6-month control period in SC-I, 0.8% (5/625) in the ACTEMRA-SC arm and 0.8% (5/627) in the IV arm developed anti-tocilizumab antibodies; of these, all developed neutralizing antibodies. In SC-II, 1.6% (7/434) in

the ACTEMRA-SC arm compared with 1.4 % (3/217) in the placebo arm developed anti- tocilizumab antibodies; of these, 1.4% (6/434) in the ACTEMRA-SC arm and 0.5% (1/217) in the placebo arm also developed neutralizing antibodies.

A total of 1454 (>99%) patients who received ACTEMRA-SC in the all exposure group have been tested for anti-tocilizumab antibodies. Thirteen patients (0.9%) developed anti-tocilizumab antibodies, and, of these, 12 patients (0.8%) developed neutralizing antibodies.

The rate is consistent with previous intravenous experience. No correlation of antibody development to adverse events or loss of clinical response was observed.

Laboratory Abnormalities

Neutropenia

During routine laboratory monitoring in the 6-month controlled clinical trials, a decrease in neutrophil count below 1×10^9/L occurred in 2.9% and 3.7% of patients receiving ACTEMRA-SC weekly and every other week, respectively.

There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

Thrombocytopenia

During routine laboratory monitoring in the ACTEMRA-SC 6-month controlled clinical trials, none of the patients had a decrease in platelet count to ≤50,000/mm^3.

Elevated Liver Enzymes

During routine laboratory monitoring in the 6-month controlled clinical trials, elevation in ALT or AST ≥3 x ULN occurred in 6.5% and 1.4% of patients, respectively, receiving ACTEMRA-SC weekly and 3.4% and 0.7% receiving ACTEMRA-SC every other week.

Lipid Parameters Elevations

During routine laboratory monitoring in the ACTEMRA-SC 6-month clinical trials, 19% of patients dosed weekly and 19.6% of patients dosed every other week and 10.2% of patients on placebo experienced sustained elevations in total cholesterol > 6.2 mmol/l (240 mg/dL), with 9%, 10.4% and 5.1% experiencing a sustained increase in LDL to 4.1 mmol/l (160 mg/dL) receiving ACTEMRA-SC weekly, every other week and placebo, respectively.

6.3 Clinical Trials Experience in Giant Cell Arteritis Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety of subcutaneous ACTEMRA (tocilizumab) has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the ACTEMRA GCA all exposure population was 138.5 patient years during the 12-month double blind, placebo-controlled phase of the study. The overall safety profile observed in the ACTEMRA treatment groups was generally consistent with the known safety profile of ACTEMRA. There was an overall higher incidence of infections in GCA patients relative to RA patients. The rate of infection/serious infection events was 200.2/9.7 events per 100 patient years in the ACTEMRA weekly group and 160.2/4.4 events per 100 patient years in the ACTEMRA every other week group as compared to 156.0/4.2 events per 100 patient years in the placebo + 26 week prednisone taper and 210.2/12.5 events per 100 patient years in the placebo + 52 week taper groups.

6.4 Clinical Trials Experience in Polyarticular Juvenile Idiopathic Arthritis Patients Treated With Intravenous ACTEMRA (ACTEMRA-IV)

The safety of ACTEMRA-IV was studied in 188 pediatric patients 2 to 17 years of age with PJIA who had an inadequate clinical response or were intolerant to methotrexate. The total patient exposure in the ACTEMRA-IV all exposure population (defined as patients who received at least one dose of ACTEMRA-IV) was 184.4 patient years. At baseline, approximately half of the patients were taking oral corticosteroids and almost 80% were taking

methotrexate. In general, the types of adverse drug reactions in patients with PJIA were consistent with those seen in RA and SJIA patients *[see Adverse Reactions (6.1 and 6.6)]*.

Infections

The rate of infections in the ACTEMRA-IV all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing less than 30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing at or above 30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing less than 30 kg treated with 10 mg/kg tocilizumab (21%) compared to patients weighing at or above 30 kg, treated with 8 mg/kg tocilizumab (8%).

Infusion Reactions

In PJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. In the ACTEMRA-IV all exposure population, 11 patients (6%) experienced an event during the infusion, and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension, and occurring within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and SJIA patients *[see Adverse Reactions (6.1 and 6.6)]*.

No clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported.

Immunogenicity

One patient, in the 10 mg/kg less than 30 kg group, developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.

Laboratory Abnormalities

Neutropenia

During routine laboratory monitoring in the ACTEMRA-IV all exposure population, a decrease in neutrophil counts below 1×10^9 per L occurred in 3.7% of patients.

There was no clear relationship between decreases in neutrophils below 1 x 10^9 per L and the occurrence of serious infections.

Thrombocytopenia

During routine laboratory monitoring in the ACTEMRA-IV all exposure population, 1% of patients had a decrease in platelet count at or less than 50,000 per mm^3 without associated bleeding events.

Elevated Liver Enzymes

During routine laboratory monitoring in the ACTEMRA-IV all exposure population, elevation in ALT or AST at or greater than 3 x ULN occurred in 4% and less than 1% of patients, respectively.

Lipids

During routine laboratory monitoring in the tocilizumab all exposure population, elevation in total cholesterol greater than 1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL greater than 1.5-2 x ULN occurred in one patient (0.5%).

6.5 Clinical Trials Experience in Polyarticular Juvenile Idiopathic Arthritis Patients Treated With Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety of ACTEMRA-SC was studied in 52 pediatric patients 1 to 17 years of age with PJIA who had an inadequate clinical response or were intolerant to methotrexate. The total patient exposure in the PJIA ACTEMRA-SC population (defined as patients who received at least one dose of ACTEMRA-SC and accounting for treatment discontinuation) was 49.5 patient years. In general, the safety observed for ACTEMRA administered

subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of injection site reactions (ISRs), and neutropenia.

Injection Site Reactions

During the 1-year study, a frequency of 28.8% (15/52) ISRs was observed in ACTEMRA-SC treated PJIA patients. These ISRs occurred in a greater proportion of patients at or above 30 kg (44.0%) compared with patients below 30 kg (14.8%). All ISRs were mild in severity and none of the ISRs required patient withdrawal from treatment or dose interruption. A higher frequency of ISRs was observed in ACTEMRA-SC treated PJIA patients compared to what was seen in adult RA or GCA patients [*see Adverse Reactions (6.1 and 6.3)*].

Immunogenicity

Three patients, 1 patient below 30 kg and 2 patients at or above 30 kg, developed positive anti-tocilizumab antibodies with neutralizing potential without developing a serious or clinically significant hypersensitivity reaction. One patient subsequently withdrew from the study.

Neutropenia

During routine laboratory monitoring in the ACTEMRA-SC all exposure population, a decrease in neutrophil counts below 1×10^9 per L occurred in 15.4% of patients, and was more frequently observed in the patients less than 30 kg (25.9%) compared to patients at or above 30 kg (4.0%). There was no clear relationship between decreases in neutrophils below 1×10^9 per L and the occurrence of serious infections.

6.6 Clinical Trials Experience in Systemic Juvenile Idiopathic Arthritis Patients Treated with Intravenous ACTEMRA (ACTEMRA-IV)

The data described below reflect exposure to ACTEMRA-IV in one randomized, double-blind, placebo-controlled trial of 112 pediatric patients with SJIA 2 to 17 years of age who had an inadequate clinical response to nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids due to toxicity or lack of efficacy. At baseline, approximately half of the patients were taking 0.3 mg/kg/day corticosteroids or more, and almost 70% were taking methotrexate. The trial included a 12 week controlled phase followed by an open-label extension. In the 12 week double-blind, controlled portion of the clinical study 75 patients received treatment with ACTEMRA-IV (8 or 12 mg per kg based upon body weight). After 12 weeks or at the time of escape, due to disease worsening, patients were treated with ACTEMRA-IV in the open-label extension phase.

The most common adverse events (at least 5%) seen in ACTEMRA-IV treated patients in the 12 week controlled portion of the study were: upper respiratory tract infection, headache, nasopharyngitis and diarrhea.

Infections

In the 12 week controlled phase, the rate of all infections in the ACTEMRA-IV group was 345 per 100 patient-years and 287 per 100 patient-years in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of infections was 304 per 100 patient-years.

In the 12 week controlled phase, the rate of serious infections in the ACTEMRA-IV group was 11.5 per 100 patient years. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of serious infections was 11.4 per 100 patient years. The most commonly reported serious infections included pneumonia, gastroenteritis, varicella, and otitis media.

Macrophage Activation Syndrome

In the 12 week controlled study, no patient in any treatment group experienced macrophage activation syndrome (MAS) while on assigned treatment; 3 per 112 (3%) developed MAS during open-label treatment with ACTEMRA-IV. One patient in the placebo group escaped to ACTEMRA-IV 12 mg per kg at Week 2 due to severe disease activity, and ultimately developed MAS at Day 70. Two additional patients developed MAS during the long-term extension. All 3 patients had ACTEMRA-IV dose interrupted (2 patients) or discontinued (1 patient) for the MAS event, received treatment, and the MAS resolved without sequelae. Based on a limited number of

cases, the incidence of MAS does not appear to be elevated in the ACTEMRA-IV SJIA clinical development experience; however no definitive conclusions can be made.

Infusion Reactions

Patients were not premedicated, however most patients were on concomitant corticosteroids as part of their background treatment for SJIA. Infusion related reactions were defined as all events occurring during or within 24 hours after an infusion. In the 12 week controlled phase, 4% of ACTEMRA-IV and 0% of placebo treated patients experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

Within 24 hours after infusion, 16% of patients in the ACTEMRA-IV treatment group and 5% of patients in the placebo group experienced an event. In the ACTEMRA-IV group the events included rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Anaphylaxis

Anaphylaxis was reported in 1 out of 112 patients (less than 1%) treated with ACTEMRA-IV during the controlled and open label extension study *[see Warnings and Precautions (5.5)]*.

Immunogenicity

All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies: one of these patients experienced serious adverse events of urticaria and angioedema consistent with an anaphylactic reaction which led to withdrawal; the other patient developed macrophage activation syndrome while on escape therapy and was discontinued from the study.

Laboratory Abnormalities

Neutropenia

During routine monitoring in the 12 week controlled phase, a decrease in neutrophil below 1×10^9 per L occurred in 7% of patients in the ACTEMRA-IV group, and in no patients in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, a decreased neutrophil count occurred in 17% of the ACTEMRA-IV group. There was no clear relationship between decrease in neutrophils below 1 x 10^9 per L and the occurrence of serious infections.

Thrombocytopenia

During routine monitoring in the 12 week controlled phase, 1% of patients in the ACTEMRA-IV group and 3% in the placebo group had a decrease in platelet count to no more than 100,000 per mm^3.

In the open label extension over an average duration of 73 weeks of treatment, decreased platelet count occurred in 4% of patients in the ACTEMRA-IV group, with no associated bleeding.

Elevated Liver Enzymes

During routine laboratory monitoring in the 12 week controlled phase, elevation in ALT or AST at or above 3x ULN occurred in 5% and 3% of patients, respectively in the ACTEMRA-IV group and in 0% of placebo patients.

In the open label extension over an average duration of 73 weeks of treatment, the elevation in ALT or AST at or above 3x ULN occurred in 13% and 5% of ACTEMRA-IV treated patients, respectively.

Lipids

During routine laboratory monitoring in the 12 week controlled phase, elevation in total cholesterol greater than 1.5x ULN – 2x ULN occurred in 1.5% of the ACTEMRA-IV group and in 0% of placebo patients. Elevation in LDL greater than 1.5x ULN – 2x ULN occurred in 1.9% of patients in the ACTEMRA-IV group and 0% of the placebo group.

In the open label extension study over an average duration of 73 weeks of treatment, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled study data.

6.7 Clinical Trials Experience in Systemic Juvenile Idiopathic Arthritis Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety profile of ACTEMRA-SC was studied in 51 pediatric patients 1 to 17 years of age with SJIA who had an inadequate clinical response to NSAIDs and corticosteroids. In general, the safety observed for ACTEMRA administered subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of ISRs where a higher frequency was observed in ACTEMRA-SC treated SJIA patients compared to PJIA patients and adult RA or GCA patients [*see Adverse Reactions (6.2 and 6.3)*].

Injection Site Reactions (ISRs)

A total of 41.2% (21/51) SJIA patients experienced ISRs to ACTEMRA-SC. The most common ISRs were erythema, pruritus, pain, and swelling at the injection site. The majority of ISRs reported were Grade 1 events and all ISRs reported were non-serious and none required patient withdrawal from treatment or dose interruption.

Immunogenicity

Forty-six of the 51 (90.2%) patients who were tested for anti-tocilizumab antibodies at baseline had at least one post-baseline screening assay result. No patient developed positive anti-tocilizumab antibodies post-baseline.

6.8 Clinical Trials Experience in Patients with Cytokine Release Syndrome Treated with Intravenous ACTEMRA (ACTEMRA-IV)

In a retrospective analysis of pooled outcome data from multiple clinical trials 45 patients were treated with tocilizumab 8 mg/kg (12 mg/kg for patients less than 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CAR T-cell-induced CRS. A median of 1 dose of tocilizumab (range, 1-4 doses) was administered. No adverse reactions related to tocilizumab were reported *[see Clinical Studies (14.7)]*.

6.9 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ACTEMRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Fatal anaphylaxis *[see Warnings and Precautions (5.5)]*
- Stevens-Johnson Syndrome
- Pancreatitis

7 DRUG INTERACTIONS

7.1 Concomitant Drugs for Treatment of Adult Indications

In RA patients, population pharmacokinetic analyses did not detect any effect of methotrexate (MTX), non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance. Concomitant administration of a single intravenous dose of 10 mg/kg ACTEMRA with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure. ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists *[see Dosage and Administration (2.1)]*.

In GCA patients, no effect of concomitant corticosteroid on tocilizumab exposure was observed.

7.2 Interactions with CYP450 Substrates

Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effect on CYP2C8 or transporters is unknown. In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and

simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of ACTEMRA, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of ACTEMRA, in patients being treated with these types of medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) and the individual dose of the medicinal product adjusted as needed. Exercise caution when coadministering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy *[see Clinical Pharmacology (12.3)]*.

7.3 Live Vaccines

Avoid use of live vaccines concurrently with ACTEMRA *[see Warnings and Precautions (5.8)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ACTEMRA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Risk Summary

The limited available data with ACTEMRA in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. Monoclonal antibodies, such as tocilizumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the *in utero* exposed infant *[see Clinical Considerations]*. In animal reproduction studies, intravenous administration of tocilizumab to Cynomolgus monkeys during organogenesis caused abortion/embryo-fetal death at doses 1.25 times and higher than the maximum recommended human dose by the intravenous route of 8 mg per kg every 2 to 4 weeks. The literature in animals suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition *[see Data]*. Based on the animal data, there may be a potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to ACTEMRA *in utero [see Warnings and Precautions (5.8)]*

Data

Animal Data

An embryo-fetal developmental toxicity study was performed in which pregnant Cynomolgus monkeys were treated intravenously with tocilizumab at daily doses of 2, 10, or 50 mg/ kg during organogenesis from gestation day (GD) 20-50. Although there was no evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at doses 1.25 times and higher the MRHD by the intravenous route at maternal intravenous doses of 10 and 50 mg/ kg. Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg intravenously with treatment every three days from implantation

(GD 6) until post-partum day 21 (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

Parturition is associated with significant increases of IL-6 in the cervix and myometrium. The literature suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition. For mice deficient in IL-6 ($Il6^{-/-}$ null mice), parturition was delayed relative to wild-type ($Il6^{+/+}$) mice. Administration of recombinant IL-6 to $Il6^{-/-}$ null mice restored the normal timing of delivery.

8.2 Lactation

Risk Summary

No information is available on the presence of tocilizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Maternal immunoglobulin G (IgG) is present in human milk. If tocilizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to tocilizumab are unknown. The lack of clinical data during lactation precludes clear determination of the risk of ACTEMRA to an infant during lactation; therefore the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ACTEMRA and the potential adverse effects on the breastfed child from tocilizumab or from the underlying maternal condition.

8.4 Pediatric Use

ACTEMRA by intravenous use is indicated for the treatment of pediatric patients with:

- Active systemic juvenile idiopathic arthritis in patients 2 years of age and older
- Active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older
- Severe or life-threatening CAR T cell-induced cytokine release syndrome (CRS) in patients 2 years of age and older.

ACTEMRA by subcutaneous use is indicated for the treatment of pediatric patients with:

- Active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older
- Active systemic juvenile idiopathic arthritis in patients 2 years of age and older

The safety and effectiveness of ACTEMRA in pediatric patients with conditions other than PJIA, SJIA or CRS have not been established. The safety and effectiveness in pediatric patients below the age of 2 have not been established in PJIA, SJIA, or CRS. The ability of pediatric patients to self-inject with the autoinjector has not been tested.

Systemic Juvenile Idiopathic Arthritis – Intravenous Use

A multi-center, open-label, single arm study to evaluate the PK, safety and exploratory PD and efficacy of ACTEMRA over 12-weeks in SJIA patients (N=11) under 2 years of age was conducted. Patients received intravenous ACTEMRA 12 mg/kg every two weeks. Concurrent use of stable background treatment with corticosteroids, MTX, and/or non-steroidal anti-inflammatory drugs was permitted. Patients who completed the 12-week period could continue to the optional extension period (a total of 52-weeks or until the age of 2 years, whichever was longer).

The primary PK endpoints (C_{max}, C_{min} and AUC_{2weeks}) of ACTEMRA at steady-state in this study were within the ranges of these parameters observed in patients with SJIA aged 2 to 17 years.

The safety and immunogenicity of ACTEMRA for patients with SJIA under 2 years of age was assessed descriptively. SAEs, AEs leading to discontinuation, and infectious AEs were reported by 27.3%, 36.4%, and

81.8% of patients. Six patients (54.5%) experienced hypersensitivity reactions, defined as all adverse events occurring during or within 24 hours after an infusion considered related to ACTEMRA. Three of these patients experienced serious hypersensitivity reactions and were withdrawn from the study. Three patients with hypersensitivity reactions (two with serious hypersensitivity reactions) developed treatment induced anti-tocilizumab antibodies after the event. There were no cases of MAS based on the protocol-specified criteria, but 2 cases of suspected MAS based on Ravelli criteria[1].

Cytokine Release Syndrome – Intravenous Use

In the retrospective analysis of pooled outcome data for patients treated with ACTEMRA for CAR T cell-induced CRS, 25 patients were children (2 years up to 12 years of age), and 17 patients were adolescents (12 years up to 18 years of age). There were no differences between the pediatric patients and the adults for safety or efficacy.

8.5 Geriatric Use

Of the 2644 patients who received ACTEMRA in Studies I to V *[see Clinical Studies (14)]*, a total of 435 rheumatoid arthritis patients were 65 years of age and older, including 50 patients 75 years and older. Of the 1069 patients who received ACTEMRA-SC in studies SC-I and SC-II there were 295 patients 65 years of age and older, including 41 patients 75 years and older. The frequency of serious infection among ACTEMRA treated subjects 65 years of age and older was higher than those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Clinical studies that included ACTEMRA for CRS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

The safety and efficacy of ACTEMRA have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology *[see Warnings and Precautions (5.7)]*.

8.7 Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. ACTEMRA has not been studied in patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

No studies on the potential for ACTEMRA to cause dependence have been performed. However, there is no evidence from the available data that ACTEMRA treatment results in dependence.

10 OVERDOSAGE

There are limited data available on overdoses with ACTEMRA. One case of accidental overdose was reported with intravenous ACTEMRA in which a patient with multiple myeloma received a dose of 40 mg per kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg per kg, although all 5 patients at the highest dose of 28 mg per kg developed dose-limiting neutropenia.

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

[1] Ravelli A, Minoia F, Davì S on behalf of the Paediatric Rheumatology International Trials Organisation, the Childhood Arthritis and Rheumatology Research Alliance, the Pediatric Rheumatology Collaborative Study Group, and the Histiocyte Society, *et al.* 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis. Annals of the Rheumatic Diseases 2016;75:481-489.

11 DESCRIPTION

Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H_2L_2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. ACTEMRA has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells.

Intravenous Infusion

ACTEMRA (tocilizumab) injection is a sterile, clear, colorless to pale yellow, preservative-free solution for further dilution prior to intravenous infusion with a pH of approximately 6.5. Each single-dose vial, formulated with a disodium phosphate dodecahydrate/sodium dihydrogen phosphate dehydrate buffered solution, is available at a concentration of 20 mg/mL containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of ACTEMRA. Each mL of solution contains polysorbate 80 (0.5 mg), sucrose (50 mg), and Water for Injection, USP.

Subcutaneous Injection

ACTEMRA (tocilizumab) injection is a sterile, clear, colorless to slightly yellowish, preservative-free, histidine buffered solution for subcutaneous use with a pH of approximately 6.0.

It is supplied in a ready-to-use, single-dose 0.9 mL prefilled syringe (PFS) with a needle safety device or a ready-to-use, single-dose 0.9 mL autoinjector that delivers 162 mg tocilizumab, L-arginine (0.132 mg), L-arginine hydrochloride (18.8 mg), L-histidine (1.4 mg), L-histidine hydrochloride monohydrate (1.9 mg), L-methionine (4.03 mg), polysorbate 80 (0.18 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.

12.2 Pharmacodynamics

In clinical studies in RA patients with the 4 mg per kg and 8 mg per kg intravenous doses or the 162 mg weekly and every other weekly subcutaneous doses of ACTEMRA, decreases in levels of C-reactive protein (CRP) to within normal ranges were seen as early as week 2. Changes in pharmacodynamic parameters were observed (i.e., decreases in rheumatoid factor, erythrocyte sedimentation rate (ESR), serum amyloid A and increases in hemoglobin) with doses, however the greatest improvements were observed with 8 mg per kg ACTEMRA. Pharmacodynamic changes were also observed to occur after ACTEMRA administration in GCA, PJIA, and SJIA patients (decreases in CRP, ESR, and increases in hemoglobin). The relationship between these pharmacodynamic findings and clinical efficacy is not known.

In healthy subjects administered ACTEMRA in doses from 2 to 28 mg per kg intravenously and 81 to 162 mg subcutaneously, absolute neutrophil counts decreased to the nadir 3 to 5 days following ACTEMRA administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Rheumatoid arthritis and GCA patients demonstrated a similar pattern of absolute neutrophil counts following ACTEMRA administration *[see Warnings and Precautions (5.3)]*.

12.3 Pharmacokinetics

Rheumatoid Arthritis—Intravenous Administration

The pharmacokinetics characterized in healthy subjects and RA patients suggested that PK is similar between the two populations. The clearance (CL) of tocilizumab decreased with increased doses. At the 10 mg per kg single dose in RA patients, mean CL was 0.29 ± 0.10 mL per hr per kg and mean apparent terminal $t_{1/2}$ was 151 ± 59 hours (6.3 days).

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis of 1793 rheumatoid arthritis patients treated with ACTEMRA 4 and 8 mg per kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in area under the curve (AUC) and trough concentration (C_{min}) was observed for doses of 4 and 8 mg per kg every 4 weeks. Maximum concentration (C_{max}) increased dose-proportionally. At steady-state, estimated AUC and C_{min} were 2.7 and 6.5-fold higher at 8 mg per kg as compared to 4 mg per kg, respectively. In a long-term study with dosing for 104 weeks, observed C_{min} was sustained over time.

For doses of ACTEMRA 4 mg per kg given every 4 weeks, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 13000 ± 5800 mcg•h per mL, 1.49 ± 2.13 mcg per mL, and 88.3 ± 41.4 mcg per mL, respectively. The accumulation ratios for AUC and C_{max} were 1.11 and 1.02, respectively. The accumulation ratio was higher for C_{min} (1.96). Steady-state was reached following the first administration for C_{max} and AUC, respectively, and after 16 weeks C_{min}. For doses of ACTEMRA 8 mg per kg given every 4 weeks, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 35000 ± 15500 mcg•h per mL, 9.74 ± 10.5 mcg per mL, and 183 ± 85.6 mcg per mL, respectively. The accumulation ratios for AUC and C_{max} were 1.22 and 1.06, respectively. The accumulation ratio was higher for C_{min} (2.35). Steady-state was reached following the first administration and after 8 and 20 weeks for C_{max}, AUC, and C_{min}, respectively. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight at or above 100 kg, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 55500 ± 14100 mcg•h per mL, 19.0 ± 12.0 mcg per mL, and 269 ± 57 mcg per mL, respectively, which are higher than mean exposure values for the patient population. Therefore, ACTEMRA doses exceeding 800 mg per infusion are not recommended *[see Dosage and Administration (2.1)]*.

Rheumatoid Arthritis—Subcutaneous Administration

The pharmacokinetics of tocilizumab was characterized using a population pharmacokinetic analysis using a database composed of 1759 rheumatoid arthritis patients treated with 162 mg subcutaneously every week, 162 mg subcutaneously every other week, and 8 mg/kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. For the 162 mg every week dose, the estimated mean (±SD) steady-state AUC_{1week}, C_{min} and C_{max} of tocilizumab were 8200 ± 3600 mcg•h/mL, 44.6 ± 20.6 mcg/mL, and 50.9 ± 21.8 mcg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 6.83, 6.37, and 5.47, respectively. Steady state was reached after 12 weeks for AUC, C_{min}, and C_{max}.

For the 162 mg every other week dose, the estimated mean (±SD) steady-state AUC_{2week}, C_{min}, and C_{max} of tocilizumab were 3200 ± 2700 mcg•h/mL, 5.6 ± 7.0 mcg/mL, and 12.3 ± 8.7 mcg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 2.67, 5.6, and 2.12, respectively. Steady state was reached after 12 weeks for AUC and C_{min}, and after 10 weeks for C_{max}.

Giant Cell Arteritis – Subcutaneous Administration

The pharmacokinetics of tocilizumab in GCA patients was determined using a population pharmacokinetic analysis on a dataset composed of 149 GCA patients treated with 162 mg subcutaneously every week or with 162 mg subcutaneously every other week.

For the 162 mg every week dose, the estimated mean (±SD) steady-state C_{avg}, C_{min} and C_{max} of tocilizumab were 71.3 ± 30.1 mcg/mL, 68.1± 29.5 mcg/mL, and 73 ± 30.4 mcg/mL, respectively. The accumulation ratios for C_{avg} or AUC_{tau}, C_{min}, and C_{max} were 10.9, 9.6, and 8.9, respectively. Steady state was reached after 17 weeks.

For the 162 mg every other week dose, the estimated mean (±SD) steady-state C_{avg}, C_{min}, and C_{max} of tocilizumab were 16.2 ± 11.8 mcg/mL, 11.1 ± 10.3 mcg/mL, and 19.3 ± 12.8 mcg/mL, respectively. The accumulation ratios for C_{avg} or AUC_{tau}, C_{min}, and C_{max} were 2.8, 5.6, and 2.3 respectively. Steady-state was reached after 14 weeks.

Polyarticular Juvenile Idiopathic Arthritis—Intravenous and Subcutaneous Administration

The pharmacokinetics of tocilizumab (TCZ) in PJIA patients was characterized by a population pharmacokinetic analysis which included 188 patients who were treated with TCZ IV or 52 patients treated with TCZ SC.

For doses of 8 mg/kg tocilizumab (patients with a body weight at or above 30 kg) given every 4 weeks intravenously, the estimated mean (± SD) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 183 ± 42.3 mcg/mL, 6.55 ± 7.93 mcg/mL and 42.2 ± 13.4 mcg/mL, respectively. For doses of 10 mg/kg tocilizumab (patients with a body weight less than 30 kg) given every 4 weeks intravenously, the estimated mean (± SD) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 168 ± 24.8 mcg/mL, 1.47 ± 2.44 mcg/mL and 31.6 ± 7.84 mcg/mL, respectively.

The accumulation ratios were 1.05 and 1.16 for AUC_{4weeks}, and 1.43 and 2.22 for C_{trough} for 10 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. No accumulation for C_{max} was observed. Following 8 mg/kg every 4 weeks TCZ IV steady state peak and trough concentrations in PJIA pediatric patients (aged 2 to 17 years old) are comparable to those in adult RA patients following 8 mg/kg IV every 4 weeks. Following 8mg/kg every 4 weeks, the average concentration (C_{mean}) of TCZ in PJIA patients after TCZ IV is slightly lower than in adult RA patients.

For doses of 162 mg tocilizumab (patients with a body weight at or above 30 kg) given every 2 weeks subcutaneously, the estimated mean (± SD) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 29.4 ± 13.5 mcg/mL, 11.8 ± 7.08 mcg/mL and 21.7 ± 10.4 mcg/mL, respectively. For doses of 162 mg tocilizumab (patients with a body weight less than 30 kg) given every 3 weeks subcutaneously, the estimated mean (± SD) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 75.5 ± 24.1 mcg/mL, 18.4 ± 12.9 mcg/mL and 45.5 ± 19.8 mcg/mL, respectively.

The accumulation ratios were 1.46 and 2.04 for AUC_{4weeks}, 2.08 and 3.58 for C_{trough}, and 1.32 and 1.72 for C_{max}, for 162 mg given every 3 weeks (BW less than 30 kg) and 162 mg given every 2 weeks (BW at or above 30 kg) subcutaneous doses, respectively. Following subcutaneous dosing, steady state C_{trough} was comparable for patients in the two body weight groups, while steady-state C_{max} and C_{mean} were higher for patients in the less than 30 kg group compared to the group at or above 30 kg. All patients treated with TCZ SC had steady-state C_{trough} at or higher than that achieved with TCZ IV across the spectrum of body weights. The average and trough concentrations in patients after subcutaneous dosing were within the range of those achieved in adult patients with RA following the subcutaneous administration of the recommended regimens.

Systemic Juvenile Idiopathic Arthritis—Intravenous and Subcutaneous Administration

The pharmacokinetics of tocilizumab (TCZ) in SJIA patients was characterized by a population pharmacokinetic analysis which included 89 patients who were treated with TCZ IV or 51 patients treated with TCZ SC.

For doses of 8 mg/kg tocilizumab (patients with a body weight at or above 30 kg) given every 2 weeks intravenously, the estimated mean (± SD) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 256 ± 60.8 mcg/mL, 69.7± 29.1 mcg/mL and 119± 36.0 mcg/mL, respectively. For doses of 12 mg/kg tocilizumab (patients with a body weight less than 30 kg) given every 2 weeks intravenously, the estimated mean (± SD) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 274 ± 63.8 mcg/mL, 68.4 ± 30.0 mcg/mL and 123 ± 36.0 mcg/mL, respectively.

The accumulation ratios were 1.95 and 2.01 for AUC_{4weeks}, and 3.41 and 3.20 for C_{trough} for 12 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. Accumulation data for C_{max} were 1.37 and 1.42 for 12 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. Following every other week dosing with tocilizumab IV, steady state was reached by 8 weeks for

both body weight groups. Mean estimated tocilizumab exposure parameters were similar between the two dose groups defined by body weight.

For doses of 162 mg tocilizumab (patients with a body weight at or above 30 kg) given every week subcutaneously, the estimated mean (± SD) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 99.8 ± 46.2 mcg/mL, 79.2 ± 35.6 mcg/mL and 91.3 ± 40.4 mcg/mL, respectively. For doses of 162 mg tocilizumab (patients with a body weight less than 30 kg) given every 2 weeks subcutaneously, the estimated mean (± SD) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 134 ± 58.6 mcg/mL, 65.9 ± 31.3 mcg/mL and 101 ± 43.2 mcg/mL, respectively.

The accumulation ratios were 2.27 and 4.28 for AUC_{4weeks}, 3.21 and 4.39 for C_{trough}, and 1.88 and 3.66 for C_{max}, for 162 mg given every 2 weeks (BW less than 30 kg) and 162 mg given every week (BW at or above 30 kg) subcutaneous doses, respectively. Following subcutaneous dosing, steady state was reached by 12 weeks for both body weight groups. All patients treated with tocilizumab SC had steady-state C_{max} lower than that achieved with tocilizumab IV across the spectrum of body weights. Trough and mean concentrations in patients after SC dosing were similar to those achieved with tocilizumab IV across body weights.

Absorption

Following subcutaneous dosing in RA and GCA patients, the absorption half-life was around 4 days. The bioavailability for the subcutaneous formulation was 80%.

Following subcutaneous dosing in PJIA patients, the absorption half-life was around 2 days, and the bioavailability for the subcutaneous formulation in PJIA patients was 96%.

Following subcutaneous dosing in SJIA patients, the absorption half-life was around 2 days, and the bioavailability for the SC formulation in SJIA patients was 95%.

In RA patients the median values of T_{max} were 2.8 days after the tocilizumab every week dose and 4.7 days after the tocilizumab every other week dose.

In GCA patients, the median values of T_{max} were 3 days after the tocilizumab every week dose and 4.5 days after the tocilizumab every other week dose.

Distribution

Following intravenous dosing, tocilizumab undergoes biphasic elimination from the circulation. In rheumatoid arthritis patients the central volume of distribution was 3.5 L and the peripheral volume of distribution was 2.9 L, resulting in a volume of distribution at steady state of 6.4 L.

In GCA patients, the central volume of distribution was 4.09 L, the peripheral volume of distribution was 3.37 L resulting in a volume of distribution at steady state of 7.46 L.

In pediatric patients with PJIA, the central volume of distribution was 1.98 L, the peripheral volume of distribution was 2.1 L, resulting in a volume of distribution at steady state of 4.08 L.

In pediatric patients with SJIA, the central volume of distribution was 1.87 L, the peripheral volume of distribution was 2.14 L resulting in a volume of distribution at steady state of 4.01 L.

Elimination

ACTEMRA is eliminated by a combination of linear clearance and nonlinear elimination. The concentration-dependent nonlinear elimination plays a major role at low tocilizumab concentrations. Once the nonlinear pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance. The saturation of the nonlinear elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of ACTEMRA do not change with time.

Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.

The linear clearance in the population pharmacokinetic analysis was estimated to be 12.5 mL per h in RA patients, 6.7 mL per h in GCA patients, 5.8 mL per h in pediatric patients with PJIA, and 5.7 mL per h in pediatric patients with SJIA.

Due to the dependence of total clearance on ACTEMRA serum concentrations, the half-life of ACTEMRA is also concentration-dependent and varies depending on the serum concentration level.

For intravenous administration in RA patients, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg per kg and up to 13 days for 8 mg per kg every 4 weeks in patients with RA at steady-state. For subcutaneous administration in RA patients, the concentration-dependent apparent $t_{1/2}$ is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state.

In GCA patients at steady state, the effective $t_{1/2}$ of tocilizumab varied between 18.3 and 18.9 days for 162 mg subcutaneously every week dosing regimen and between 4.2 and 7.9 days for 162 mg subcutaneously every other week dosing regimen.

The $t_{1/2}$ of tocilizumab in children with PJIA is up to 17 days for the two body weight categories (8 mg/kg for body weight at or above 30 kg or 10 mg/kg for body weight below 30 kg) during a dosing interval at steady state. For subcutaneous administration, the $t_{1/2}$ of tocilizumab in PJIA patients is up to 10 days for the two body weight categories (every other week regimen for body weight at or above 30 kg or every 3 week regimen for body weight less than 30 kg) during a dosing interval at steady state.

The $t_{1/2}$ of tocilizumab intravenous in pediatric patients with SJIA is up to 16 days for the two body weight categories (8 mg/kg for body weight at or above 30 kg and 12 mg/kg for body weight below 30 kg every other week) during a dosing interval at steady-state. Following subcutaneous administration, the effective $t_{1/2}$ of tocilizumab subcutaneous in SJIA patients is up to 14 days for both the body weight categories (162 mg every week for body weight at or above 30 kg and 162 mg every two weeks for body weight below 30 kg) during a dosing interval at steady state.

Pharmacokinetics in Special Populations

Population pharmacokinetic analyses in adult rheumatoid arthritis patients and GCA patients showed that age, gender and race did not affect the pharmacokinetics of tocilizumab. Linear clearance was found to increase with body size. In RA patients, the body weight-based dose (8 mg per kg) resulted in approximately 86% higher exposure in patients who are greater than 100 kg in comparison to patients who are less than 60 kg. There was an inverse relationship between tocilizumab exposure and body weight for flat dose subcutaneous regimens.

In GCA patients, higher exposure was observed in patients with lower body weight. For the 162 mg every week dosing regimen, the steady-state Cavg was 51% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. For the 162 mg every other week regimen, the steady-state Cavg was 129% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. There is limited data for patients above 100 kg (n=7).

Hepatic Impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab was conducted.

Renal Impairment

No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab was conducted.

Most of the RA and GCA patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance less than 80 mL per min and at or above 50 mL per min based on Cockcroft-Gault formula) did not impact the pharmacokinetics of tocilizumab.

Approximately one-third of the patients in the GCA clinical trial had moderate renal impairment at baseline (estimated creatinine clearance of 30-59 mL/min). No impact on tocilizumab exposure was noted in these patients.

No dose adjustment is required in patients with mild or moderate renal impairment.

Drug Interactions

In vitro data suggested that IL-6 reduced mRNA expression for several CYP450 isoenzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and this reduced expression was reversed by co-incubation with tocilizumab at clinically relevant concentrations. Accordingly, inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. Its effect on CYP2C8 or transporters (e.g., P-gp) is unknown. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation of ACTEMRA, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Caution should be exercised when ACTEMRA is coadministered with drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives (CYP3A4 substrates) *[see Drug Interactions (7.2)]*.

Simvastatin

Simvastatin is a CYP3A4 and OATP1B1 substrate. In 12 RA patients not treated with ACTEMRA, receiving 40 mg simvastatin, exposures of simvastatin and its metabolite, simvastatin acid, was 4- to 10-fold and 2-fold higher, respectively, than the exposures observed in healthy subjects. One week following administration of a single infusion of ACTEMRA (10 mg per kg), exposure of simvastatin and simvastatin acid decreased by 57% and 39%, respectively, to exposures that were similar or slightly higher than those observed in healthy subjects. Exposures of simvastatin and simvastatin acid increased upon withdrawal of ACTEMRA in RA patients. Selection of a particular dose of simvastatin in RA patients should take into account the potentially lower exposures that may result after initiation of ACTEMRA (due to normalization of CYP3A4) or higher exposures after discontinuation of ACTEMRA.

Omeprazole

Omeprazole is a CYP2C19 and CYP3A4 substrate. In RA patients receiving 10 mg omeprazole, exposure to omeprazole was approximately 2 fold higher than that observed in healthy subjects. In RA patients receiving 10 mg omeprazole, before and one week after ACTEMRA infusion (8 mg per kg), the omeprazole AUC_{inf} decreased by 12% for poor (N=5) and intermediate metabolizers (N=5) and by 28% for extensive metabolizers (N=8) and were slightly higher than those observed in healthy subjects.

Dextromethorphan

Dextromethorphan is a CYP2D6 and CYP3A4 substrate. In 13 RA patients receiving 30 mg dextromethorphan, exposure to dextromethorphan was comparable to that in healthy subjects. However, exposure to its metabolite, dextrorphan (a CYP3A4 substrate), was a fraction of that observed in healthy subjects. One week following administration of a single infusion of ACTEMRA (8 mg per kg), dextromethorphan exposure was decreased by approximately 5%. However, a larger decrease (29%) in dextrorphan levels was noted after ACTEMRA infusion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab. Literature indicates that the IL-6 pathway can mediate anti-tumor responses by promoting increased immune cell surveillance of the tumor microenvironment. However, available published evidence also supports that IL-6 signaling through the IL-6 receptor may be involved in pathways that lead to tumorigenesis. The malignancy risk in humans from an antibody that disrupts signaling through the IL-6 receptor, such as tocilizumab, is presently unknown.

Fertility and reproductive performance were unaffected in male and female mice that received a murine analogue of tocilizumab administered by the intravenous route at a dose of 50 mg/kg every three days.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis—Intravenous Administration

The efficacy and safety of intravenously administered ACTEMRA was assessed in five randomized, double-blind, multicenter studies in patients greater than 18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline. ACTEMRA was given intravenously every 4 weeks as monotherapy (Study I), in combination with methotrexate (MTX) (Studies II and III) or other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV) in patients with an inadequate response to those drugs, or in combination with MTX in patients with an inadequate response to TNF antagonists (Study V).

Study I evaluated patients with moderate to severe active rheumatoid arthritis who had not been treated with MTX within 24 weeks prior to randomization, or who had not discontinued previous methotrexate treatment as a result of clinically important toxic effects or lack of response. In this study, 67% of patients were MTX-naïve, and over 40% of patients had rheumatoid arthritis less than 2 years. Patients received ACTEMRA 8 mg per kg monotherapy or MTX alone (dose titrated over 8 weeks from 7.5 mg to a maximum of 20 mg weekly). The primary endpoint was the proportion of ACTEMRA patients who achieved an ACR 20 response at Week 24.

Study II was a 104-week study with an ongoing optional 156-week extension phase that evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). Upon completion of 52-weeks, patients received open-label treatment with ACTEMRA 8 mg per kg through 104 weeks or they had the option to continue their double-blind treatment if they maintained a greater than 70% improvement in swollen/tender joint count. Two pre-specified interim analyses at week 24 and week 52 were conducted. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At weeks 52 and 104, the primary endpoints were change from baseline in modified total Sharp-Genant score and the area under the curve (AUC) of the change from baseline in HAQ-DI score.

Study III evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Study IV evaluated patients who had an inadequate response to their existing therapy, including one or more DMARDs. Patients received ACTEMRA 8 mg per kg or placebo every four weeks, in combination with the stable DMARDs. The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Study V evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomization. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Clinical Response

The percentages of intravenous ACTEMRA-treated patients achieving ACR 20, 50 and 70 responses are shown in **Table 3.** In all intravenous studies, patients treated with 8 mg per kg ACTEMRA had higher ACR 20, ACR 50, and ACR 70 response rates versus MTX- or placebo-treated patients at week 24.

During the 24 week controlled portions of Studies I to V, patients treated with ACTEMRA at a dose of 4 mg per kg in patients with inadequate response to DMARDs or TNF antagonist therapy had lower response rates compared to patients treated with ACTEMRA 8 mg per kg.

Table 3　Clinical Response at Weeks 24 and 52 in Active and Placebo Controlled Trials of Intravenous ACTEMRA (Percent of Patients)

Percent of Patients												
	Study I		Study II			Study III			Study IV		Study V		
Response Rate	MTX N=284	ACTEMRA 8 mg per kg N=286 (95% CI)[a]	Placebo + MTX N=393	ACTEMRA 4 mg per kg + MTX N=399 (95% CI)[a]	ACTEMRA 8 mg per kg + MTX N=398 (95% CI)[a]	Placebo + MTX N=204	ACTEMRA 4 mg per kg + MTX N=213 (95% CI)[a]	ACTEMRA 8 mg per kg + MTX N=205 (95% CI)[a]	Placebo + DMARDs N=413	ACTEMRA 8 mg per kg + DMARDs N=803 (95% CI)[a]	Placebo + MTX N=158	ACTEMRA 4 mg per kg + MTX N=161 (95% CI)[a]	ACTEMRA 8 mg per kg + MTX N=170 (95% CI)[a]
ACR 20													
Week 24	53%	70% (0.11, 0.27)	27%	51% (0.17, 0.29)	56% (0.23, 0.35)	27%	48% (0.15, 0.32)	59% (0.23, 0.41)	24%	61% (0.30, 0.40)	10%	30% (0.15, 0.36)	50% (0.36, 0.56)
Week 52	N/A	N/A	25%	47% (0.15, 0.28)	56% (0.25, 0.38)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ACR 50													
Week 24	34%	44% (0.04, 0.20)	10%	25% (0.09, 0.20)	32% (0.16, 0.28)	11%	32% (0.13, 0.29)	44% (0.25, 0.41)	9%	38% (0.23, 0.33)	4%	17% (0.05, 0.25)	29% (0.21, 0.41)
Week 52	N/A	N/A	10%	29% (0.14, 0.25)	36% (0.21, 0.32)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ACR 70													
Week 24	15%	28% (0.07, 0.22)	2%	11% (0.03, 0.13)	13% (0.05, 0.15)	2%	12% (0.04, 0.18)	22% (0.12, 0.27)	3%	21% (0.13, 0.21)	1%	5% (-0.06, 0.14)	12% (0.03, 0.22)
Week 52	N/A	N/A	4%	16% (0.08, 0.17)	20% (0.12, 0.21)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Major Clinical Responses[b]													
Week 52	N/A	N/A	1%	4% (0.01, 0.06)	7% (0.03, 0.09)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

[a] CI: 95% confidence interval of the weighted difference to placebo adjusted for site (and disease duration for Study I only)
[b] Major clinical response is defined as achieving an ACR 70 response for a continuous 24 week period

In study II, a greater proportion of patients treated with 4 mg per kg and 8 mg per kg ACTEMRA + MTX achieved a low level of disease activity as measured by a DAS 28-ESR less than 2.6 compared with placebo +MTX treated patients at week 52. The proportion of ACTEMRA-treated patients achieving DAS 28-ESR less than 2.6, and the number of residual active joints in these responders in Study II are shown in **Table 4**.

Table 4　Proportion of Patients with DAS28-ESR Less Than 2.6 with Number of Residual Active Joints in Trials of Intravenous ACTEMRA

Study II			
	Placebo + MTX N = 393	**ACTEMRA 4 mg per kg + MTX N = 399**	**ACTEMRA 8 mg per kg + MTX N = 398**
DAS28-ESR less than 2.6			
Proportion of responders at week 52 (n) 95% confidence interval	3% (12)	18% (70) 0.10, 0.19	32% (127) 0.24, 0.34
Of responders, proportion with 0 active joints (n)	33% (4)	27% (19)	21% (27)
Of responders, proportion with 1 active joint (n)	8% (1)	19% (13)	13% (16)
Of responders, proportion with 2 active joints (n)	25% (3)	13% (9)	20% (25)
Of responders, proportion with 3 or more active joints (n)	33% (4)	41% (29)	47% (59)

*n denotes numerator of all the percentage. Denominator is the intent-to-treat population. Not all patients received DAS28 assessments at Week 52.

The results of the components of the ACR response criteria for Studies III and V are shown in **Table 5**. Similar results to Study III were observed in Studies I, II and IV.

Table 5　Components of ACR Response at Week 24 in Trials of Intravenous ACTEMRA

	Study III						**Study V**					
	ACTEMRA 4 mg per kg + MTX N=213		**ACTEMRA 8 mg per kg + MTX N=205**		**Placebo + MTX N=204**		**ACTEMRA 4 mg per kg + MTX N=161**		**ACTEMRA 8 mg per kg + MTX N=170**		**Placebo + MTX N=158**	
Component (mean)	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24**
Number of tender joints (0-68)	33	19 -7.0 (-10.0, -4.1)	32	14.5 -9.6 (-12.6, -6.7)	33	25	31	21 -10.8 (-14.6, -7.1)	32	17 -15.1 (-18.8, -11.4)	30	30
Number of swollen joints (0-66)	20	10 -4.2 (-6.1, -2.3)	19.5	8 -6.2 (-8.1, -4.2)	21	15	19.5	13 -6.2 (-9.0, -3.5)	19	11 -7.2 (-9.9, -4.5)	19	18
Pain[b]	61	33 -11.0 (-17.0, -5.0)	60	30 -15.8 (-21.7, -9.9)	57	43	63.5	43 -12.4 (-22.1, -2.1)	65	33 -23.9 (-33.7, -14.1)	64	48
Patient global assessment[b]	66	34 -10.9 (-17.1, -4.8)	65	31 -14.9 (-20.9, -8.9)	64	45	70	46 -10.0 (-20.3, 0.3)	70	36 -17.4 (-27.8, -7.0)	71	51
Physician global assessment[b]	64	26 -5.6 (-10.5, -0.8)	64	23 -9.0 (-13.8, -4.2)	64	32	66.5	39 -10.5 (-18.6, -2.5)	66	28 -18.2 (-26.3, -10.0)	67.5	43
Disability index (HAQ)[c]	1.64	1.01 -0.18 (-0.34, -0.02)	1.55	0.96 -0.21 (-0.37, -0.05)	1.55	1.21	1.67	1.39 -0.25 (-0.42, -0.09)	1.75	1.34 -0.34 (-0.51, -0.17)	1.70	1.58
CRP (mg per dL)	2.79	1.17 -1.30 (-2.0, -0.59)	2.61	0.25 -2.156 (-2.86, -1.46)	2.36	1.89	3.11	1.77 -1.34 (-2.5, -0.15)	2.80	0.28 -2.52 (-3.72, -1.32)	3.705	3.06

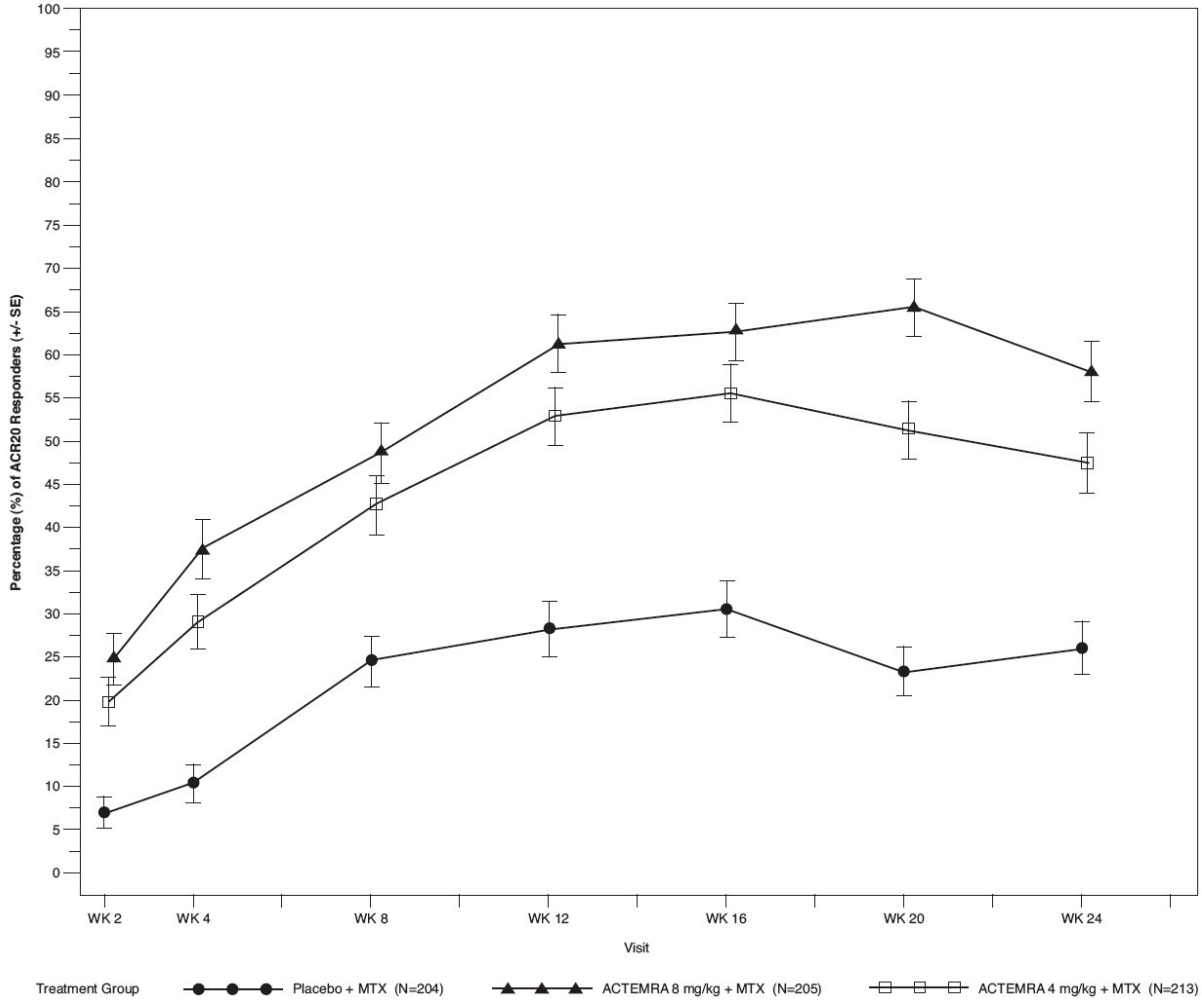
[a] Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference

[b] Visual analog scale: 0 = best, 100 = worst

[c] Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities

The percent of ACR 20 responders by visit for Study III is shown in **Figure 1**. Similar response curves were observed in studies I, II, IV, and V.

Figure 1　Percent of ACR 20 Responders by Visit for Study III (Inadequate Response to MTX)*



*The same patients may not have responded at each timepoint.

Radiographic Response

In Study II, structural joint damage was assessed radiographically and expressed as change in total Sharp-Genant score and its components, the erosion score and joint space narrowing score. Radiographs of hands/wrists and forefeet were obtained at baseline, 24 weeks, 52 weeks, and 104 weeks and scored by readers unaware of treatments group and visit number. The results from baseline to week 52 are shown in **Table 6**. ACTEMRA 4 mg per kg slowed (less than 75% inhibition compared to the control group) and ACTEMRA 8 mg per kg inhibited (at least 75% inhibition compared to the control group) the progression of structural damage compared to placebo plus MTX at week 52.

Table 6　Mean Radiographic Change from Baseline to Week 52 in Study II

	Placebo + MTX N=294	**ACTEMRA 4 mg per kg + MTX N=343**	**ACTEMRA 8 mg per kg + MTX N=353**
Week 52*			
Total Sharp-Genant Score, Mean (SD)	1.17 (3.14)	0.33 (1.30)	0.25 (0.98)
Adjusted Mean difference (95%CI)**		-0.83 (-1.13, -0.52)	-0.90 (-1.20, -0.59)
Erosion Score, Mean (SD)	0.76 (2.14)	0.20 (0.83)	0.15 (0.77)
Adjusted Mean difference (95%CI)**		-0.55 (-0.76, -0.34)	-0.60 (-0.80, -0.39)
Joint Space Narrowing Score, Mean (SD)	0.41 (1.71)	0.13 (0.72)	0.10 (0.49)
Adjusted Mean difference (95%CI)**		-0.28 (-0.44, -0.11)	-0.30 (-0.46, -0.14)

* Week 52 analysis employs linearly extrapolated data for patients after escape, withdrawal, or loss to follow up.
** Difference between the adjusted means (ACTEMRA + MTX - Placebo + MTX)
SD = standard deviation

The mean change from baseline to week 104 in Total Sharp-Genant Score for the ACTEMRA 4 mg per kg groups was 0.47 (SD = 1.47) and for the 8 mg per kg groups was 0.34 (SD = 1.24). By the week 104, most patients in the control (placebo + MTX) group had crossed over to active treatment, and results are therefore not included for comparison. Patients in the active groups may have crossed over to the alternate active dose group, and results are reported per original randomized dose group.

In the placebo group, 66% of patients experienced no radiographic progression (Total Sharp-Genant Score change ≤ 0) at week 52 compared to 78% and 83% in the ACTEMRA 4 mg per kg and 8 mg per kg, respectively. Following 104 weeks of treatment, 75% and 83% of patients initially randomized to ACTEMRA 4 mg per kg and 8 mg per kg, respectively, experienced no progression of structural damage compared to 66% of placebo treated patients.

Health Related Outcomes

In Study II, physical function and disability were assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI). Both dosing groups of ACTEMRA demonstrated a greater improvement compared to the placebo group in the AUC of change from baseline in the HAQ-DI through week 52. The mean change from baseline to week 52 in HAQ-DI was 0.6, 0.5, and 0.4 for ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, and placebo treatment groups, respectively. Sixty-three percent (63%) and sixty percent (60%) of patients in the ACTEMRA 8 mg per kg and ACTEMRA 4 mg per kg treatment groups, respectively, achieved a clinically relevant improvement in HAQ-DI (change from baseline of ≥ 0.3 units) at week 52 compared to 53% in the placebo treatment group.

Other Health-Related Outcomes

General health status was assessed by the Short Form Health Survey (SF-36) in Studies I – V. Patients receiving ACTEMRA demonstrated greater improvement from baseline compared to placebo in the Physical Component Summary (PCS), Mental Component Summary (MCS), and in all 8 domains of the SF-36.

14.2 Rheumatoid Arthritis—Subcutaneous Administration

The efficacy and safety of subcutaneously administered ACTEMRA was assessed in two double-blind, controlled, multicenter studies in patients with active RA. One study (SC-I) was a non-inferiority study that compared the efficacy and safety of ACTEMRA 162 mg administered every week subcutaneously to 8 mg per kg intravenously every four weeks. The second study (SC-II) was a placebo controlled superiority study that evaluated the safety and efficacy of ACTEMRA 162 mg administered every other week subcutaneously to placebo. Both SC-I and SC-II required patients to be >18 years of age with moderate to severe active rheumatoid arthritis diagnosed according to ACR criteria who had at least 4 tender and 4 swollen joints at baseline (SC-I) or at least 8 tender and 6 swollen joints at baseline (SC-II), and an inadequate response to their existing DMARD therapy, where approximately 20% also had a history of inadequate response to at least one TNF inhibitor. All patients in both SC studies received background non-biologic DMARD(s).

In SC-I, 1262 patients were randomized 1:1 to receive ACTEMRA-SC 162 mg every week or intravenous ACTEMRA 8 mg/kg every four weeks in combination with DMARD(s). In SC-II, 656 patients were randomized 2:1 to ACTEMRA-SC 162 mg every other week or placebo, in combination with DMARD(s). The primary endpoint in both studies was the proportion of patients who achieved an ACR20 response at Week 24.

The clinical response to 24 weeks of ACTEMRA-SC therapy is shown in **Table 7**. In SC-I, the primary outcome measure was ACR20 at Week 24. The pre-specified non-inferiority margin was a treatment difference of 12%. The study demonstrated non-inferiority of ACTEMRA with respect to ACR20 at Week 24; ACR50, ACR70, and DAS28 responses are also shown in **Table 7**. In SC-II, a greater portion of patients treated with ACTEMRA 162 mg subcutaneously every other week achieved ACR20, ACR50, and ACR70 responses compared to placebo-treated patients (Table 7). Further, a greater proportion of patients treated with ACTEMRA 162 mg subcutaneously every other week achieved a low level of disease activity as measured by a DAS28-ESR less than 2.6 at Week 24 compared to those treated with placebo (Table 7).

Table 7 Clinical Response at Week 24 in Trials of Subcutaneous ACTEMRA (Percent of Patients)

	SC-I[a]		SC-II[b]	
	TCZ SC 162 mg every week + DMARD N=558	TCZ IV 8mg/kg + DMARD N=537	TCZ SC 162 mg every other week + DMARD N=437	Placebo + DMARD N=219
ACR20				
Week 24	69%	73.4%	61%	32%
Weighted difference (95% CI)	-4% (-9.2, 1.2)		30% (22.0, 37.0)	
ACR50				
Week 24	47%	49%	40%	12%
Weighted difference (95% CI)	-2% (-7.5, 4.0)		28% (21.5, 34.4)	
ACR70				
Week 24	24%	28%	20%	5%
Weighted difference (95% CI)	-4% (-9.0, 1.3)		15% (9.8, 19.9)	
Change in DAS28 [Adjusted mean]				
Week 24	-3.5	-3.5	-3.1	-1.7
Adjusted mean difference (95% CI)	0 (-0.2, 0.1)		-1.4 (-1.7; -1.1)	
DAS28 < 2.6				
Week 24	38.4%	36.9%	32.0%	4.0%
Weighted difference (95% CI)	0.9 (-5.0, 6.8)		28.6 (22.0, 35.2)	

TCZ = tocilizumab

[a] Per Protocol Population

[b] Intent To Treat Population

The results of the components of the ACR response criteria and the percent of ACR20 responders by visit for ACTEMRA-SC in Studies SC-I and SC-II were consistent with those observed for ACTEMRA-IV.

Radiographic Response

In study SC-II, the progression of structural joint damage was assessed radiographically and expressed as a change from baseline in the van der Heijde modified total Sharp score (mTSS). At week 24, significantly less radiographic progression was observed in patients receiving ACTEMRA-SC every other week plus DMARD(s) compared to placebo plus DMARD(s); mean change from baseline in mTSS of 0.62 vs. 1.23, respectively, with an adjusted mean difference of -0.60 (-1.1, -0.1). These results are consistent with those observed in patients treated with intravenous ACTEMRA.

Health Related Outcomes

In studies SC-I and SC-II, the mean decrease from baseline to week 24 in HAQ-DI was 0.6, 0.6, 0.4 and 0.3, and the proportion of patients who achieved a clinically relevant improvement in HAQ-DI (change from baseline of ≥ 0.3 units) was 65%, 67%, 58% and 47%, for the subcutaneous every week, intravenous 8 mg/kg, subcutaneous every other week, and placebo treatment groups, respectively.

Other Health-Related Outcomes

General health status was assessed by the SF-36 in Studies SC-I and SC-II. In Study SC-II, patients receiving ACTEMRA every other week demonstrated greater improvement from baseline compared to placebo in the PCS, MCS, and in all 8 domains of the SF-36. In Study SC-I, improvements in these scores were similar between ACTEMRA-SC every week and ACTEMRA-IV 8 mg/kg.

14.3 Giant Cell Arteritis—Subcutaneous Administration

The efficacy and safety of subcutaneously administered ACTEMRA was assessed in a single, randomized, double-blind, multicenter study in patients with active GCA. In Study WA28119, 251 screened patients with new-onset or relapsing GCA were randomized to one of four treatment arms. Two subcutaneous doses of ACTEMRA (162 mg every week and 162 mg every other week) were compared to two different placebo control groups (pre-specified prednisone-taper regimen over 26 weeks and 52 weeks) randomized 2:1:1:1. The study consisted of a 52-week blinded period, followed by a 104-week open-label extension.

All patients received background glucocorticoid (prednisone) therapy. Each of the ACTEMRA-treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen with the aim to reach 0 mg by 26 weeks, while the second placebo-treated group followed a pre-specified prednisone-taper regimen with the aim to reach 0 mg by 52 weeks designed to be more in keeping with standard practice.

The primary efficacy endpoint was the proportion of patients achieving sustained remission from Week 12 through Week 52. Sustained remission was defined by a patient attaining a sustained (1) absence of GCA signs and symptoms from Week 12 through Week 52, (2) normalization of erythrocyte sedimentation rate (ESR) (to < 30 mm/hr without an elevation to ≥ 30 mm/hr attributable to GCA) from Week 12 through Week 52, (3) normalization of C-reactive protein (CRP) (to < 1 mg/dL, with an absence of successive elevations to ≥ 1mg/dL) from Week 12 through Week 52, and (4) successful adherence to the prednisone taper defined by not more than 100 mg of excess prednisone from Week 12 through Week 52. ACTEMRA 162 mg weekly and 162 mg every other week + 26 weeks prednisone taper both showed superiority in achieving sustained remission from Week 12 through Week 52 compared with placebo + 26 weeks prednisone taper (Table 8). Both ACTEMRA treatment arms also showed superiority compared to the placebo + 52 weeks prednisone taper (Table 8).

Table 8　Efficacy Results from Study WA28119

	PBO + 26 weeks prednisone taper N=50	PBO + 52 weeks prednisone taper N=51	TCZ 162mg SC QW + 26 weeks prednisone taper N=100	TCZ 162 mg SC Q2W + 26 weeks prednisone taper N=49
Sustained remission[a]				
Responders, n (%)	7 (14.0%)	9 (17.6%)	56 (56.0%)	26 (53.1%)
Unadjusted difference in proportions vs PBO + 26 weeks taper (99.5% CI)	N/A	N/A	42.0% (18.0, 66.0)	39.1% (12.5 , 65.7)
Unadjusted difference in proportions vs PBO + 52 weeks taper (99.5% CI)	N/A	N/A	38.4% (14.4, 62.3)	35.4% (8.6, 62.2)
Components of Sustained Remission				
Sustained absence of GCA signs and symptoms[b], n (%)	20 (40.0%)	23 (45.1%)	69 (69.0%)	28 (57.1%)
Sustained ESR<30 mm/hr[c], n (%)	20 (40.0%)	22 (43.1%)	83 (83.0%)	37 (75.5%)
Sustained CRP normalization[d], n (%)	17 (34.0%)	13 (25.5%)	72 (72.0%)	34 (69.4%)
Successful prednisone tapering[e], n (%)	10 (20.0%)	20 (39.2%)	60 (60.0%)	28 (57.1%)

[a] Sustained remission was achieved by a patient meeting all of the following components: absence of GCA signs and symptoms[b], normalization of ESR[c], normalization of CRP[d] and adherence to the prednisone taper regimen[e].
[b] Patients who did not have any signs or symptoms of GCA recorded from Week 12 up to Week 52.
[c] Patients who did not have an elevated ESR ≥30 mm/hr which was classified as attributed to GCA from Week 12 up to Week 52.
[d] Patients who did not have two or more consecutive CRP records of ≥ 1mg/dL from Week 12 up to Week 52.
[e] Patients who did not enter escape therapy and received ≤ 100mg of additional concomitant prednisone from Week 12 up to Week 52.
Patients not completing the study to week 52 were classified as non-responders in the primary and key secondary analysis: PBO+26: 6 (12.0%), PBO+52: 5 (9.8%), TCZ QW: 15 (15.0%), TCZ Q2W: 9 (18.4%).
CRP = C-reactive protein
ESR = erythrocyte sedimentation rate
PBO = placebo
Q2W = every other week dose
QW = every week dose
TCZ = tocilizumab

The estimated annual cumulative prednisone dose was lower in the two ACTEMRA dose groups (medians of 1887 mg and 2207 mg on ACTEMRA QW and Q2W, respectively) relative to the placebo arms (medians of 3804 mg and 3902 mg on placebo + 26 weeks prednisone and placebo + 52 weeks prednisone taper, respectively).

14.4 Polyarticular Juvenile Idiopathic Arthritis—Intravenous Administration

The efficacy of ACTEMRA was assessed in a three-part study including an open-label extension in children 2 to 17 years of age with active polyarticular juvenile idiopathic arthritis (PJIA), who had an inadequate response to methotrexate or inability to tolerate methotrexate. Patients had at least 6 months of active disease (mean disease duration of 4.2 ± 3.7 years), with at least five joints with active arthritis (swollen or limitation of movement accompanied by pain and/or tenderness) and/or at least 3 active joints having limitation of motion (mean, 20 ± 14 active joints). The patients treated had subtypes of JIA that at disease onset included Rheumatoid Factor Positive or Negative Polyarticular JIA, or Extended Oligoarticular JIA. Treatment with a stable dose of methotrexate was permitted but was not required during the study. Concurrent use of disease modifying antirheumatic drugs (DMARDs), other than methotrexate, or other biologics (e.g., TNF antagonists or T cell costimulation modulator) were not permitted in the study.

Part I consisted of a 16-week active ACTEMRA treatment lead-in period (n=188) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period, followed by Part III, a 64-week open-label period. Eligible patients weighing at or above 30 kg received ACTEMRA at 8 mg/kg intravenously once every four weeks. Patients weighing less than 30 kg were randomized 1:1 to receive either ACTEMRA 8 mg/kg or 10 mg/kg intravenously every four weeks. At the conclusion of the open-label Part I, 91% of patients taking background MTX in addition to tocilizumab and 83% of patients on tocilizumab monotherapy achieved an ACR 30 response at week 16 compared to baseline and entered the blinded withdrawal period (Part II) of the study. The proportions of patients with JIA ACR 50/70 responses in Part I were 84.0%, and 64%, respectively for patients taking background MTX in addition to tocilizumab and 80% and 55% respectively for patients on tocilizumab monotherapy.

In Part II, patients (ITT, n=163) were randomized to ACTEMRA (same dose received in Part I) or placebo in a 1:1 ratio that was stratified by concurrent methotrexate use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR 30 flare criteria (relative to Week 16) and qualified for escape.

The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 relative to week 16. JIA ACR 30 flare was defined as 3 or more of the 6 core outcome variables worsening by at least 30% with no more than 1 of the remaining variables improving by more than 30% relative to Week 16.

ACTEMRA treated patients experienced significantly fewer disease flares compared to placebo-treated patients (26% [21/82] versus 48% [39/81]; adjusted difference in proportions -21%, 95% CI: -35%, -8%).

During the withdrawal phase (Part II), more patients treated with ACTEMRA showed JIA ACR 30/50/70 responses at Week 40 compared to patients withdrawn to placebo.

14.5 Polyarticular Juvenile Idiopathic Arthritis—Subcutaneous Administration

Subcutaneously administered ACTEMRA in pediatric patients with polyarticular juvenile idiopathic arthritis (PJIA) was assessed in a 52-week, open-label, multicenter, PK-PD and safety study to determine the appropriate subcutaneous dose of ACTEMRA that achieved comparable PK/PD profiles to the ACTEMRA-IV regimen. PJIA patients aged 1 to 17 years with an inadequate response or inability to tolerate MTX, including patients with well-controlled disease on treatment with ACTEMRA-IV and ACTEMRA-naïve patients with active disease, were treated with subcutaneous ACTEMRA based on body weight.

Patients weighing at or above 30 kg (n = 25) were treated with 162 mg of ACTEMRA-SC every 2 weeks and patients weighing less than 30 kg (n = 27) received 162 mg of ACTEMRA-SC every 3 weeks for 52 weeks. Of these 52 patients, 37 (71%) were naive to ACTEMRA and 15 (29%) had been receiving ACTEMRA-IV and switched to ACTEMRA-SC at baseline.

The efficacy of subcutaneous ACTEMRA in children 2 to 17 years of age is based on pharmacokinetic exposure and extrapolation of the established efficacy of intravenous ACTEMRA in polyarticular JIA patients and subcutaneous ACTEMRA in patients with RA [*see Clinical Pharmacology (12.3) and Clinical Studies (14.2 and 14.4*)].

14.6 Systemic Juvenile Idiopathic Arthritis—Intravenous Administration

The efficacy of ACTEMRA for the treatment of active SJIA was assessed in a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study. Patients treated with or without MTX, were randomized (ACTEMRA:placebo = 2:1) to one of two treatment groups: 75 patients received ACTEMRA infusions every two weeks at either 8 mg per kg for patients at or above 30 kg or 12 mg per kg for patients less than 30 kg and 37 were randomized to receive placebo infusions every two weeks. Corticosteroid tapering could occur from week six for patients who achieved a JIA ACR 70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated with ACTEMRA in the open-label extension phase at weight appropriate dosing.

The primary endpoint was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR 30 response) at Week 12 and absence of fever (no temperature at or above 37.5°C in the preceding 7 days).

JIA ACR (American College of Rheumatology) responses are defined as the percentage improvement (e.g., 30%, 50%, 70%) in 3 of any 6 core outcome variables compared to baseline, with worsening in no more than 1 of the remaining variables by 30% or more. Core outcome variables consist of physician global assessment, parent per patient global assessment, number of joints with active arthritis, number of joints with limitation of movement, erythrocyte sedimentation rate (ESR), and functional ability (childhood health assessment questionnaire-CHAQ).

Primary endpoint result and JIA ACR response rates at Week 12 are shown in **Table 9**.

Table 9　　Efficacy Findings at Week 12

	ACTEMRA N=75	**Placebo N=37**
Primary Endpoint: JIA ACR 30 response + absence of fever		
Responders	**85%**	**24%**
Weighted difference (95% CI)	**62 (45, 78)**	**-**
JIA ACR Response Rates at Week 12		
JIA ACR 30		
Responders Weighted difference[a] (95% CI)[b]	91% 67 (51, 83)	24% -
JIA ACR 50		
Responders Weighted difference[a] (95% CI) [b]	85% 74 (58, 90)	11% -
JIA ACR 70		
Responders Weighted difference[a] (95% CI) [b]	71% 63 (46, 80)	8% -

[a]The weighted difference is the difference between the ACTEMRA and Placebo response rates, adjusted for the stratification factors (weight, disease duration, background oral corticosteroid dose and background methotrexate use).
[b] CI: confidence interval of the weighted difference.

The treatment effect of ACTEMRA was consistent across all components of the JIA ACR response core variables. JIA ACR scores and absence of fever responses in the open label extension were consistent with the controlled portion of the study (data available through 44 weeks).

Systemic Features

Of patients with fever or rash at baseline, those treated with ACTEMRA had fewer systemic features; 35 out of 41 (85%) became fever free (no temperature recording at or above 37.5°C in the preceding 14 days) compared to 5 out of 24 (21%) of placebo-treated patients, and 14 out of 22 (64%) became free of rash compared to 2 out of 18 (11%) of placebo-treated patients. Responses were consistent in the open label extension (data available through 44 weeks).

Corticosteroid Tapering

Of the patients receiving oral corticosteroids at baseline, 8 out of 31 (26%) placebo and 48 out of 70 (69%), ACTEMRA patients achieved a JIA ACR 70 response at week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) ACTEMRA patients versus 1 (3%) placebo patient were able to reduce the dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR 30 flare or occurrence of systemic symptoms to week 12. In the open label portion of the study, by week 44, there were 44 out of 103 (43%) ACTEMRA patients off oral corticosteroids. Of these 44 patients 50% were off corticosteroids 18 weeks or more.

Health Related Outcomes

Physical function and disability were assessed using the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI). Seventy-seven percent (58 out of 75) of patients in the ACTEMRA treatment group achieved a minimal clinically important improvement in CHAQ-DI (change from baseline of ≥ 0.13 units) at week 12 compared to 19% (7 out of 37) in the placebo treatment group.

14.7 Systemic Juvenile Idiopathic Arthritis—Subcutaneous Administration

Subcutaneously administered ACTEMRA in pediatric patients with systemic juvenile idiopathic arthritis (SJIA) was assessed in a 52-week, open-label, multicenter, PK-PD and safety study to determine the appropriate subcutaneous dose of ACTEMRA that achieved comparable PK/PD profiles to the ACTEMRA-IV regimen.

Eligible patients received ACTEMRA subcutaneously dosed according to body weight, with patients weighing at or above 30 kg (n = 26) dosed with 162 mg of ACTEMRA every week and patients weighing below 30 kg (n = 25) dosed with 162 mg of ACTEMRA every 10 days (n=8) or every 2 weeks (n=17) for 52 weeks. Of these 51 patients, 26 (51%) were naive to subcutaneous ACTEMRA and 25 (49%) had been receiving ACTEMRA intravenously and switched to subcutaneous ACTEMRA at baseline.

The efficacy of subcutaneous ACTEMRA in children 2 to 17 years of age is based on pharmacokinetic exposure and extrapolation of the established efficacy of intravenous ACTEMRA in systemic JIA patients [*see Clinical Pharmacology (12.3) and Clinical Studies (14.2 and 14.6*)]

14.8 Cytokine Release Syndrome—Intravenous Administration

The efficacy of ACTEMRA for the treatment of CRS was assessed in a retrospective analysis of pooled outcome data from clinical trials of CAR T-cell therapies for hematological malignancies. Evaluable patients had been treated with tocilizumab 8 mg/kg (12 mg/kg for patients < 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CRS; only the first episode of CRS was included in the analysis. The study population included 24 males and 21 females (total 45 patients) of median age 12 years (range, 3–23 years); 82% were Caucasian. The median time from start of CRS to first dose of tocilizumab was 4 days (range, 0-18 days). Resolution of CRS was defined as lack of fever and off vasopressors for at least 24 hours. Patients were considered responders if CRS resolved within 14 days of the first dose of tocilizumab, if no more than 2 doses of tocilizumab were needed, and if no drugs other than tocilizumab and corticosteroids were used for treatment. Thirty-one patients (69%; 95% CI: 53%–82%) achieved a response. Achievement of resolution of CRS within 14 days was confirmed in a second study using an independent cohort that included 15 patients (range: 9–75 years old) with CAR T cell-induced CRS.

16 HOW SUPPLIED/STORAGE AND HANDLING

For Intravenous Infusion

ACTEMRA (tocilizumab) injection is a preservative-free, sterile clear, colorless to pale yellow solution. ACTEMRA is supplied as 80 mg/4 mL (NDC 50242-135-01), 200 mg/10 mL (NDC 50242-136-01), and 400 mg/20 mL (NDC 50242-137-01) individually packaged 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

For Subcutaneous Injection

ACTEMRA (tocilizumab) injection is supplied as a preservative-free, sterile, clear, colorless to slightly yellowish solution for subcutaneous administration. The following packaging configurations are available:

- Each single-dose prefilled syringe delivers 162 mg/0.9 mL (NDC 50242-138-01).
- Each single-dose autoinjector (ACTPen^{TM}) delivers 162 mg/0.9 mL (NDC 50242-143-01).

Storage and Stability: Do not use beyond expiration date on the container, package, prefilled syringe, or autoinjector. ACTEMRA must be refrigerated at 2ºC to 8ºC (36°F to 46°F). Do not freeze. Protect the vials, syringes, and autoinjectors from light by storage in the original package until time of use, and keep syringes and autoinjectors dry.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Patient Counseling

Advise patients and parents or guardians of minors with PJIA, SJIA, or CRS of the potential benefits and risks of ACTEMRA.

- **Infections:**

  Inform patients that ACTEMRA may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.
- **Gastrointestinal Perforation:**
  Inform patients that some patients who have been treated with ACTEMRA have had serious side effects in the stomach and intestines. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assure rapid evaluation and appropriate treatment.
- **Hypersensitivity and Serious Allergic Reactions**
  Assess patient suitability for home use for subcutaneous injection. Inform patients that some patients who have been treated with ACTEMRA have developed serious allergic reactions, including anaphylaxis. Advise patients to seek immediate medical attention if they experience any symptom of serious allergic reactions.

Instruction on Injection Technique

Perform the first injection under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer subcutaneous ACTEMRA, instruct him/her in injection techniques and assess his/her ability to inject subcutaneously to ensure proper administration of subcutaneous ACTEMRA and the suitability for home use *[See Patient Instructions for Use]*.

Prior to use, remove the prefilled syringe (PFS) or autoinjector from the refrigerator and allow to sit at room temperature outside of the carton for 30 minutes (PFS) or 45 minutes (autoinjector), out of the reach of children. Do not warm ACTEMRA in any other way.

Advise patients to consult their healthcare provider if the full dose is not received.

A puncture-resistant container for disposal of needles, syringes and autoinjectors should be used and should be kept out of the reach of children. Instruct patients or caregivers in the technique as well as proper needle, syringe and autoinjector disposal, and caution against reuse of these items.

Pregnancy Exposure Registry

Inform patients that there is a pregnancy registry to monitor fetal outcomes of pregnant women exposed to ACTEMRA *[see Use in Specific Populations (8.1)]*.

Pregnancy

Inform female patients of reproductive potential that ACTEMRA may cause fetal harm and to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

ACTEMRA® (tocilizumab)
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License No. 1048

MEDICATION GUIDE

ACTEMRA® (AC-TEM-RA)
(tocilizumab) injection
for intravenous use

ACTEMRA® (AC-TEM-RA)
(tocilizumab) injection
for subcutaneous use

What is the most important information I should know about ACTEMRA?
ACTEMRA can cause serious side effects including:

1. **Serious Infections**. ACTEMRA is a medicine that affects your immune system. ACTEMRA can lower the ability of your immune system to fight infections. Some people have serious infections while taking ACTEMRA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections. Your healthcare provider should test you for TB before starting ACTEMRA.

Your healthcare provider should monitor you closely for signs and symptoms of TB during treatment with ACTEMRA.

- You should not start taking ACTEMRA if you have any kind of infection unless your healthcare provider says it is okay.

Before starting ACTEMRA, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection, with or without a fever, such as:
  - sweating or chills
  - shortness of breath
  - warm, red, or painful skin or sores on your body
  - feel very tired
  - muscle aches
  - blood in phlegm
  - diarrhea or stomach pain
  - cough
  - weight loss
  - burning when you urinate or urinating more often than normal
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidiomycosis, or blastomycosis). These infections may happen or become more severe if you use ACTEMRA. Ask your healthcare provider, if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B.

After starting ACTEMRA, call your healthcare provider right away if you have any symptoms of an infection. ACTEMRA can make you more likely to get infections or make worse any infection that you have.

2. **Tears (perforation) of the stomach or intestines.**
   - Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking ACTEMRA get tears in their stomach or intestine. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
   - Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

3. **Changes in certain laboratory test results**. Your healthcare provider should do blood tests before you start receiving ACTEMRA. If you have rheumatoid arthritis (RA) or giant cell arteritis (GCA) your healthcare provider should do blood tests 4 to 8 weeks after you start receiving ACTEMRA and then every 3 months after that. If you have polyarticular juvenile idiopathic arthritis (PJIA) you will have blood tests done every 4 to 8 weeks during treatment. If you have systemic juvenile idiopathic arthritis (SJIA) you will have blood tests done every 2 to 4 weeks during treatment. These blood test are to check for the following side effects of ACTEMRA:
   - low neutrophil count. Neutrophils are white blood cells that help the body fight off bacterial infections.
   - low platelet count. Platelets are blood cells that help with blood clotting and stop bleeding.
   - increase in certain liver function tests.
   - increase in blood cholesterol levels. You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start receiving ACTEMRA, and then every 6 months after that.

You should not receive ACTEMRA if your neutrophil or platelet counts are too low or your liver function tests are too high.
Your healthcare provider may stop your ACTEMRA treatment for a period of time or change your dose of medicine if needed because of changes in these blood test results.

4. **Cancer.** ACTEMRA may increase your risk of certain cancers by changing the way your immune system works. Tell your healthcare provider if you have ever had any type of cancer.

See **"What are the possible side effects with ACTEMRA?"** for more information about side effect.

What is ACTEMRA?
ACTEMRA is a prescription medicine called an Interleukin-6 (IL-6) receptor antagonist. ACTEMRA is used to treat:

- Adults with moderately to severely active rheumatoid arthritis (RA), after at least one other medicine called a Disease-Modifying Anti-Rheumatic Drug (DMARD) has been used and did not work well.
- Adults with giant cell arteritis (GCA).
- People with active PJIA ages 2 and above.
- People with active SJIA ages 2 and above.
- People age 2 years and above who experience severe or life-threatening Cytokine Release Syndrome (CRS) following chimeric antigen receptor (CAR) T cell treatment
- ACTEMRA is not approved for subcutaneous use in people with CRS.

It is not known if ACTEMRA is safe and effective in children with PJIA, SJIA, or CRS under 2 years of age or in children with conditions other than PJIA, SJIA or CRS.

Do not take ACTEMRA: if you are allergic to tocilizumab, or any of the ingredients in ACTEMRA. See the end of this Medication Guide for a complete list of ingredients in ACTEMRA.

Before you receive ACTEMRA, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection. **See "What is the most important information I should know about ACTEMRA?"**
- have liver problems.
- have any stomach-area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines.
- have had a reaction to tocilizumab or any of the ingredients in ACTEMRA before.
- have or had a condition that affects your nervous system, such as multiple sclerosis.
- have recently received or are scheduled to receive a vaccine:
  - All vaccines should be brought up-to-date before starting ACTEMRA.
  - People who take ACTEMRA should not receive live vaccines.
  - People taking ACTEMRA can receive non-live vaccines.
- plan to have surgery or a medical procedure.
- plan to become pregnant or are pregnant. It is not known if ACTEMRA will harm your unborn baby.
- **Pregnancy Registry:** Genentech has a registry for pregnant women who take ACTEMRA. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant while taking ACTEMRA, talk to your healthcare provider about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.
- plan to breastfeed or are breastfeeding. You and your healthcare provider should decide if you will take ACTEMRA or breast-feed. You should not do both.

Tell your healthcare provider about all of the medicines you take, including prescription, over-the-counter medicines, vitamins and herbal supplements. ACTEMRA and other medicines may affect each other causing side effects.
Especially tell your healthcare provider if you take:

- any other medicines to treat your RA. You should not take etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), rituximab (Rituxan®), abatacept (Orencia®), anakinra (Kineret®), certolizumab (Cimzia®), or golimumab (Simponi®), while you are taking ACTEMRA. Taking ACTEMRA with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How will I receive ACTEMRA?
Into a vein (IV or intravenous infusion) for Rheumatoid Arthritis, PJIA, SJIA, or CRS:

- If your healthcare provider prescribes ACTEMRA as an IV infusion, you will receive ACTEMRA from a healthcare provider through a needle placed in a vein in your arm. The infusion will take about 1 hour to give you the full dose of medicine.
- For rheumatoid arthritis or PJIA you will receive a dose of ACTEMRA about every 4 weeks.

- For SJIA you will receive a dose of ACTEMRA about every 2 weeks.
- For CRS you will receive a single dose of ACTEMRA, and if needed additional doses.
- While taking ACTEMRA, you may continue to use other medicines that help treat your rheumatoid arthritis, PJIA, or SJIA such as methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as instructed by your healthcare provider.
- Keep all of your follow-up appointments and get your blood tests as ordered by your healthcare provider.

Under the skin (SC or subcutaneous injection) for Rheumatoid Arthritis or Giant Cell Arteritis or PJIA or SJIA:

- **See the Instructions for Use at the end of this Medication Guide for instructions about the right way to prepare and give your ACTEMRA injections at home.**
- ACTEMRA is available as a single-dose Prefilled Syringe or single-dose Autoinjector (ACTPen™)
- You may also receive ACTEMRA as injection under your skin (subcutaneous). If your healthcare provider decides that you or a caregiver can give your injections of ACTEMRA at home, you or your caregiver should receive training on the right way to prepare and inject ACTEMRA. Do not try to inject ACTEMRA until you have been shown the right way to give the injections by your healthcare provider.
- For PJIA, you may self-inject with the Prefilled Syringe or your caregiver can give you ACTEMRA if both your healthcare provider and parent/legal guardian find it appropriate.
- For SJIA, you may self-inject with the Prefilled Syringe or your caregiver can give you ACTEMRA if both your healthcare provider and parent/legal guardian find it appropriate.
- Your healthcare provider will tell you how much ACTEMRA to use and when to use it.

What are the possible side effects with ACTEMRA?

ACTEMRA can cause serious side effects, including:

- See **"What is the most important information I should know about ACTEMRA?"**
- **Hepatitis B infection** in people who carry the virus in their blood. If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus may become active while you use ACTEMRA. Your healthcare provider may do blood tests before you start treatment with ACTEMRA and while you are using ACTEMRA. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B infection:
  - feel very tired
  - vomiting
  - chills
  - dark urine
  - skin or eyes look yellow
  - clay-colored bowel movements
  - stomach discomfort
  - skin rash
  - little or no appetite
  - fevers
  - muscle aches
- **Serious Allergic Reactions.** Serious allergic reactions, including death, can happen with ACTEMRA. These reactions can happen with any infusion or injection of ACTEMRA, even if they did not occur with an earlier infusion or injection. Tell your healthcare provider before your next dose if you had hives, rash or flushing after your injection. Seek medical attention right away if you have any of the following signs of a serious allergic reaction:
  - shortness of breath or trouble breathing
  - swelling of the lips, tongue, or face
  - chest pain
  - feeling dizzy or faint
  - moderate or severe abdominal pain or vomiting
- **Nervous system problems**. While rare, Multiple Sclerosis has been diagnosed in people who take ACTEMRA. It is not known what effect ACTEMRA may have on some nervous system disorders.

The most common side effects of ACTEMRA include:

- upper respiratory tract infections (common cold, sinus infections)
- headache
- increased blood pressure (hypertension)
- injection site reactions

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Genentech at 1-888-835-2555.

General information about the safe and effective use of ACTEMRA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not give ACTEMRA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ACTEMRA that is written for health professionals.

What are the ingredients in ACTEMRA?

Active ingredient: tocilizumab

Inactive ingredients of Intravenous ACTEMRA: disodium phosphate dodecahydrate, polysorbate 80, sodium dihydrogen phosphate dihydrate, sucrose, and water for injection.

Inactive ingredients of Subcutaneous ACTEMRA: L-arginine, L-arginine hydrochloride, L-methionine, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, and water for injection.

ACTEMRA is a registered trademark of Chugai Seiyaku Kabushiki Kaisha Corp., a member of the Roche Group.
Genentech, Inc.,A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990 US License No.1048
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For more information, go to www.ACTEMRA.com or call 1-800-ACTEMRA.
Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 11/2018

Instructions for Use
ACTEMRA® (AC-TEM-RA)
(tocilizumab)
Prefilled Syringe

Read and follow the Instructions for Use that come with your ACTEMRA prefilled syringe before you start using it and each time you get a prescription refill. Before you use ACTEMRA prefilled syringe for the first time, make sure your healthcare provider shows you the right way to use it.

- **Do not remove the needle cap until you are ready to inject ACTEMRA.**
- **Do not try to take apart the syringe at any time.**
- **Do not reuse the same syringe.**

Parts of your ACTEMRA Prefilled Syringe **(See Figure A).**

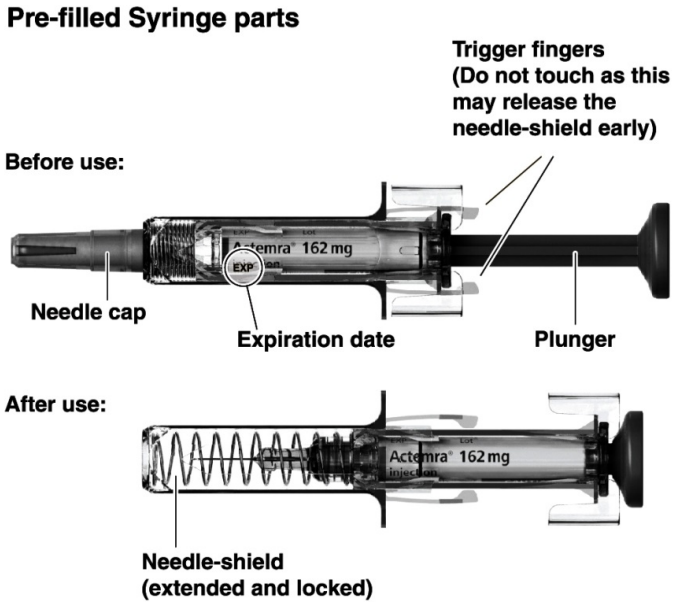


Figure A

Supplies needed for your ACTEMRA Prefilled Syringe Injection (See Figure B):

- ACTEMRA prefilled syringe
- alcohol pad
- sterile cotton ball or gauze
- puncture-resistant container or sharps container for safe disposal of needle cap and used syringe (see **Step 4 "Dispose of the syringe"**)

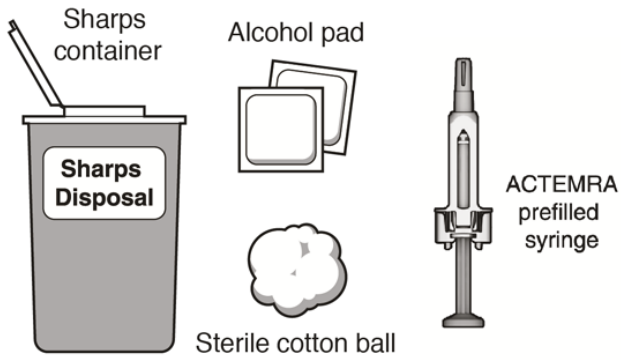


Figure B

Step 1. Preparing for an ACTEMRA Injection

Find a comfortable space with a clean, flat, working surface.

- Take the box containing the syringe out of the refrigerator and open the box. **Do not** touch the trigger fingers on the syringe as this may damage the syringe.
- Remove 1 single-use ACTEMRA prefilled syringe from the box and let it warm up for 30 minutes to allow it to reach room temperature. If the syringe does not reach room temperature, this could cause your injection to feel uncomfortable and make it difficult to push the plunger in.
- **Do not** speed up the warming process in any way, such as using the microwave or placing the syringe in warm water.
- Check the expiration date on the ACTEMRA prefilled syringe **(See Figure A). Do not** use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed safely dispose of the syringe in a sharps container and get a new one.

Do not remove the needle cap while allowing your ACTEMRA prefilled syringe to reach room temperature.

- Keep your unused syringes in the original carton and keep in the refrigerator at 36°F to 46°F (2°C to 8°C). **Do not** freeze.
- Hold your ACTEMRA prefilled syringe with the covered needle pointing down **(see Figure C).**

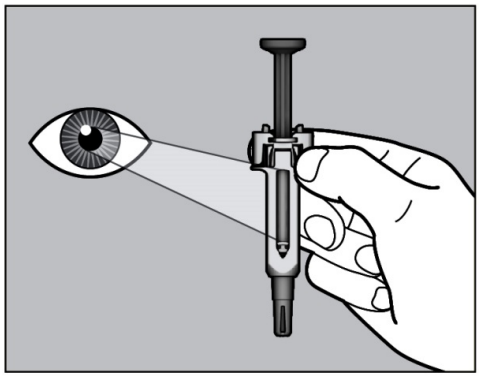


Figure C

- Check the liquid in the ACTEMRA prefilled syringe. It should be clear and colorless to pale yellow. Do not inject ACTEMRA if the liquid is cloudy, discolored, or has lumps or particles in it because it may not be safe to use. Safely dispose of the syringe in a sharps container and get a new one.
- Wash your hands well with soap and water.

Step 2. Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh and your abdomen except for the 2-inch area around your navel are the recommended injection sites **(See Figure D).**
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. Do not attempt to use the upper arm area by yourself **(See Figure D).**

Rotate Injection Site

- Choose a different injection site for each new injection at least 1 inch from the last area you injected.
- Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.

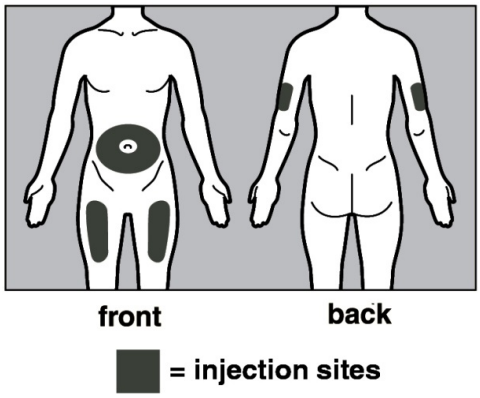


Figure D

Prepare the Injection Site

- Wipe the injection site with an alcohol pad in a circular motion and let it air dry to reduce the chance of getting an infection. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

Step 3. Inject ACTEMRA

- Hold the ACTEMRA prefilled syringe with 1 hand and pull the needle cap straight off with your other hand **(See Figure E). Do not** hold the plunger while you remove the needle cap. If you cannot remove the needle cap you should ask a caregiver for help or contact your healthcare provider.

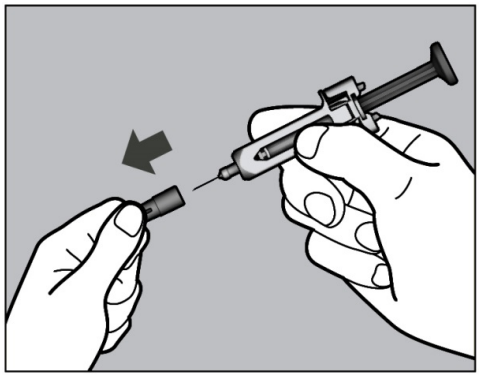


Figure E

- Throw away the needle cap in a sharps container.
- There may be a small air bubble in the ACTEMRA prefilled syringe. You do not need to remove it.
- You may see a drop of liquid at the end of the needle. This is normal and will not affect your dose.
- **Do not** touch the needle or let it touch any surfaces.
- **Do not** use the prefilled syringe if it is dropped.
- If it is not used within 5 minutes of needle cap removal, the syringe should be disposed of in the puncture resistant container or sharps container and a new syringe should be used.
- Never reattach the needle cap after removal.
- Hold the ACTEMRA prefilled syringe in 1 hand between the thumb and index finger **(See Figure F).**

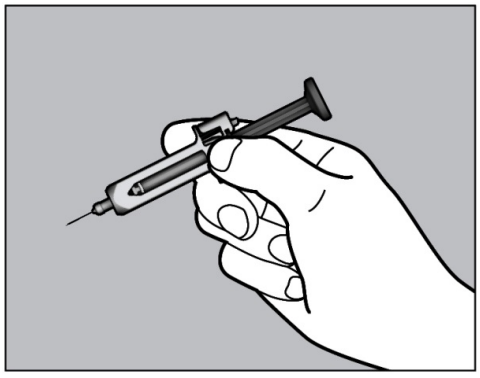


Figure F

- **Do not** pull back on the plunger of the syringe.
- Use your other hand and gently pinch the area of skin you cleaned. Hold the pinched skin firmly. Pinching the skin is important to make sure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could cause the injection to feel uncomfortable.
- **Do not** hold or push on the plunger while inserting the needle into the skin.
- Use a quick, dart-like motion to insert the needle all the way into the pinched skin at an angle between 45° to 90° **(See Figure G).** It is important to use the correct angle to make sure the medicine is delivered under the skin (into fatty tissue), or the injection could be painful and the medicine may not work.

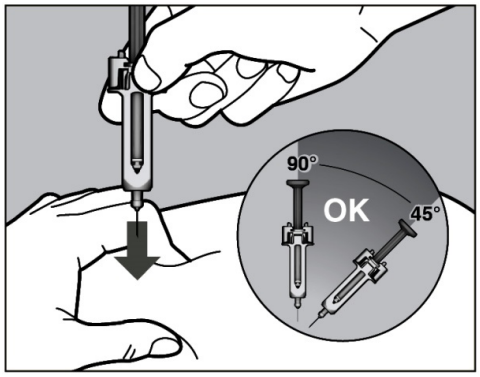


Figure G

- Keep the syringe in position and let go of the pinch of skin.
- Slowly inject all of the medicine by gently pushing the plunger all the way down **(See Figure H).** You must press the plunger all the way down to get the full dose of medicine and to ensure the trigger fingers are completely pushed to the side. If the plunger is not fully depressed the needle shield will not extend to cover the needle when it is removed. If the needle is not covered, carefully place the syringe into the puncture resistant container to avoid injury with the needle.

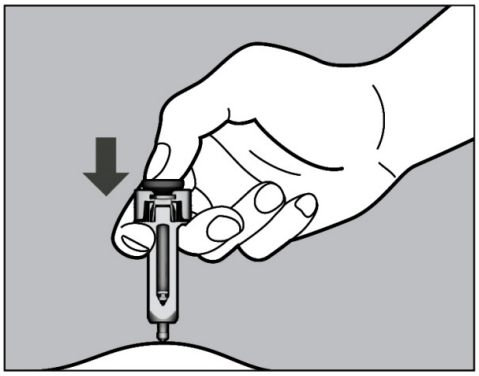


Figure H

- After the plunger is pushed all the way down, keep pressing down on the plunger to be sure all of the medicine is injected before taking the needle out of the skin.
- Keep pressing down on the plunger while you take the needle out of the skin at the same angle as inserted **(See Figure I).**

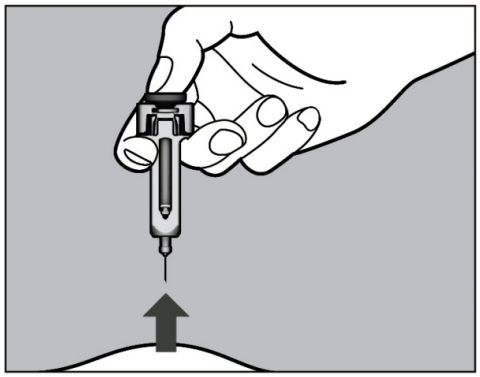


Figure I

- After the needle is removed completely from the skin, release the plunger, allowing the needle-shield to protect the needle **(See Figure J).**

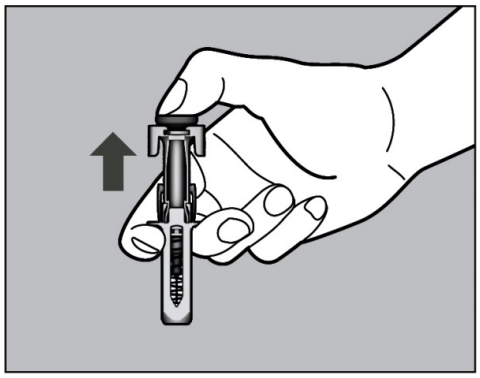


Figure J

After the Injection

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

Step 4. Dispose of the syringe

- The ACTEMRA prefilled syringe should not be reused.
- Put the used syringe into your puncture resistant container (see **"How do I throw away used syringes?")**
- **Do not** put the needle cap back on the needle.
- **If your injection is given by another person, this person must also be careful when removing the syringe and disposing of the syringe to prevent accidental needle stick injury and passing infection.**

How do I throw away used syringes?

- Put your used needles and syringes including ACTEMRA in a FDA-cleared sharps disposal container right away after use **(See Figure K). Do not throw away (dispose of) loose needles and syringes in your household trash.**

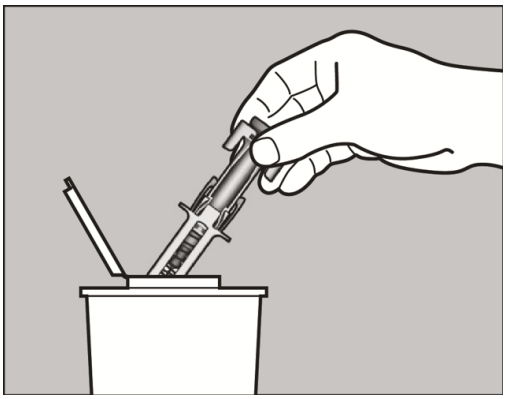


Figure K

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
    - upright stable during use
    - leak-resistant
    - properly labeled to warn of hazardous waste inside the container
        - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
        - Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- **Keep ACTEMRA prefilled syringes and the disposal container out of the reach of children.**

Record your Injection

- Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any questions or concerns about the injection so you can ask your healthcare provider.

If you have questions or concerns about your ACTEMRA prefilled syringe, please contact your healthcare provider familiar with ACTEMRA or call 1-800-ACTEMRA.

This Medication Guide and Instructions for Use has been approved by the U.S. Food and Drug Administration.
Medication Guide Revised: November 2018
ACTEMRA is a registered trademark of Chugai Seiyaku Kabushiki Kaisha Corp., a member of the Roche Group.

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Instructions for Use
ACTEMRA® (AC-TEM-RA)
(tocilizumab)
Autoinjector

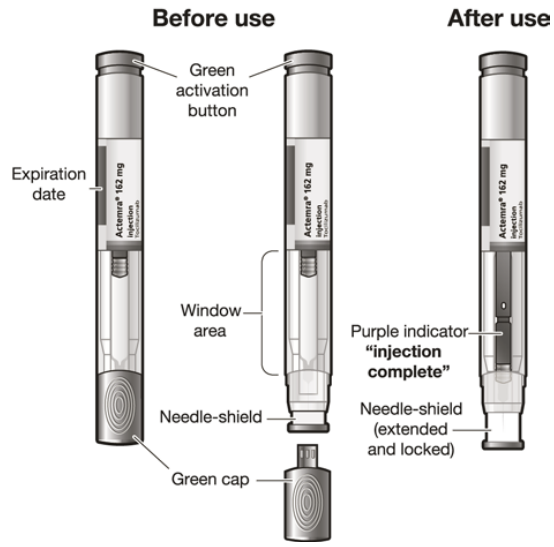
Read and follow the Instructions for Use that come with your ACTEMRA Autoinjector before you start using it and each time you get a prescription refill. Before you use the ACTEMRA Autoinjector for the first time, make sure your healthcare provider shows you the right way to use it.

Important: Keep your unused Autoinjectors in the original carton and keep in the refrigerator at 36˚F to 46˚F (2˚C to 8˚C). **Do not** freeze.

- **Do not** remove the Autoinjector cap until you are ready to inject ACTEMRA.
- **Do not** try to take apart the Autoinjector at any time.
- **Do not** reuse the same Autoinjector.
- **Do not** use the Autoinjector through clothing.
- **Do not** leave the Autoinjector unattended.
- Keep out of the reach of children.

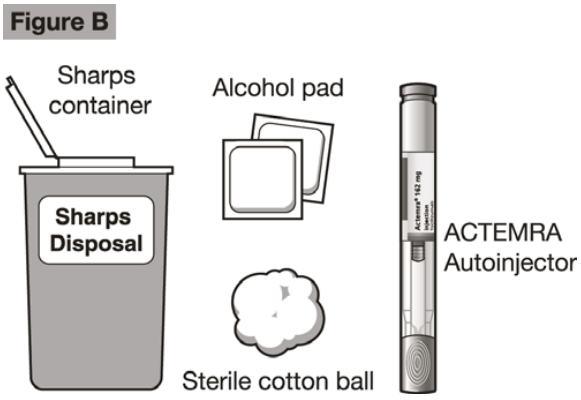
Parts of your ACTEMRA Autoinjector **(See Figure A).**

Figure A



Supplies needed for an injection using your ACTEMRA Autoinjector (See Figure B):

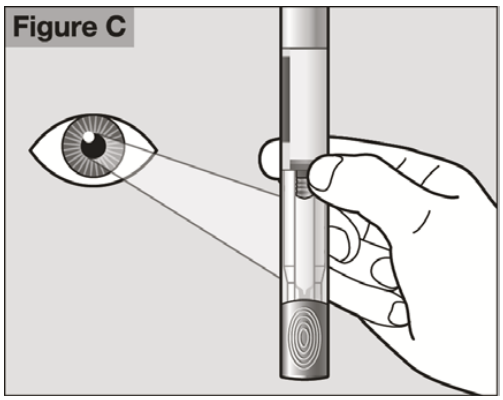
- 1 ACTEMRA Autoinjector
- 1 Alcohol pad
- 1 Sterile cotton ball or gauze
- 1 Puncture-resistant container or sharps container for safe disposal of Autoinjector cap and used Autoinjector (see Step 4 “Dispose of the Autoinjector”)



Step 1. Preparing for an ACTEMRA Injection

Find a comfortable space with a clean, flat, working surface.

- Take the box containing the Autoinjector out of the refrigerator.
- If you are opening the box for the first time, check to make sure that it is properly sealed. **Do not** use the Autoinjector if the box looks like it has already been opened.
- Check that the Autoinjector box is not damaged. **Do not** use Actemra Autoinjector if the box looks damaged.
- **Check the expiration date on the Autoinjector box**. **Do not** use the Autoinjector if the expiration date has passed because it may not be safe to use.
- Open the box, and remove 1 single-use ACTEMRA Autoinjector from the box.
- Return any remaining autoinjectors in the box to the refrigerator.
- **Check the expiration date on the ACTEMRA Autoinjector (See Figure A). Do not** use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed, safely dispose of the Autoinjector in a sharps container and get a new one.
- **Check the Autoinjector to make sure it is not damaged. Do not** use the Autoinjector if it appears to be damaged or if you have accidentally dropped the Autoinjector.
- Place the Autoinjector on a clean, flat surface and let the Autoinjector warm up for 45 minutes to allow it to reach room temperature. If the Autoinjector does not reach room temperature, this could cause your injection to feel uncomfortable and it could take longer to inject.
    - **Do not** speed up the warming process in any way, such as using the microwave or placing the Autoinjector in warm water.
    - **Do not** leave the Autoinjector to warm up in direct sunlight.
    - **Do not** remove the green cap while allowing your ACTEMRA Autoinjector to reach room temperature.
- Hold your ACTEMRA Autoinjector with the green cap pointing down **(See Figure C).**



- Look in the clear Window area. Check the liquid in the ACTEMRA Autoinjector **(See Figure C)**. It should be clear and colorless to pale yellow. **Do not** inject ACTEMRA if the liquid is cloudy, discolored, or has lumps or particles in it because it may not be safe to use. Safely dispose of the Autoinjector in a sharps container and get a new one.
- Wash your hands well with soap and water.

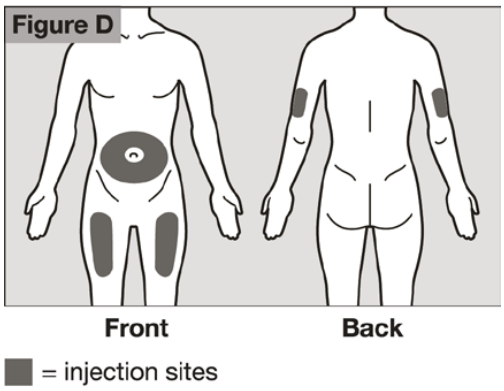
Step 2. Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh or your abdomen except for the 2-inch (5cm) area around your navel are the recommended injection sites **(See Figure D).**
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. **Do not** attempt to use the upper arm area by yourself **(See Figure D).**

Rotate Injection Site

- Choose a different injection site for each new injection at least 1 inch (2.5cm) from the last area you injected.
- **Do not** inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.

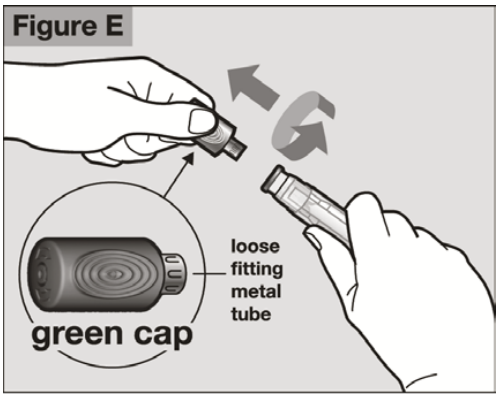


Prepare the Injection Site

- Wipe the injection site with an alcohol pad in a circular motion and let it air dry to reduce the chance of getting an infection. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

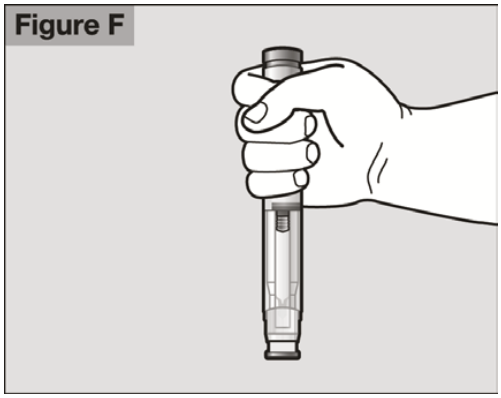
Step 3. Inject ACTEMRA

- Hold the ACTEMRA Autoinjector firmly with one hand. Twist and pull off the green cap with the other hand **(See Figure E).** The green cap contains a loose fitting metal tube.
- If you cannot remove the green cap you should ask a caregiver for help or contact your healthcare provider.

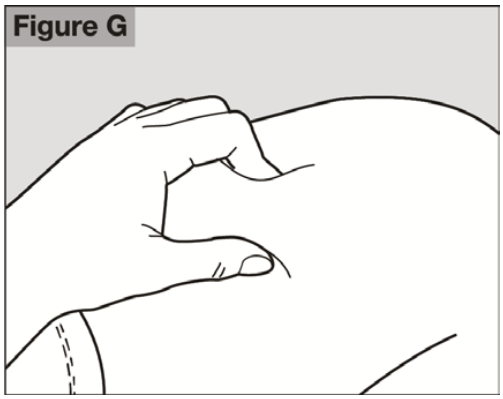


Important: Do not touch the needle shield which is located at the tip of the Autoinjector below the Window area (see Figure A), to avoid accidental needle stick injury.

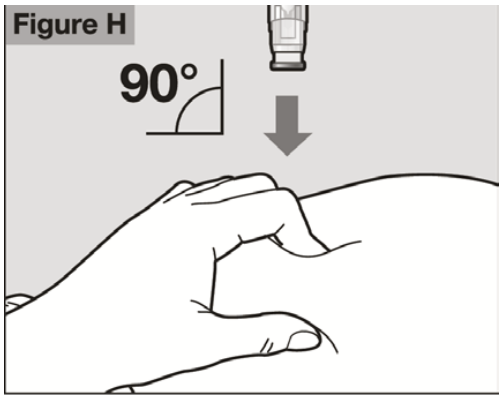
- Throw away the green cap in a sharps container.
- After you remove the green cap, the Autoinjector is ready for use. If the Autoinjector is not used within 3 minutes of the cap removal, the Autoinjector should be disposed of in the sharps container and a new Autoinjector should be used.
- Never reattach the green cap after removal.
- Hold the Autoinjector comfortably in 1 hand by the upper part, so that you can see the Window area of the Autoinjector **(See Figure F)**.



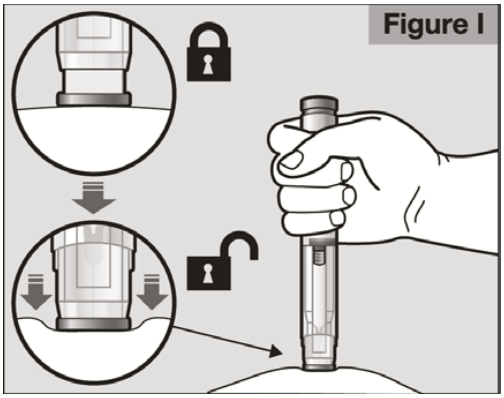
- Use your other hand to gently pinch the area of skin you cleaned, to prepare a firm injection site **(See Figure G)**. The Autoinjector requires a firm injection site to properly activate. Pinching the skin is important to make sure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could cause the injection to feel uncomfortable.



- **Do not** press the green activation button yet.
  Place the needle-shield of the Autoinjector against your pinched skin at a 90° angle **(See Figure H)**.
- It is important to use the correct angle to make sure the medicine is delivered under the skin (into fatty tissue), or the injection could be painful and the medicine may not work.

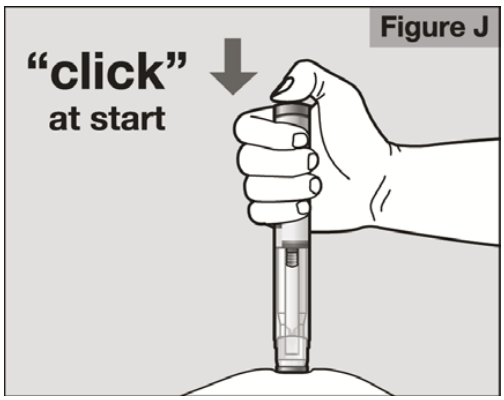


- To use the Autoinjector, you first have to unlock the green Activation button. To unlock it, press the Autoinjector firmly against your pinched skin until the needle-shield is completely pushed in **(See Figure I)**.

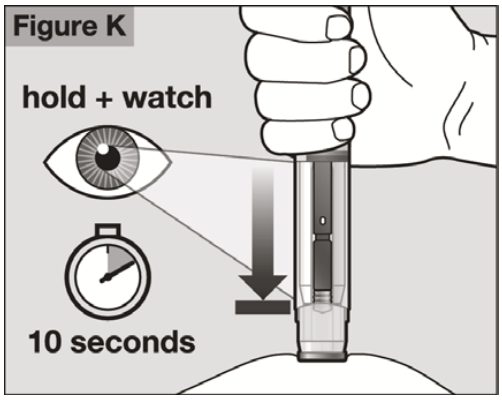


- Continue to keep the needle-shield pushed in. If you do not keep the needle-shield completely pushed against the skin, the green Activation button will not work. Continue to pinch the skin while you keep the Autoinjector in place.

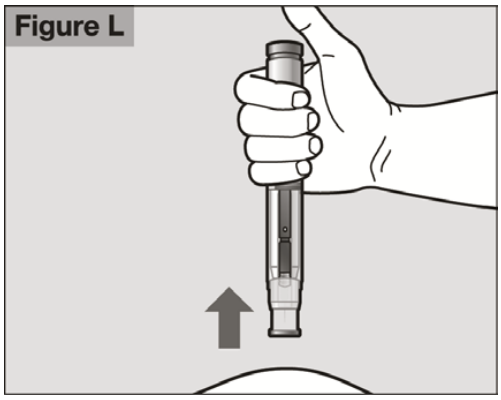
- Press the green Activation button to start the injection. A “click” sound indicates the **start** of the injection. Keep the green button pressed in and continue holding the Autoinjector pressed firmly against your skin **(See Figure J)**. If you cannot start the injection you should ask for help from a caregiver or contact your healthcare provider.



- The purple indicator will move along the Window area during the injection **(See Figure K)**.
- **Watch the purple indicator until it stops moving** to be sure the full dose of medicine is injected. This may take up to **10 seconds**.



- You may hear a second “click” during the injection but you should continue to hold the Autoinjector firmly against your skin until the purple indicator stops moving.
- When the purple indicator has stopped moving, release the green button. Lift the Autoinjector straight off of the injection site at a 90° angle to remove the needle from the skin. The needle-shield will then move out and lock into place covering the needle **(See Figure L)**.



- Check the Window area to see that it is filled with the purple indicator **(See Figure L).**

- If the Window area is not filled by the purple indicator then:
  - The needle-shield may not have locked. **Do not** touch the needle-shield of the Autoinjector, because you may stick yourself with the needle. If the needle is not covered, carefully place the Autoinjector into the sharps container to avoid any injury with the needle.
  - You may not have received your full dose of ACTEMRA. **Do not** try to re-use the Autoinjector. **Do not** repeat the injection with another Autoinjector. Call your healthcare provider for help.

After the Injection

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

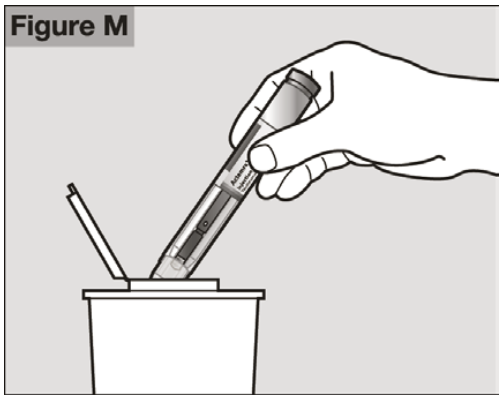
Step 4. Dispose of the Autoinjector

- The ACTEMRA Autoinjector should not be reused.
- Put the used Autoinjector into your sharps container **(see"How do I dispose of used Autoinjectors?").**
- **Do not** put the cap back on the Autoinjector.
- **If your injection is given by another person, this person must also be careful when removing the Autoinjector and disposing of it to prevent accidental needle stick injury and passing infection.**

How do I dispose of used Autoinjectors?

- Put your used ACTEMRA Autoinjector and green cap in a FDA-cleared sharps disposal container right away after use **(See Figure M)**.
- **Do not** throw away (dispose of) the Autoinjector and the green cap in your household trash.

Figure M



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
    - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should dispose of used Autoinjectors. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
    - **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Keep the ACTEMRA Autoinjector and disposal container out of the reach of children.

Record your Injection

- Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any questions or concerns about the injection so you can ask your healthcare provider.

If you have any questions or concerns about your ACTEMRA Autoinjector, talk to your healthcare provider familiar with ACTEMRA or call 1-800-ACTEMRA.

This Medication Guide and Instructions for Use has been approved by the U.S. Food and Drug Administration.
Medication Guide Revised: November 2018
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1.6.4　EU における添付文書

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 20 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL concentrate contains 20 mg tocilizumab*.

Each vial contains 80 mg of tocilizumab* in 4 mL (20 mg/mL).
Each vial contains 200 mg of tocilizumab* in 10 mL (20 mg/mL).
Each vial contains 400 mg of tocilizumab* in 20 mL (20 mg/mL).

*humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients with known effects
Each 80 mg vial contains 0.10 mmol (2.21 mg) sodium.
Each 200 mg vial contains 0.20 mmol (4.43 mg) sodium.
Each 400 mg vial contains 0.39 mmol (8.85 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RoActemra, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

RoActemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX.

RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

RoActemra is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA, sJIA, pJIA or CRS.
All patients treated with RoActemra should be given the Patient Alert Card.

Posology
RA Patients

The recommended posology is 8 mg/kg body weight, given once every four weeks.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended (see section 5.2).

Doses above 1.2 g have not been evaluated in clinical studies (see section 5.1).

Dose adjustments due to laboratory abnormalities (see section 4.4).

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x Upper Limit of Normal (ULN)	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, reduce RoActemra dose to 4 mg/kg or interrupt RoActemra until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate
> 3 to 5 x ULN (confirmed by repeat testing, see section 4.4).	Interrupt RoActemra dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN For persistent increases > 3 x ULN, discontinue RoActemra
> 5 x ULN	Discontinue RoActemra

- Low absolute neutrophil count (ANC)

In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/l.

Laboratory Value (cells x 10^9/ l)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases > 1 x 10^9/ l resume RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 0.5	Discontinue RoActemra

- Low platelet count

Laboratory Value (cells x 10^3/ μL)	Action
50 to 100	Interrupt RoActemra dosing When platelet count > 100 x 10^3/ μ resume RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 50	Discontinue RoActemra

Cytokine Release Syndrome (CRS) (adults and paediatrics)
The recommended posology for treatment of CRS given as a 60-minute intravenous infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg. RoActemra can be given alone or in combination with corticosteroids.

If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of RoActemra may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CRS patients.

Patients with severe or life-threatening CRS frequently have cytopenias or elevated ALT or AST due to the underlying malignancy, preceding lymphodepleting chemotherapy or the CRS.

Special populations

Paediatric patients

sJIA Patients

The recommended posology in patients above 2 years of age is 8 mg/kg once every 2 weeks in patients weighing greater than or equal to 30 kg or 12 mg/kg once every 2 weeks in patients weighing less than 30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

The safety and efficacy of intravenous RoActemra in children below 2 years of age has not been established.

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in sJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may affect laboratory values in sJIA,

the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Liver enzyme abnormalities

Laboratory Value	**Action**
> 1 to 3 x ULN	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, interrupt RoActemra until ALT/AST have normalized.
> 3 x ULN to 5x ULN	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN
> 5x ULN	Discontinue RoActemra. The decision to discontinue RoActemra in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/ l)	**Action**
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases to > 1 x 10^9/ l resume RoActemra
ANC < 0.5	Discontinue RoActemra The decision to discontinue RoActemra in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

Laboratory Value (cells x 10^3/μl)	**Action**
50 to 100	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing When platelet count is > 100 x 10^3/μl resume RoActemra
< 50	Discontinue RoActemra. The decision to discontinue RoActemra in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in sJIA patients.

Available data suggest that clinical improvement is observed within 6 weeks of initiation of treatment with RoActemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

pJIA Patients

The recommended posology in patients above 2 years of age is 8 mg/kg once every 4 weeks in patients weighing greater than or equal to 30 kg or 10 mg/kg once every 4 weeks in patients weighing less than 30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

The safety and efficacy of intravenous RoActemra in children below 2 years of age has not been established.

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in pJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may effect laboratory values in pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Liver enzyme abnormalities

Laboratory Value	**Action**
> 1 to 3 x ULN	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, interrupt RoActemra until ALT/AST have normalized.
> 3 x ULN to 5x ULN	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN
> 5x ULN	Discontinue RoActemra. The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/ l)	**Action**
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases to > 1 x 10^9/ l resume RoActemra
ANC < 0.5	Discontinue RoActemra The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

Laboratory Value (cells x 10^3/μl)	**Action**
50 to 100	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing When platelet count is > 100 x 10^3/μl resume RoActemra
< 50	Discontinue RoActemra. The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in pJIA patients.

Available data suggest that clinical improvement is observed within 12 weeks of initiation of treatment with RoActemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

Elderly No dose adjustment is required in patients aged 65 years and older.

Renal impairment
No dose adjustment is required in patients with mild renal impairment. RoActemra has not been studied in patients with moderate to severe renal impairment (see section 5.2). Renal function should be monitored closely in these patients.

Hepatic impairment
RoActemra has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made.

Method of administration

After dilution, RoActemra for RA, sJIA, pJIA, and CRS patients should be administered as an intravenous infusion over 1 hour.

RA, sJIA, pJIA and CRS Patients ≥ 30 kg
RoActemra should be diluted to a final volume of 100 mL with sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection using aseptic technique.

For instructions on dilution of the medicinal product before administration, see section 6.6.

sJIA,pJIA and CRS Patients < 30 kg
RoActemra should be diluted to a final volume of 50 mL with sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection using aseptic technique.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections
Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra (see section 4.8, undesirable effects). RoActemra treatment must not be initiated in patients with active infections (see section 4.3). Administration of RoActemra should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). Healthcare professionals should exercise caution when considering the use of RoActemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes and interstitial lung disease which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving biological treatments for moderate to severe RA, sJIA or pJIA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reaction. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients (which includes younger children with sJIA or pJIA who may be less able to communicate their symptoms) and parents/guardians of sJIA or pJIA patients, should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Tuberculosis
As recommended for other biological treatments, RA, sJIA and pJIA patients should be screened for latent tuberculosis (TB) infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoActemra. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised.

Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with RoActemra.

Viral reactivation
Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for RA. In clinical studies with tocilizumab, patients who screened positive for hepatitis were excluded.

Complications of diverticulitis
Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with RoActemra in RA patients (see section 4.8). RoActemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation.

Hypersensitivity reactions
Serious hypersensitivity reactions have been reported in association with infusion of RoActemra (see section 4.8). Such reactions may be more severe, and potentially fatal in patients who have experienced hypersensitivity reactions during previous infusions even if they have received premedication with steroids and antihistamines. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with RoActemra. If an anaphylactic reaction or other serious hypersensitivity / serious infusion related reaction occurs,

administration of RoActemra should be stopped immediately and RoActemra should be permanently discontinued.

Active hepatic disease and hepatic impairment
Treatment with RoActemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases, therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8).

Hepatic transaminase elevations
In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with RoActemra treatment, without progression to hepatic injury (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with RoActemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Caution should be exercised when considering initiation of RoActemra treatment in patients with elevated ALT or AST > 1.5 x ULN. In patients with baseline ALT or AST > 5 x ULN, treatment is not recommended.

In RA patients, ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see section 4.2. For ALT or AST elevations > 3–5 x ULN, confirmed by repeat testing, RoActemra treatment should be interrupted.

In sJIA and pJIA patients, ALT and AST levels should be monitored at the time of the second infusion and thereafter according to good clinical practice, see section 4.2.

Haematological abnormalities
Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/l. Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/ µL). In patients who develop an ANC < 0.5 x 10^9/ l or a platelet count < 50 x 10^3/µL, continued treatment is not recommended.

Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with RoActemra to date.

In RA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2.

In sJIA and pJIA patients, neutrophils and platelets should be monitored at the time of second infusion and thereafter according to good clinical practice, see section 4.2.

Lipid parameters
Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with tocilizumab (see section 4.8). In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents.

In sJIA, pJIA and RA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of RoActemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Neurological disorders
Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with RoActemra is currently unknown.

Malignancy
The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy.

Vaccinations
Live and live attenuated vaccines should not be given concurrently with RoActemra as clinical safety has not been established. In a randomized open-label study, adult RA patients treated with RoActemra and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus toxoid vaccines which was comparable to the response seen in patients on MTX only. It is recommended that all patients, particularly sJIA and pJIA patients, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating RoActemra therapy. The interval between live vaccinations and initiation of RoActemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Cardiovascular risk
RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care.

Combination with TNF antagonists
There is no experience with the use of RoActemra with TNF antagonists or other biological treatments for RA, sJIA or pJIA patients. RoActemra is not recommended for use with other biological agents.

Sodium
This medicinal product contains 1.17 mmol (or 26.55 mg) sodium per maximum dose of 1200 mg. To be taken into consideration by patients on a controlled sodium diet. Doses below 1025 mg of this medicinal product contain less than 1 mmol sodium (23 mg), i.e. essentially ‘sodium free’.

Paediatric population

sJIA Patients
Macrophage activation syndrome (MAS) is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, tocilizumab has not been studied in patients during an episode of active MAS.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Concomitant administration of a single dose of 10 mg/kg tocilizumab with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids on tocilizumab clearance.

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as tocilizumab, is introduced.

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzyme expression. Tocilizumab normalises expression of these enzymes.

In a study in RA patients, levels of simvastatin (CYP3A4) were decreased by 57% one week following a single dose of tocilizumab, to the level similar to, or slightly higher than, those observed in healthy subjects.

When starting or stopping therapy with tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2 or 2C9 (e.g. . methylprednisolone, dexamethasone, (with the possibility for oral glucocorticoid withdrawal syndrome), atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Pregnancy
There are no adequate data from the use of tocilizumab in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose (see section 5.3). The potential risk for humans is unknown.

RoActemra should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether tocilizumab is excreted in human breast milk. The excretion of tocilizumab in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with RoActemra should be made taking into account the benefit of breast-feeding to the child and the benefit of RoActemra therapy to the woman.

Fertility
Available non-clinical data do not suggest an effect on fertility under tocilizumab treatment.

4.7 Effects on ability to drive and use machines

RoActemra has minor influence on the ability to drive and use machines (see section 4.8, dizziness).

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported ADRs (occurring in ≥ 5% of patients treated with tocilizumab monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The most serious ADRs were serious infections, complications of diverticulitis, and hypersensitivity reactions.

RA Patients
The safety profile of tocilizumab has been studied in 4 placebo-controlled studies (studies II, III, IV and V), 1 MTX-controlled study (study I) and their extension periods (see section 5.1).

The double-blind controlled period was 6 months in four studies (studies I, III, IV and V) and was up to 2 years in one study (study II). In the double-blind controlled studies, 774 patients received tocilizumab 4 mg/kg in combination with MTX, 1870 patients received tocilizumab 8 mg/kg in combination with MTX or other DMARDs and 288 patients received tocilizumab 8 mg/kg monotherapy.

The long-term exposure population includes all patients who received at least one dose of tocilizumab either in the double-blind control period or open label extension phase in the studies. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year, 2806 received treatment for at least 2 years and 1222 for 3 years.

ADRs from clinical trials and/or post marketing experience with RoActemra based on spontaneous case reports, literature cases and cases from non-interventional study programs are listed in Table 1 and are presented by MedDRA system organ class. The corresponding frequency category for each ADR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (>1/10,000 to <1/1,000) or very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. List of ADRs occurring in patients with RA receiving tocilizumab as monotherapy or in combination with MTX or other DMARDs in the double-blind controlled period or during postmarketing experience

MedDRA System Organ Class	Frequency categories with preferred terms		
	Very Common	**Common**	**Uncommon**
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria	
Nervous system disorders		Headache, Dizziness	
Investigations		Hepatic transaminases increased, Weight increased, Total bilirubin increased*	
Vascular disorders		Hypertension	
Blood and lymphatic system disorders		Leukopenia, Neutropenia, Hypofibrinogenaemia	
Metabolism and nutrition disorders	Hypercholesterolaemia*		Hypertriglyceridaemia
General disorders and administration site conditions		Peripheral oedema, Hypersensitivity reactions	
Eye disorders		Conjunctivitis	
Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea	
Renal disorders			Nephrolithiasis
Endocrine disorders			Hypothyroidism

* Includes elevations collected as part of routine laboratory monitoring (see text below)

Infections
In the 6-month controlled studies the rate of all infections reported with tocilizumab 8 mg/kg plus DMARD treatment was 127 events per 100 patient years compared to 112 events per 100 patient years in the placebo plus DMARD group. In the long-term exposure population, the overall rate of infections with RoActemra was 108 events per 100 patient years exposure.

In 6-month controlled clinical studies, the rate of serious infections with tocilizumab 8 mg/kg plus DMARDs was 5.3 events per 100 patient years exposure compared to 3.9 events per 100 patient years exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 patient years of exposure in the tocilizumab group and 1.5 events per 100 patient years of exposure in the MTX group.

In the long-term exposure population, the overall rate of serious infections (bacterial, viral and fungal) was 4.7 events per 100 patient years. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive

pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported.

Interstitial Lung Disease
Impaired lung function may increase the risk for developing infections. There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Gastrointestinal Perforation
During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with tocilizumab therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Reports of gastrointestinal perforation on tocilizumab were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.

Infusion reactions
In the 6-month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the tocilizumab 8 mg/kg plus DMARD group and 5.1% of patients in the placebo plus DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment limiting.

The rate of anaphylactic reactions (occurring in a total of 8/4,009 patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported in a total of 56 out of 4,009 patients (1.4%) treated with tocilizumab during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with tocilizumab (see section 4.4).

Immunogenicity
A total of 2,876 patients have been tested for anti-tocilizumab antibodies in the 6-month controlled clinical trials. Of the 46 patients (1.6%) who developed anti-tocilizumab antibodies, 6 had an associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. Thirty patients (1.1%) developed neutralising antibodies.

Haematological abnormalities:
Neutrophils
In the 6-month controlled trials decreases in neutrophil counts below 1 x 10^9/ l occurred in 3.4% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < 1 x 10^9/ l did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/ l were reported in 0.3% patients receiving tocilizumab 8 mg/kg plus DMARDs. Infections with neutropenia have been reported.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials.

Platelets
In the 6-month controlled trials decreases in platelet counts below 100 x 10^3/ μL occurred in 1.7% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 1% on placebo plus DMARDs. These decreases occurred without associated bleeding events.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials.

Very rare reports of pancytopenia have occurred in the post marketing setting.

Hepatic transaminase elevations
During the 6-month controlled trials transient elevations in ALT/AST > 3 x ULN were observed in 2.1% of patients on tocilizumab 8 mg/kg compared to 4.9% of patients on MTX and in 6.5% of patients who received 8 mg/kg tocilizumab plus DMARDs compared to 1.5% of patients on placebo plus DMARDs.

The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 x ULN were observed in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab plus DMARD patients, the majority of whom were discontinued permanently from tocilizumab treatment. These elevations were not associated with clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment. During the double-blind controlled period, the incidence of indirect bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, is 6.2% in patients treated with 8 mg/kg tocilizumab + DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of > 1 to 2 x ULN and 0.4% had an elevation of > 2 x ULN.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevation in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials.

Lipid parameters
During the 6-month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving RoActemra in clinical trials experienced sustained elevations in total cholesterol ≥ 6.2 mmol/ l, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/ l. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled trials.

Malignancies
The clinical data are insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long-term safety evaluations are ongoing.

Skin Reactions
Very rare reports of Stevens-Johnson Syndrome have occurred in the post marketing setting.

<u>sJIA and pJIA Patients</u>

The safety profile of tocilizumab in the pediatric population is summarized in the sections on pJIA and sJIA below. In general, the ADRs in pJIA and sJIA patients were similar in type to those seen in RA patients, see section 4.8.

The ADRs in the pJIA and sJIA patients treated with tocilizumab are described below and are presented in the Table 2 by MedDRA system organ class and frequency categories, defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1,000 to <1/100)

Table 2: List of ADRs occurring in clinical trial patients with sJIA or pJIA receiving tocilizumab as monotherapy or in combination with MTX.

MedDRA SOC	**Preferrred term (PT)**	**Frequency**		
Infections and Infestations		Very Common	Common	Uncommon
	Upper Respiratory Tract Infections	pJIA, sJIA		
	Nasopharyngitis	pJIA, sJIA		
Gastrointestinal Disorders				
	Nausea		pJIA	
	Diarrhea		pJIA, sJIA	
General disorders and administration site conditions				
	Infusion related reactions		pJIA[1], sJIA[2]	
Nervous system disorders				
	Headache	pJIA	sJIA	
Investigations				
	Hepatic transaminases increased		pJIA	
	Decrease in neutrophil count	sJIA	pJIA	
	Platelet count decreased		sJIA	pJIA
	Cholesterol increased		sJIA	pJIA

1. Infusion related reaction events in pJIA patients included but were not limited to headache, nausea and hypotension
2. Infusion related reaction events in sJIA patients included but were not limited to rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache

pJIA Patients

The safety profile of intravenous RoActemra in pJIA has been studied in 188 patients from 2 to 17 years of age. The total patient exposure was 184.4 patient years. The frequency of ADRs in pJIA patients can be found in Table 2. The types of ADRs in pJIA patients were similar to those seen in RA and sJIA patients, see section 4.8. When compared to the adult RA population, events of nasopharyngitis, headache, nausea, and decreased neutrophil count were more frequently reported in the pJIA population. Events of cholesterol increased were less frequently reported in the pJIA population than in the adult RA population.

Infections

The rate of infections in the tocilizumab all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (7.6%).

Infusion Reactions

In pJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the tocilizumab all exposure population, 11 patients (5.9%) experienced infusion reactions during the infusion and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension and within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients, see section 4.8.

No clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported.

Immunogenicity
One patient in the 10 mg/kg < 30kg group developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.

Neutrophils
During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below 1×10^9/L occurred in 3.7% of patients.

Platelets
During routine laboratory monitoring in the tocilizumab all exposure population, 1% of patients had a decrease in platelet count to $\leq 50 \times 10^3$/μL without associated bleeding events.

Hepatic transaminase elevations
During routine laboratory monitoring in the tocilizumab all exposure population, elevation in ALT or AST ≥ 3xULN occurred in 3.7% and <1% of patients, respectively.

Lipid parameters
During routine laboratory monitoring in the intravenous RoActemra study WA19977 3.4% and 10.4% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during the study treatment, respectively.

sJIA Patients
The safety profile of intravenous RoActemra in sJIA has been studied in 112 patients from 2 to 17 years of age. In the 12 week double-blind, controlled phase, 75 patients received treatment with tocilizumab (8 mg/kg or 12 mg/kg based upon body weight). After 12 weeks or at the time of switching to RoActemra, due to disease worsening, patients were treated in the open label extension phase.

In general, the ADRs in sJIA patients were similar in type to those seen in RA patients, see section 4.8. The frequency of ADRs in sJIA patients can be found in Table 2. When compared to the adult RA population, patients with sJIA experienced a higher frequency of nasopharyngitis, decrease in neutrophil counts, hepatic transaminases increased, and diarrhea. Events of cholesterol increased were less frequently reported in the sJIA population than in the adult RA population.

Infections
In the 12 week controlled phase, the rate of all infections in the intravenous RoActemra group was 344.7 per 100 patient years and 287.0 per 100 patient years in the placebo group. In the open label extension phase (Part II), the overall rate of infections remained similar at 306.6 per 100 patient years.

In the 12 week controlled phase, the rate of serious infections in the intravenous RoActemra group was 11.5 per 100 patient years. At one year in the open label extension phase the overall rate of serious infections remained stable at 11.3 per 100 patient years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media.

Infusion Reactions
Infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12 week controlled phase, 4% of patients from the tocilizumab group experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

In the 12 week controlled phase, 16% of patients in the tocilizumab group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. In the tocilizumab group, the events included, but were not limited to rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation, were reported in 1 out of 112 patients (< 1%) treated with tocilizumab during the controlled and up to and including the open label clinical trial.

Immunogenicity
All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal. The incidence of anti-tocilizumab antibody formation might be underestimated because of interference of tocilizumab with the assay and higher drug concentration observed in children compared to adults.

Neutrophils
During routine laboratory monitoring in the 12 week controlled phase, a decrease in neutrophil counts below 1 x 10^9/l occurred in 7% of patients in the tocilizumab group, and no decreases in the placebo group.

In the open label extension phase, decreases in neutrophil counts below 1 x 10^9/l, occurred in 15% of the tocilizumab group.

Platelets
During routine laboratory monitoring in the 12 week controlled phase, 3% of patients in the placebo group and 1% in the tocilizumab group had a decrease in platelet count to ≤ 100 x 10^3/µl.

In the open label extension phase, decreases in platelet counts below 100 x 10^3/µl, occurred in 3% of patients in the tocilizumab group, without associated bleeding events.

Hepatic transaminase elevations
During routine laboratory monitoring in the 12 week controlled phase, elevation in ALT or AST ≥ 3 x ULN occurred in 5% and 3% of patients, respectively, in the tocilizumab group, and 0% in the placebo group.

In the open label extension phase, elevation in ALT or AST ≥ 3 x ULN occurred in 12% and 4% of patients, respectively, in the tocilizumab group.

Immunoglobulin G
IgG levels decrease during therapy. A decrease to the lower limit of normal occurred in 15 patients at some point in the study.

Lipid parameters
During routine laboratory monitoring in the 12 week controlled phase (study WA18221), 13.4% and 33.3% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively.

In the open label extension phase (study WA18221), 13.2% and 27.7% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively.

<u>CRS Patients</u>
The safety of tocilizumab in CRS has been evaluated in a retrospective analysis of data from clinical trials, where 51 patients were treated with intravenous tocilizumab 8 mg/kg (12 mg/kg for patients less than 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CAR T-cell-induced CRS. A median of 1 dose of tocilizumab (range, 1-4 doses) was administered.

<u>Reporting of suspected adverse reactions</u>
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are limited data available on overdose with RoActemra. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg. No adverse reactions were observed.

No serious adverse reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg, although dose limiting neutropenia was observed.

Paediatric population

No case of an overdose in the paediatric population has been observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors; ATC code: L04AC07.

Mechanism of action
Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.

RA Patients
Pharmacodynamic effects
In clinical studies with tocilizumab, rapid decreases in CRP, erythrocyte sedimentation rate (ESR), serum amyloid A (SAA) and fibrinogen were observed. Consistent with the effect on acute phase reactants, treatment with tocilizumab was associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability. In tocilizumab-treated patients, decreases in the levels of CRP to within normal ranges were seen as early as week 2, with decreases maintained while on treatment.

In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts decreased to their lowest 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Rheumatoid arthritis patients demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration (see section 4.8).

Clinical efficacy and safety
The efficacy of tocilizumab in alleviating the signs and symptoms of RA was assessed in five randomised, double-blind, multi-centre studies. Studies I-V enrolled patients ≥ 18 years of age with active RA diagnosed according to the American College of Rheumatology (ACR) criteria and who had at least eight tender and six swollen joints at baseline.

In Study I, tocilizumab was administered intravenously every four weeks as monotherapy. In Studies II, III and V, tocilizumab was administered intravenously every four weeks in combination with MTX vs. placebo and MTX. In Study IV, tocilizumab was administered intravenously every 4 weeks in

combination with other DMARDs vs. placebo and other DMARDs. The primary endpoint for each of the five studies was the proportion of patients who achieved an ACR 20 response at week 24.

Study I evaluated 673 patients who had not been treated with MTX within six months prior to randomisation and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response. The majority (67%) of patients were MTX-naïve. Doses of 8 mg/kg of tocilizumab were given every four weeks as monotherapy. The comparator group was weekly MTX (dose titrated from 7.5 mg to a maximum of 20 mg weekly over an eight week period).

Study II, a two year study with planned analyses at week 24, week 52 and week 104, evaluated 1,196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of tocilizumab or placebo were given every four weeks as blinded therapy for 52 weeks in combination with stable MTX (10 mg to 25 mg weekly). After week 52, all patients could receive open-label treatment with tocilizumab 8 mg/kg. Of the patients who completed the study who were originally randomised to placebo + MTX, 86% received open-label tocilizumab 8 mg/kg in year 2. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At week 52 and week 104 the co-primary endpoints were prevention of joint damage and improvement in physical function.

Study III evaluated 623 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg tocilizumab or placebo were given every four weeks, in combination with stable MTX (10 mg to 25 mg weekly).

Study IV evaluated 1,220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg tocilizumab or placebo were given every four weeks in combination with stable DMARDs.

Study V evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomisation. Doses of 4 or 8 mg/kg tocilizumab or placebo were given every four weeks in combination with stable MTX (10 mg to 25 mg weekly).

Clinical response
In all studies, patients treated with tocilizumab 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 3). In study I, superiority of tocilizumab 8 mg/kg was demonstrated against the active comparator MTX.

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the open label extension studies I-V.

In patients treated with tocilizumab 8 mg/kg, significant improvements were noted on all individual components of the ACR response including: tender and swollen joint counts; patients and physician global assessment; disability index scores; pain assessment and CRP compared to patients receiving placebo plus MTX or other DMARDs in all studies.

Patients in studies I – V had a mean Disease Activity Score (DAS28) of 6.5–6.8 at baseline. Significant reduction in DAS28 from baseline (mean improvement) of 3.1–3.4 were observed in tocilizumab-treated patients compared to control patients (1.3-2.1). The proportion of patients achieving a DAS28 clinical remission (DAS28 < 2.6) was significantly higher in patients receiving tocilizumab (28–34%) compared to 1–12% of control patients at 24 weeks. In study II, 65% of patients achieved a DAS28 < 2.6 at week 104 compared to 48% at 52 weeks and 33% of patients at week 24.

In a pooled analysis of studies II, III and IV, the proportion of patients achieving an ACR 20, 50 and 70 response was significantly higher (59% vs. 50%, 37% vs. 27%, 18% vs. 11%, respectively) in the tocilizumab 8 mg/kg plus DMARD vs. the tocilizumab 4 mg/kg plus DMARD group ($p< 0.03$). Similarly the proportion of patients achieving a DAS28 remission (DAS28 < 2.6) was significantly

higher (31% vs. 16% respectively) in patients receiving tocilizumab 8 mg/kg plus DMARD than in patients receiving tocilizumab 4 mg/kg plus DMARD (p< 0.0001).

Table 3. ACR responses in placebo-/MTX-/DMARDs-controlled studies (% patients)

	Study I AMBITION		**Study II LITHE**		**Study III OPTION**		**Study IV TOWARD**		**Study V RADIATE**	
Week	**TCZ 8 mg/kg**	**MTX**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**	**TCZ 8 mg/kg + DMARD**	**PBO + DMARD**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**
	N = 286	**N = 284**	**N = 398**	**N = 393**	**N = 205**	**N = 204**	**N = 803**	**N = 413**	**N = 170**	**N = 158**
ACR 20										
24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
52			56%***	25%						
ACR 50										
24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%
52			36%***	10%						
ACR 70										
24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%
52			20%***	4%						

TCZ - Tocilizumab
MTX - Methotrexate
PBO - Placebo
DMARD - Disease modifying anti-rheumatic drug
** *- p< 0.01, TCZ vs. PBO + MTX/DMARD*
*** *- p< 0.0001, TCZ vs. PBO + MTX/DMARD*

Major Clinical Response
After 2 years of treatment with tocilizumab plus MTX, 14% of patients achieved a major clinical response (maintenance of an ACR70 response for 24 weeks or more).

Radiographic response
In Study II, in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with significantly less radiographic progression in patients receiving tocilizumab compared to control (Table 4).

In the open-label extension of Study II the inhibition of progression of structural joint damage in tocilizumab plus MTX-treated patients was maintained in the second year of treatment. The mean change from baseline at week 104 in total Sharp-Genant score was significantly lower for patients randomised to tocilizumab 8 mg/kg plus MTX (p<0.0001) compared with patients who were randomised to placebo plus MTX.

Table 4. Radiographic mean changes over 52 weeks in Study II

	PBO + MTX (+ TCZ from week 24) N = 393	**TCZ 8 mg/kg + MTX N = 398**
Total Sharp-Genant score	1.13	0.29*
Erosion score	0.71	0.17*
JSN score	0.42	0.12**

PBO - Placebo
MTX - Methotrexate
TCZ - Tocilizumab
JSN - Joint space narrowing
* *- p≤ 0.0001, TCZ vs. PBO + MTX*
** *- p< 0.005, TCZ vs. PBO + MTX*

Following 1 year of treatment with tocilizumab plus MTX, 85% of patients (n=348) had no progression of structural joint damage, as defined by a change in the Total Sharp Score of zero or less, compared with 67% of placebo plus MTX-treated patients (n=290) ($p \leq 0.001$). This remained consistent following 2 years of treatment (83%; n=353). Ninety three percent (93%; n=271) of patients had no progression between week 52 and week 104.

Health-related and quality of life outcomes
Tocilizumab-treated patients reported an improvement in all patient-reported outcomes (Health Assessment Questionnaire Disability Index - HAQ-DI), Short Form-36 and Functional Assessment of Chronic Illness Therapy questionnaires. Statistically significant improvements in HAQ-DI scores were observed in patients treated with RoActemra compared with patients treated with DMARDs. During the open-label period of Study II, the improvement in physical function has been maintained for up to 2 years. At Week 52, the mean change in HAQ-DI was -0.58 in the tocilizumab 8 mg/kg plus MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at Week 104 in the tocilizumab 8 mg/kg plus MTX group (-0.61).

Haemoglobin levels
Statistically significant improvements in haemoglobin levels were observed with tocilizumab compared with DMARDs ($p< 0.0001$) at week 24. Mean haemoglobin levels increased by week 2 and remained within normal range through to week 24.

Tocilizumab versus adalimumab in monotherapy
Study VI (WA19924), a 24 week double-blinded study that compared tocilizumab monotherapy with adalimumab monotherapy, evaluated 326 patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the tocilizumab arm received an intravenous (IV) infusion of tocilizumab (8 mg/kg) every 4 weeks (q4w) and a subcutaneous (SC) placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab SC injection (40 mg) q2w plus an IV placebo infusion q4w. A statistically significant superior treatment effect was seen in favour of tocilizumab over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 5).

Table 5: Efficacy Results for Study VI (WA19924)

	ADA + Placebo (IV) N = 162	TCZ + Placebo (SC) N = 163	p-value[(a)]
Primary Endpoint - Mean Change from baseline at Week 24			
DAS28 (adjusted mean)	**-1.8**	**-3.3**	
Difference in adjusted mean (95% CI)	**-1.5 (-1.8, -1.1)**		**<0.0001**
Secondary Endpoints - Percentage of Responders at Week 24 [(b)]			
DAS28 < 2.6, n (%)	17 (10.5)	65 (39.9)	<0.0001
DAS28 ≤ 3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001
ACR20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR70 response, n (%)	29 (17.9)	53 (32.5)	0.0023

[a] *p value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.*
[b] *Non-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure*

The overall clinical adverse event profile was similar between tocilizumab and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (tocilizumab 11.7% vs. adalimumab 9.9%). The types of adverse drug reactions in the tocilizumab arm were consistent with the known safety profile of tocilizumab and adverse drug reactions were reported at a similar frequency compared with Table 1. A higher incidence of infections and infestations was reported in the tocilizumab arm (48% vs. 42%), with no difference in the incidence of serious infections (3.1%). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with tocilizumab compared with adalimumab. Four (2.5%) patients in the tocilizumab arm and two (1.2%) patients in the adalimumab arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the tocilizumab arm and five (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/L (25 mg/dL) for patients in the tocilizumab arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the tocilizumab arm was consistent with the known safety profile of tocilizumab and no new or unexpected adverse drug reactions were observed (see Table 1).

MTX naïve, Early RA

Study VII (WA19926), a 2 year study with the planned primary analysis at week 52 evaluated 1162 MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months). Approximately 20% of patients had received prior treatment with DMARDs other than MTX. This study evaluated the efficacy of IV tocilizumab 4 or 8 mg/kg every 4 weeks/MTX combination therapy, IV tocilizumab 8 mg/kg monotherapy and MTX monotherapy in reducing the signs and symptoms and rate of progression of joint damage for 104 weeks. The primary endpoint was the proportion of patients achieving DAS28 remission (DAS28 < 2.6) at week 24. A significantly higher proportion of patients in the tocilizumab 8 mg/kg + MTX and tocilizumab monotherapy groups met the primary endpoint compared with MTX alone. The tocilizumab 8 mg/kg + MTX group also showed statistically significant results across the key secondary endpoints. Numerically greater responses compared with MTX alone were observed in the tocilizumab 8 mg/kg monotherapy group in all secondary endpoints, including radiographic endpoints. In this study, ACR/EULAR remission (Boolean and Index) were also analysed as pre-specified exploratory endpoints, with higher responses observed in the tocilizumab groups. The results from study VII are shown in Table 6.

Table 6: Efficacy Results for Study VII (WA19926) on MTX-naïve, early RA patients

			TCZ 8 mg/kg + MTX N=290	TCZ 8 mg/kg + placebo N=292	TCZ 4 mg/kg + MTX N=288	Placebo + MTX N=287
		Primary Endpoint				
DAS28 Remission						
	Week 24	n (%)	130 (44.8)***	113 (38.7)***	92 (31.9)	43 (15.0)
		Key Secondary Endpoints				
DAS 28 remission						
	Week 52	n (%),	142 (49.0)***	115 (39.4)	98 (34.0)	56 (19.5)
ACR						
	Week 24	ACR20, n (%)	216 (74.5)*	205 (70.2)	212 (73.6)	187 (65.2)
		ACR50, n (%)	165 (56.9)**	139 (47.6)	138 (47.9)	124 (43.2)
		ACR70, n (%)	112 (38.6)**	88 (30.1)	100 (34.7)	73 (25.4)
	Week 52	ACR20, n (%)	195 (67.2)*	184 (63.0)	181 (62.8)	164 (57.1)
		ACR50, n (%)	162 (55.9)**	144 (49.3)	151 (52.4)	117 (40.8)
		ACR70, n (%)	125 (43.1)**	105 (36.0)	107 (37.2)	83 (28.9)
HAQ-DI (adjusted mean change from baseline)						
	Week 52		-0.81*	-0.67	-0.75	-0.64
		Radiographic Endpoints (mean change from baseline)				
	Week 52	mTSS	0.08***	0.26	0.42	1.14
		Erosion Score	0.05**	0.15	0.25	0.63
		JSN	0.03	0.11	0.17	0.51
		Radiographic Non-Progression n (%) (change from baseline in mTSS of ≤0)	226 (83)‡	226 (82)‡	211 (79)	194 (73)
		Exploratory Endpoints				
		Week 24: ACR/EULAR Boolean Remission, n (%)	47 (18.4)‡	38 (14.2)	43 (16.7)‡	25 (10.0)
		ACR/EULAR Index Remission, n (%)	73 (28.5)‡	60 (22.6)	58 (22.6)	41 (16.4)
		Week 52: ACR/EULAR Boolean Remission, n (%)	59 (25.7)‡	43 (18.7)	48 (21.1)	34 (15.5)
		ACR/EULAR Index Remission, n (%)	83 (36.1)‡	69 (30.0)	66 (29.3)	49 (22.4)

mTSS - modified Total Sharp Score
JSN - Joint space narrowing
All efficacy comparisons vs Placebo + MTX. ***p≤0.0001; **p<0.001; *p<0.05;
‡p-value < 0.05 vs. Placebo + MTX, but endpoint was exploratory (not included in the hierarchy of statistical testing and has therefore not been controlled for multiplicity)

Paediatric population

sJIA Patients

Clinical efficacy

The efficacy of tocilizumab for the treatment of active sJIA was assessed in a 12 week randomised, double blind, placebo-controlled, parallel group, two arm study. Patients included in the trial had a total disease duration of at least 6 months and active disease but were not experiencing an acute flare requiring corticosteroid doses of more than 0.5 mg/kg prednisone equivalent. Efficacy for the treatment of macrophage activation syndrome has not been investigated.

Patients (treated with or without MTX) were randomised (tocilizumab:placebo = 2:1) to one of two treatment groups, 75 patients received tocilizumab infusions every two weeks, either 8 mg/kg for

patients ≥ 30 kg or 12 mg/kg for patients < 30 kg and 37 patients were assigned to receiving placebo infusions every two weeks. Corticosteroid tapering was permitted from week six for patients who achieved a JIA ACR70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated in the open label phase at weight appropriate dosing.

Clinical response
The primary endpoint was the proportion of patients with at least 30% improvement in the JIA ACR core set (JIA ACR30 response) at week 12 and absence of fever (no temperature recording ≥ 37.5°C in the preceding 7 days). Eighty five percent (64/75) of tocilizumab treated patients and 24.3% (9/37) of placebo treated patients achieved this endpoint. These proportions were highly significantly different (p<0.0001).

The percent of patients achieving JIA ACR 30, 50, 70 and 90 responses are shown in Table 7.

Table 7. JIA ACR response rates at week 12 (% patients)

Response Rate	**Tocilizumab N = 75**	**Placebo N = 37**
JIA ACR 30	90.7%[1]	24.3%
JIA ACR 50	85.3%[1]	10.8%
JIA ACR 70	70.7%[1]	8.1%
JIA ACR 90	37.3%[1]	5.4%

[1] *p<0.0001, tocilizumab vs. placebo*

Systemic Effects
In the tocilizumab treated patients, 85% who had fever due to sJIA at baseline were free of fever (no temperature recording ≥ 37.5°C in the preceding 14 days) at week 12 versus 21% of placebo patients (p<0.0001).

The adjusted mean change in the pain VAS after 12 weeks of tocilizumab treatment was a reduction of 41 points on a scale of 0 - 100 compared to a reduction of 1 for placebo patients (p<0.0001).

Corticosteroid Tapering
Patients achieving a JIA ACR70 response were permitted corticosteroid dose reduction. Seventeen (24%) tocilizumab treated patients versus 1 (3%) placebo patient were able to reduce their dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR30 flare or occurrence of systemic symptoms to week 12 (p=0.028). Reductions in corticosteroids continued, with 44 patients off oral corticosteroids at week 44, while maintaining JIA ACR responses.

Health related and quality of life outcomes
At week 12, the proportion of tocilizumab treated patients showing a minimally clinically important improvement in the Childhood Health Assessment Questionnaire – Disability Index (defined as an individual total score decrease of ≥ 0.13) was significantly higher than in placebo treated patients, 77% versus 19% (p<0.0001).

Laboratory Parameters
Fifty out of seventy five (67%) tocilizumab treated patients had a haemoglobin < LLN at baseline. Forty (80%) of these patients had an increase in their haemoglobin to within the normal range at week 12, in comparison to 2 out of 29 (7%) of placebo treated patients with haemoglobin < LLN at baseline (p<0.0001).

pJIA Patients
Clinical efficacy
The efficacy of tocilizumab was assessed in a three-part study WA19977 including an open-label extension in children with active pJIA. Part I consisted of a 16-week active tocilizumab treatment lead-in period (n=188) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period (n=163), followed by Part III, a 64-week open-label period. In Part 1, eligible patients ≥ 30 kg received tocilizumab at 8 mg/kg IV every 4 weeks for 4 doses. Patients < 30 kg were

randomized 1:1 to receive either tocilizumab 8 mg/kg or 10 mg/kg IV every 4 weeks for 4 doses. Patients who completed Part I of the study and achieved at least a JIA ACR30 response at week 16 compared to baseline were eligible to enter the blinded withdrawal period (Part II) of the study. In Part II, patients were randomized to tocilizumab (same dose received in Part I) or placebo in a 1:1 ratio, stratified by concurrent MTX use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR30 flare criteria (relative to Week 16) and qualified for escape to tocilizumab therapy (same dose received in Part I).

Clinical response
The primary endpoint was the proportion of patients with a JIA ACR30 flare at week 40 relative to week 16. Forty eight percent (48.1%, 39/81) of the patients treated with placebo flared compared with 25.6% (21/82) of tocilizumab treated patients. These proportions were statistically significantly different (p=0.0024).

At the conclusion of Part I, JIA ACR 30/50/70/90 responses were 89.4%, 83.0%, 62.2%, and 26.1%, respectively.

During the withdrawal phase (Part II), the percentage of patients achieving JIA ACR 30, 50, and 70 responses at Week 40 relative to baseline are shown in Table 8. In this statistical analysis, patients who flared (and escaped to TCZ) during Part II or who withdrew, were classified as non-responders. An additional analyses of JIA ACR responses, considering observed data at Week 40, regardless of flare status, showed that by Week 40, 95.1% of patients who had received continuous TCZ therapy, had achieved JIA ACR30 or higher.

Table 8. JIA ACR Response Rates at Week 40 Relative to baseline (Percentage of Patients)

Response Rate	Tocilizumab N=82	Placebo N=81
ACR 30	74.4%*	54.3%*
ACR 50	73.2%*	51.9%*
ACR 70	64.6%*	42.0%*

** p<0.01, tocilizumab vs. placebo*

The number of active joints was significantly reduced compared to baseline in patients receiving tocilizumab compared to placebo (adjusted mean changes of -14.3 vs -11.4, p=0.0435). The physician's global assessment of disease activity, as measured on a 0-100 mm scale, showed a greater reduction in disease activity for tocilizumab compared to placebo (adjusted mean changes of -45.2 mm vs -35.2 mm, p=0.0031).

The adjusted mean change in the pain VAS after 40 weeks of tocilizumab treatment was 32.4 mm on a 0-100 mm scale compared to a reduction of 22.3 mm for placebo patients (highly statistically significant; p=0.0076).

The ACR response rates were numerically lower for patients with prior biologic treatment as shown in Table 9 below.

Table 9. Number and Proportion of Patients with a JIA ACR30 Flare and Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 40, by Previous Biologic Use (ITT Population - Study Part II)

	Placebo		All TCZ	
Biologic Use	**Yes (N = 23)**	**No (N = 58)**	**Yes (N = 27)**	**No (N = 55)**
JIA ACR30 Flare	18 (78.3)	21 (36.2)	12 (44.4)	9 (16.4)
JIA ACR30 Response	6 (26.1)	38 (65.5)	15 (55.6)	46 (83.6)
JIA ACR50 Response	5 (21.7)	37 (63.8)	14 (51.9)	46 (83.6)
JIA ACR70 Response	2 (8.7)	32 (55.2)	13 (48.1)	40 (72.7)
JIA ACR90 Response	2 (8.7)	17 (29.3)	5 (18.5)	32 (58.2)

Patients randomized to tocilizumab had fewer ACR30 flares and higher overall ACR responses than patients receiving placebo regardless of a history of prior biologic use.

CRS

The efficacy of RoActemra for the treatment of CRS was assessed in a retrospective analysis of data from clinical trials of CAR T-cell therapies (tisagenlecleucel and axicabtagene ciloleucel) for hematological malignancies. Evaluable patients had been treated with tocilizumab 8 mg/kg (12 mg/kg for patients < 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CRS; only the first episode of CRS was included in the analysis. The efficacy population for the tisagenlecleucel cohort included 28 males and 23 females (total 51 patients) of median age 17 years (range, 3–68 years). The median time from start of CRS to first dose of tocilizumab was 3 days (range, 0–18 days). Resolution of CRS was defined as lack of fever and off vasopressors for at least 24 hours. Patients were considered responders if CRS resolved within 14 days of the first dose of tocilizumab, if no more than 2 doses of RoActemra were needed, and no drugs other than RoActemra and corticosteroids were used for treatment. Thirty-nine patients (76.5%; 95% CI: 62.5%–87.2%) achieved a response. In an independent cohort of 15 patients (range: 9–75 years old) with axicabtagene ciloleucel-induced CRS, 53% responded.

The European Medicines Agency has waived the obligation to submit the results of studies with RoActemra in all subsets of the paediatric population in treatment of cytokine release syndrome associated with chimeric antigen receptor (CAR) T cell therapy.

5.2 Pharmacokinetic properties

RA Patients

Intravenous use

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with a one-hour infusion of 4 or 8 mg/kg tocilizumab every 4 weeks for 24 weeks or with 162 mg tocilizumab given subcutaneously either once a week or every other week for 24 weeks.

The following parameters (predicted mean ± SD) were estimated for a dose of 8 mg/kg tocilizumab given every 4 weeks: steady-state area under curve (AUC) = 38000 ± 13000 h µg/mL, trough concentration (C_{min}) = 15.9 ± 13.1 µg/mL and maximum concentration (C_{max}) = 182 ± 50.4 µg/mL, and the accumulation ratios for AUC and C_{max} were small, 1.32 and 1.09, respectively. The accumulation ratio was higher for C_{min} (2.49), which was expected based on the non-linear clearance contribution at lower concentrations. Steady-state was reached following the first administration for C_{max} and after 8 and 20 weeks for AUC and C_{min}, respectively. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 50000 ± 16800 µg•h/mL, 24.4 ± 17.5 µg/mL, and 226 ± 50.3 µg/mL, respectively, which are higher than mean exposure values for the patient population (i.e. all body weights) reported above. The dose-response curve for tocilizumab flattens at higher exposure,

resulting in smaller efficacy gains for each incremental increase in tocilizumab concentration such that clinically meaningful increases in efficacy were not demonstrated in patients treated with > 800 mg of tocilizumab. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended (see section 4.2).

Distribution
In RA patients the central volume of distribution was 3.72, the peripheral volume of distribution was 3.35 resulting in a volume of distribution at steady state of 7.07.

Elimination
Following intravenous administration, tocilizumab undergoes biphasic elimination from the circulation. The total clearance of tocilizumab was concentration-dependent and is the sum of the linear and non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 9.5 mL/h. The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

The $t_{1/2}$ of tocilizumab was concentration-dependent. At steady-state following a dose of 8 mg/kg every 4 weeks, the effective $t_{1/2}$ decreased with decreasing concentrations within a dosing interval from 18 days to 6 days.

Linearity
Pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in the AUC and C_{min} was observed for doses of 4 and 8 mg/kg every 4 weeks. C_{max} increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 3.2 and 30 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

Special populations
Renal impairment: No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been conducted. Most of the patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 mL/min and ≥ 50 mL/min) did not impact the pharmacokinetics of tocilizumab.

Hepatic impairment: No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been conducted.

Age, gender and ethnicity: Population pharmacokinetic analyses in RA patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of tocilizumab.

sJIA Patients:
The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 140 sJIA patients treated with 8 mg/kg IV every 2 weeks (patients with a body weight ≥ 30 kg) 12 mg/kg IV every 2 weeks (patients with a body weight < 30 kg), 162 mg SC every week (patients weighing ≥ 30 kg), 162 mg SC every 10 days or every 2 weeks (patients weighing below 30 kg).

Table 10. Predicted mean ± SD PK parameters at steady-state after IV dosing in sJIA

RoActemra PK Parameter	**8 mg/kg Q2W ≥ 30 kg**	**12 mg/kg Q2W below 30 kg**
C_{max} (µg/mL)	256 ± 60.8	274 ± 63.8
C_{trough} (µg/mL)	69.7 ± 29.1	68.4 ± 30.0
C_{mean} (µg/mL)	119 ± 36.0	123 ± 36.0
Accumulation C_{max}	1.42	1.37
Accumulation C_{trough}	3.20	3.41
Accumulation C_{mean} or AUC_{τ}*	2.01	1.95

*τ = 2 weeks for IV regimens

After IV dosing, approximately 90% of the steady-state was reached by week 8 for both the 12 mg/kg (BW < 30 kg) and 8 mg/kg Q2W (BW ≥ 30 kg) regimens.

In sJIA patients, the central volume of distribution was 1.87 L and the peripheral volume of distribution was 2.14 L resulting in a volume of distribution at a steady state of 4.01 L. The linear clearance estimated as a parameter in the population pharmacokinetic analysis, was 5.7 mL/h.

The half life of tocilizumab in sJIA patients is up to 16 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 12 mg/kg for body weight < 30 kg) at week 12.

pJIA Patients:
The pharmacokinetics of tocilizumab in pJIA patients was characterized by a population pharmacokinetic analysis which included 237 patients who were treated with 8 mg/kg IV every 4 weeks (patients weighing ≥ 30 kg), 10 mg/kg IV every 4 weeks (patients weighing below 30 kg), 162 mg SC every 2 weeks (patients weighing ≥ 30 kg), or 162 mg SC every 3 weeks (patients weighing below 30 kg).

Table 11. Predicted mean ± SD PK parameters at steady-state after IV dosing in pJIA

RoActemra PK Parameter	**8 mg/kg Q4W ≥ 30 kg**	**10 mg/kg Q4W below 30 kg**
C_{max} (µg/mL)	183 ± 42.3	168 ± 24.8
C_{trough} (µg/mL)	6.55 ± 7.93	1.47 ± 2.44
C_{mean} (µg/mL)	42.2 ± 13.4	31.6 ± 7.84
Accumulation C_{max}	1.04	1.01
Accumulation C_{trough}	2.22	1.43
Accumulation C_{mean} or AUC_{τ}*	1.16	1.05

*τ = 4 weeks for IV regimens

After IV dosing, approximately 90% of the steady-state was reached by week 12 for the 10 mg/kg (BW < 30 kg), and by week 16 for the 8 mg/kg (BW ≥ 30 kg) dose.

The half life of tocilizumab in pJIA patients is up to 16 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 10 mg/kg for body weight < 30 kg) during a dosing interval at steady state.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Carcinogenicity studies were not performed because IgG1 monoclonal antibodies are not deemed to have intrinsic carcinogenic potential.

Available non-clinical data demonstrated the effect of IL-6 on malignant progression and apoptosis resistance to various cancer types. This data does not suggest a relevant risk for cancer initiation and progression under tocilizumab treatment. Additionally, proliferative lesions were not observed in a 6-month chronic toxicity study in cynomolgus monkeys or in IL-6 deficient mice.

Available non-clinical data do not suggest an effect on fertility under tocilizumab treatment. Effects on endocrine active and reproductive system organs were not observed in a chronic cynomolgus monkey toxicity study and reproductive performance was not affected in IL-6 deficient mice. Tocilizumab administered to cynomolgus monkeys during early gestation, was observed to have no direct or indirect harmful effect on pregnancy or embryonal-foetal development. However, a slight increase in abortion/embryonal-foetal death was observed with high systemic exposure (> 100 x human exposure) in the 50 mg/kg/day high-dose group compared to placebo and other low-dose groups. Although IL-6 does not seem to be a critical cytokine for foetal growth or the immunological control of the maternal/foetal interface, a relation of this finding to tocilizumab cannot be excluded.

Treatment with a murine analogue did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Polysorbate 80
Disodium phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 30 months

Diluted product: After dilution, the prepared solution for infusion is physically and chemically stable in sodium chloride 9 mg/mL (0.9%) solution for injection at 30ºC for 24 hours.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store vials in a refrigerator (2°C–8°C). Do not freeze.

Keep the vial(s) in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

RoActemra is supplied in a vial (type I glass) with a stopper (butyl rubber) containing 4 mL, 10 mL or 20 mL concentrate. Pack sizes of 1 and 4 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for dilution prior to administration
Parenteral medicinal products should be inspected visually for particulate matter or discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted.

RA and CRS Patients (≥ 30 kg)
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (0.4 mL/kg) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

Use in the paediatric population

sJIA, pJIA and CRS Patients ≥ 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.4 mL/kg**) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

sJIA and CRS Patients < 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 50 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.6 mL/kg**) should be withdrawn from the vial and placed in the 50 mL infusion bag. This should be a final volume of 50 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

pJIA Patients < 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 50 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.5 mL/kg**) should be withdrawn from the vial and placed in the 50 mL infusion bag. This should be a final volume of 50 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

RoActemra is for single-use only.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/001
EU/1/08/492/002
EU/1/08/492/003
EU/1/08/492/004
EU/1/08/492/005
EU/1/08/492/006

9. DATE OF FIRST AUTHORISATION/DATE OF LATEST RENEWAL

Date of first authorisation: 16 January 2009
Date of last renewal: 25 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 162 mg of tocilizumab in 0.9 mL.

Tocilizumab is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against soluble and membrane-bound interleukin 6 receptors.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

A colourless to slightly yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RoActemra, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

RoActemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

RoActemra is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

4.2 Posology and method of administration

Tocilizumab SC formulation is administered with a single-use PFS+NSD. Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA, sJIA, pJIA and / or GCA. The first injection should be performed under the supervision of a qualified health care professional. A patient or parent/guardian can self-inject RoActemra only if the physician determines that it is appropriate and the patient or parent/guardian agrees to medical follow-up as necessary and has been trained in proper injection technique.

Patients who transition from tocilizumab IV therapy to SC administration should administer the first SC dose at the time of the next scheduled IV dose under the supervision of a qualified health care professional.

All patients treated with RoActemra should be given the Patient Alert Card.

Suitability of the patient or parent/guardian for subcutaneous home use should be assessed and patients or parent/guardian instructed to inform a healthcare professional before administering the next dose if they experience symptoms of an allergic reaction. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see section 4.4).

Posology

RA
The recommended posology is subcutaneous 162 mg once every week.

Limited information is available regarding switching patients from RoActemra intravenous formulation to RoActemra subcutaneous fixed dose-formulation. The once every week dosing interval should be followed.

Patients transitioning from intravenous to subcutaneous formulation should administer their first subcutaneous dose instead of the next scheduled intravenous dose under the supervision of a qualified healthcare professional.

GCA
The recommended posology is subcutaneous 162 mg once every week in combination with a tapering course of glucocorticoids. RoActemra can be used alone following discontinuation of glucocorticoids. RoActemra monotherapy should not be used for the treatment of acute relapses (see 4.4).

Based upon the chronic nature of GCA, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

RA and GCA
Dose adjustments due to laboratory abnormalities (see section 4.4).

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x Upper Limit of Normal (ULN)	Dose modify concomitant DMARDs (RA) or immunomodulatory agents (GCA) if appropriate. For persistent increases in this range, reduce RoActemra dose frequency to every other week injection or interrupt RoActemra until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised. Restart with weekly or every other week injection, as clinically appropriate.
> 3 to 5 x ULN	Interrupt RoActemra dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN. For persistent increases > 3 x ULN (confirmed by repeat testing, see 4.4.), discontinue RoActemra.
> 5 x ULN	Discontinue RoActemra.

- Low absolute neutrophil count (ANC)

In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/L

Laboratory Value (cells x 10^9/ L)	Action
ANC > 1	Maintain dose.
ANC 0.5 to 1	Interrupt RoActemra dosing. When ANC increases > 1 x 10^9/ L resume RoActemra dosing every other week and increase to every week injection, as clinically appropriate.
ANC < 0.5	Discontinue RoActemra.

- Low platelet count

Laboratory Value (cells x 10^3/ μL)	Action
50 to 100	Interrupt RoActemra dosing. When platelet count > 100 x 10^3/ μL resume RoActemra dosing every other week and increase to every week injection as clinically appropriate.
< 50	Discontinue RoActemra.

RA and GCA
Missed dose
If a patient misses a subcutaneous weekly injection of RoActemra within 7 days of the scheduled dose, he/she should be instructed to take the missed dose on the next scheduled day. If a patient misses a subcutaneous once every other week injection of RoActemra within 7 days of the scheduled dose, he/she should be instructed to take the missed dose immediately and the next dose on the next scheduled day.

Special populations

Elderly:
No dose adjustment is required in patients aged 65 years and older.

Renal impairment:
No dose adjustment is required in patients with mild or moderate renal impairment. RoActemra has not been studied in patients with severe renal impairment (see section 5.2). Renal function should be monitored closely in these patients.

Hepatic impairment:
RoActemra has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made.

Paediatric patients
The safety and efficacy of RoActemra subcutaneous formulation in children from birth to less than 1 year have not been established. There is no data.

A change in dose should only be based on a consistent change in the patient's body weight over time. RoActemra can be used alone or in combination with MTX.

sJIA Patients
The recommended posology in patients above 1 year of age is subcutaneous 162 mg once every week in patients weighing greater than or equal to 30 kg or subcutaneous 162 mg once every 2 weeks in patients weighing less than 30 kg.
Patients must have a minimum body weight of 10 kg when receiving RoActemra subcutaneously.

pJIA Patients:
The recommended posology in patients above 2 years of age is subcutaneous 162 mg once every 2 weeks in patients weighing greater than or equal to 30 kg or subcutaneous 162 mg once every 3 weeks in patients weighing less than 30 kg.

Dose adjustments due to laboratory abnormalities (sJIA and pJIA)

If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may effect laboratory values in sJIA or pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Liver enzyme abnormalities

Laboratory Value	**Action**
> 1 to 3 x ULN	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, interrupt RoActemra until ALT/AST have normalized.
> 3 x ULN to 5x ULN	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN
> 5x ULN	Discontinue RoActemra. The decision to discontinue RoActemra in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/ L)	**Action**
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases to > 1 x 10^9/ L resume RoActemra
ANC < 0.5	Discontinue RoActemra The decision to discontinue RoActemra in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

Laboratory Value (cells x $10^3/\mu L$)	**Action**
50 to 100	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing When platelet count is > 100 x $10^3/\mu l$ resume RoActemra
< 50	Discontinue RoActemra. The decision to discontinue RoActemra in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Reduction of tocilizumab dosing frequency due to laboratory abnormalities has not been studied in sJIA or pJIA patients.

The safety and efficacy of RoActemra subcutaneous formulation in children with conditions other than sJIA or pJIA have not been established.

Available data with the IV formulation suggest that clinical improvement is observed within 12 weeks of initiation of treatment with RoActemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

Missed dose
If a sJIA patient misses a subcutaneous weekly injection of RoActemra within 7 days of the scheduled dose, he/she should be instructed to take the missed dose on the next scheduled day. If a patient misses a subcutaneous once every 2 week injection of RoActemra within 7 days of the scheduled dose, he/she should be instructed to take the missed dose immediately and the next dose on the next scheduled day.

If a pJIA patient misses a subcutaneous injection of RoActemra within 7 days of the scheduled dose, he/she should take the missed dose as soon as they remember and take the next dose at the regular scheduled time. If a patient misses a subcutaneous injection of RoActemra by more than 7 days of the scheduled dose or is unsure when to inject RoActemra, call the doctor or pharmacist.

Method of administration
RoActemra is for subcutaneous use.
After proper training in injection technique, patients may self-inject with RoActemra if their physician determines that it is appropriate. The total content (0.9 mL) of the pre-filled syringe should be administered as a subcutaneous injection. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

The pre-filled syringe should not be shaken.

Comprehensive instructions for the administration of RoActemra in a pre-filled syringe are given in the package leaflet, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

RoActemra subcutaneous formulation is not intended for intravenous administration.

RoActemra subcutaneous formulation is not intended to be given to children with sJIA weighing less than 10 kg.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections
Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra (see section 4.8, Undesirable effects). RoActemra treatment must not be initiated in patients with active infections (see section 4.3). Administration of RoActemra should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). Healthcare professionals should exercise caution when considering the use of RoActemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g.) diverticulitis, diabetes and interstitial lung disease which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents such as RoActemra as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients (which includes younger children with sJIA or pJIA who may be less able to communicate their symptoms) and parents/guardians of sJIA or pJIA patients, should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Tuberculosis
As recommended for other biological treatments, all patients should be screened for latent tuberculosis (TB) infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoActemra. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised.

Patients should be advised to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade (fever) suggestive of a tuberculosis infection occur during or after therapy with RoActemra.

Viral reactivation
Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for RA. In clinical studies with RoActemra, patients who screened positive for hepatitis were excluded.

Complications of diverticulitis
Events of diverticular perforations as complications of diverticulitis have been reported uncommonly in patients treated with RoActemra (see section 4.8). RoActemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation.

Hypersensitivity reactions
Serious hypersensitivity reactions, including anaphylaxis have been reported in association with RoActemra (see section 4.8). Such reactions may be more severe, and potentially fatal in patients who

have experienced hypersensitivity reactions during previous treatment with RoActemra even if they have received premedication with steroids and antihistamines. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of RoActemra should be stopped immediately, appropriate therapy initiated and tocilizumab should be permanently discontinued.

Active hepatic disease and hepatic impairment
Treatment with RoActemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases, therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8).

Hepatic transaminase elevations
In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with RoActemra treatment, without progression to hepatic injury (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with RoActemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Caution should be exercised when considering initiation of RoActemra treatment in patients with elevated ALT or AST > 1.5 x ULN. In patients with baseline ALT or AST > 5 x ULN, treatment is not recommended.

In RA and GCA patients, ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see section 4.2. For ALT or AST elevations > 3–5 x ULN, RoActemra treatment should be interrupted.

In sJIA and pJIA patients, ALT and AST should be monitored at the time of the second administration and thereafter according to good clinical practice (see section 4.2).

Haematological abnormalities
Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

In patients not previously treated with RoActemra, initiation is not recommended in patients with an ANC below 2 x 10^9/L. Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/ μL). In patients who develop an ANC < 0.5 x 10^9/ L or a platelet count < 50 x 10^3/μL, continued treatment is not recommended.

Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with RoActemra to date.

In RA and GCA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2.

In sJIA and pJIA patients, neutrophils and platelets should be monitored at the time of the second administration and thereafter according to good clinical practice (see section 4.2).

Lipid parameters
Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with RoActemra (see section 4.8). In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents.

In all patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of RoActemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Neurological disorders
Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with RoActemra is currently unknown.

Malignancy
The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy.

Vaccinations
Live and live attenuated vaccines should not be given concurrently with RoActemra as clinical safety has not been established. In a randomized open-label study, adult RA patients treated with RoActemra and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus toxoid vaccines which was comparable to the response seen in patients on MTX only. It is recommended that all patients particularly paediatric or elderly patients, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating RoActemra therapy. The interval between live vaccinations and initiation of RoActemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Cardiovascular risk
RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care.

Combination with TNF antagonists
There is no experience with the use of RoActemra with TNF antagonists or other biological treatments for RA patients. RoActemra is not recommended for use with other biological agents.

GCA
RoActemra monotherapy should not be used for the treatment of acute relapses as efficacy in this setting has not been established. Glucocorticoids should be given according to medical judgement and practice guidelines.

sJIA
Macrophage activation syndrome (MAS) is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, RoActemra has not been studied in patients during an episode of active MAS.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Concomitant administration of a single dose of 10 mg/kg RoActemra with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids on RoActemra clearance in RA patients. In GCA patients, no effect of cumulative corticosteroid dose on RoActemra exposure was observed.

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as RoActemra, is introduced.

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression. RoActemra normalises expression of these enzymes.

In a study in RA patients, levels of simvastatin (CYP3A4) were decreased by 57% one week following a single dose of tocilizumab, to the level similar to, or slightly higher than, those observed in healthy subjects.

When starting or stopping therapy with tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2 or 2C9 (e.g. methylprednisolone, dexamethasone, (with the possibility for oral glucocorticoid withdrawal syndrome), atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Pregnancy

There are no adequate data from the use of RoActemra in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose (see section 5.3). The potential risk for humans is unknown.

RoActemra should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is unknown whether tocilizumab is excreted in human breast milk. The excretion of RoActemra in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with RoActemra should be made taking into account the benefit of breast-feeding to the child and the benefit of RoActemra therapy to the woman.

Fertility

Available non-clinical data do not suggest an effect on fertility under RoActemra treatment.

4.7 Effects on ability to drive and use machines

RoActemra has a minor influence on the ability to drive and use machines (see section 4.8, dizziness).

4.8 Undesirable effects

Summary of the safety profile

The safety profile comes from 4510 patients exposed to RoActemra in clinical trials; the majority of these patients were participating in adult RA studies (n=4009), while the remaining experience comes from GCA (n=149), pJIA (n=240) and sJIA (n=112) studies. The safety profile of RoActemra across these indications remains similar and undifferentiated.

The most commonly reported Adverse Drug Reactions (ADRs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The most serious ADRs were serious infections, complications of diverticulitis, and hypersensitivity reactions.

Tabulated list of adverse reactions
ADRs from clinical trials and/or post marketing experience with RoActemra based on spontaneous case reports, literature cases and cases from non-interventional study programs are listed in Table 1 and are presented by MedDRA system organ class. The corresponding frequency category for each AR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) rare, (≥1/10,000 to <1/1,000) or very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. List of ADRs occurring in patients treated with RoActemra.

MedDRA System Organ Class	**Frequency categories with preferred terms**		
	Very Common	**Common**	**Uncommon**
Blood and lymphatic system disorders		Leukopenia, Neutropenia, Hypofibrinogenaemia	
Endocrine disorders			Hypothyroidism
Eye disorders		Conjunctivitis	
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer
General disorders and administration site conditions	Injection site reaction	Peripheral oedema Hypersensitivity reaction,	
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis
Investigations		Hepatic transaminases increased, Weight increased, Total bilirubin increased*	
Metabolism and nutrition disorders	Hypercholesterolaemia*		Hypertriglyceridaemia
Nervous system disorders		Headache, Dizziness	
Renal and urinary disorders			Nephrolithiasis
Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea	
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria	
Vascular disorders		Hypertension	

* Includes elevations collected as part of routine laboratory monitoring (see text below)

RA
Intravenous use
The safety of RoActemra has been studied in 5 Phase III, double-blind controlled trials and their extension periods.

The *all control* population includes all patients from the double-blind phases of each core study from randomization until either the first change in the treatment regimen, or two years is reached. The control period in 4 of the studies was 6 months and in 1 study was up to 2 years. In the double-blind

controlled studies 774 patients received RoActemra 4 mg/kg in combination with MTX, 1870 patients received tocilizumab 8 mg/kg in combination with MTX/other DMARDs and 288 patients received tocilizumab 8 mg/kg monotherapy.

The *all exposure* population includes all patients who received at least one dose of RoActemra either in the double-blind control period or open label extension phase in studies. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year; 2806 received treatment for at least 2 years and 1222 for 3 years.

Description of selected adverse reactions

Infections
In the 6-month controlled studies the rate of all infections reported with RoActemra 8 mg/kg plus DMARD treatment was 127 events per 100 patient years compared to 112 events per 100 patient years in the placebo plus DMARD group. In the long-term exposure population, the overall rate of infections with RoActemra was 108 events per 100 patient years exposure.

In 6-month controlled clinical studies, the rate of serious infections with RoActemra 8 mg/kg plus DMARDs was 5.3 events per 100 patient years exposure compared to 3.9 events per 100 patient years exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 patient years of exposure in the RoActemra group and 1.5 events per 100 patient years of exposure in the MTX group.

In the all exposure population the overall rate of serious infections was 4.7 events per 100 pt years. Reported serious infections, some with fatal outcome, included pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, bacterial arthritis. Cases of opportunistic infections have also been reported.
Interstitial lung disease
Impaired lung function may increase the risk for developing infections. There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Gastrointestinal perforation
During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with RoActemra therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Reports of gastrointestinal perforation on RoActemra were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.

Infusion reactions
In the 6-month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the tocilizumab 8 mg/kg plus DMARD group and 5.1% of patients in the placebo plus DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment limiting.

The rate of anaphylactic reactions (occurring in a total of 6/3778patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with RoActemra and requiring treatment discontinuation were reported in a total of 13 out of 3778 patients (0.3%) treated with RoActemra during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with intravenous RoActemra (see section 4.4).

Immunogenicity
A total of 2,876 patients have been tested for anti-RoActemra antibodies in the 6-month controlled clinical trials. Of the 46 patients (1.6%) who developed anti-RoActemra antibodies, 6 had an

associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. Thirty patients (1.1%) developed neutralising antibodies.

Haematological abnormalities:
Neutrophils
In the 6-month controlled trials decreases in neutrophil counts below 1 x 10^9/ L occurred in 3.4% of patients on RoActemra 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < 1 x 10^9/ L did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/ L were reported in 0.3% patients receiving RoActemra 8 mg/kg plus DMARDs. Infections with neutropenia have been reported.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials.

Platelets
In the 6-month controlled trials decreases in platelet counts below 100 x 10^3/ μL occurred in 1.7% of patients on RoActemra 8 mg/kg plus DMARDs compared to < 1% on placebo plus DMARDs. These decreases occurred without associated bleeding events.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials.

Very rare reports of pancytopenia have occurred in the post marketing setting.

Hepatic transaminase elevations
During the 6-month controlled trials transient elevations in ALT/AST > 3 x ULN were observed in 2.1% of patients on RoActemra 8 mg/kg compared to 4.9% of patients on MTX and in 6.5% of patients who received 8 mg/kg RoActemra plus DMARDs compared to 1.5% of patients on placebo plus DMARDs.

The addition of potentially hepatotoxic drugs (e.g. MTX) to RoActemra monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 x ULN were observed in 0.7% of RoActemra monotherapy patients and 1.4% of RoActemra plus DMARD patients, the majority of whom were discontinued permanently from tocilizumab treatment. These elevations were not associated with clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment. During the double-blind controlled period, the incidence of indirect bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, is 6.2% in patients treated with 8 mg/kg RoActemra + DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of > 1 to 2 x ULN and 0.4% had an elevation of > 2 x ULN.
During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevation in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials.

Lipid parameters
During the 6-month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving RoActemra in clinical trials experienced sustained elevations in total cholesterol ≥ 6.2 mmol/ L, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/ L. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled trials.

Malignancies
The clinical data are insufficient to assess the potential incidence of malignancy following exposure to RoActemra. Long-term safety evaluations are ongoing.

Skin Reactions
Very rare reports of Stevens-Johnson Syndrome have occurred in the post marketing setting.

Subcutaneous use
RA
The safety of subcutaneous RoActemra in RA includes a double-blind, controlled, multicenter study, SC-I. SC-I was a non-inferiority study that compared the efficacy and safety of RoActemra 162 mg administered every week versus 8 mg/kg intravenous in 1262 patients with RA. All patients received background non-biologic DMARD(s). The safety and immunogenicity observed for RoActemra administered subcutaneous was consistent with the known safety profile of intravenous RoActemra and no new or unexpected adverse drug reactions were observed (see Table 1). A higher frequency of injection site reactions was observed in the subcutaneous arms compared with placebo subcutaneous injections in the intravenous arms.

Injection site reactions
During the 6-month controlled period, in SC-I, the frequency of injection site reactions was 10.1% (64/631) and 2.4% (15/631) for the subcutaneous RoActemra and the subcutaneous placebo (intravenous group) weekly injections, respectively. These injection site reactions (including erythema, pruritus, pain and haematoma) were mild to moderate in severity. The majority was resolved without any treatment and none necessitated drug discontinuation.

Immunogenicity
In SC-I, a total of 625 patients treated with RoActemra 162mg weekly were tested for anti-RoActemra antibodies in the 6 month controlled period. Five patients (0.8%) developed positive anti-RoActemra antibodies; of these, all developed neutralizing anti-RoActemra antibodies. One patient was tested positive for IgE isotype (0.2%).

In SC-II, a total of 434 patients treated with RoActemra 162mg every other week were tested for anti-RoActemra antibodies in the 6 month controlled period. Seven patients (1.6%) developed positive antiRoActemra antibodies; of these, six (1.4%) developed neutralizing anti-RoActemra antibodies. Four patients were tested positive for IgE isotype (0.9%).

No correlation of antibody development to clinical response or adverse events was observed.

Haematological abnormalities:
Neutrophils
During routine laboratory monitoring in the RoActemra 6 month controlled clinical trial SC-I, a decrease in neutrophil count below 1×10^9/L occurred in 2.9% of patients on the subcutaneous weekly dose.

There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

Platelets
During routine laboratory monitoring in the RoActemra 6 month clinical trial SC-I, none of the patients on the SC weekly dose had a decrease in platelet count to $\leq 50 \times 10^3$ / μL.

Hepatic transaminase elevations
During routine laboratory monitoring in the RoActemra 6-month controlled clinical trial SC-I, elevation in ALT or AST ≥3 x ULN occurred in 6.5% and 1.4% of patients, respectively on the subcutaneous weekly dose.

Lipid parameters
During routine laboratory monitoring in the RoActemra 6 month controlled clinical trial SC-I, 19% of patients experienced sustained elevations in total cholesterol > 6.2 mmol/L (240 mg/dl), with 9% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L(160 mg/dL) on the subcutaneous weekly dose.

Subcutaneous Use
sJIA
The safety profile of subcutaneous RoActemra was evaluated in 51 paediatric patients (1 to 17 years of age) with sJIA. In general, the adverse drug reactions in patients with sJIA were similar in type to those seen in RA patients (see Undesirable Effects section above).

Infections
The rate of infection in sJIA patients treated with SC RoActemra was comparable to sJIA patients treated with IV RoActemra.

Injection Site Reactions (ISRs)
In the SC Study (WA28118), a total of 41.2% (21/51) sJIA patients experienced ISRs to RoActemra SC. The most common ISRs were erythema, pruritus, pain, and swelling at the injection site. The majority of ISRs reported were Grade 1 events and all ISRs reported were non-serious and none required patient withdrawal from treatment or dose interruption.

Immunogenicity
In the SC Study (WA28118), 46 of the 51 (90.2%) patients tested for anti-tocilizumab antibodies at baseline had at least one post-baseline screening assay result. No patient developed positive anti-tocilizumab antibodies post baseline.

Laboratory Abnormalities
In the 52-week open-label SC Study (WA28118), neutrophil count decrease to below 1×10^9/L occurred in 23.5% of patients treated with RoActemra SC. Decreases in platelet counts to below 100×10^3/μL occurred in 2% of the patients treated with RoActemra SC. An elevation in ALT or AST to ≥3 x ULN occurred in 9.8% and 4.0% patients treated with RoActemra SC, respectively.

Lipid parameters
In the 52-week open-label SC Study (WA28118), 23.4% and 35.4% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥130 mg/dL and total cholesterol value to ≥200 mg/dL at any time during study treatment, respectively.

Subcutaneous use
pJIA
The safety profile of subcutaneous RoActemra was also evaluated in 52 paediatric patients with pJIA. The total patient exposure to RoActemra in the pJIA all exposure population was 184.4 patient years for IV and 50.4 patient years for SC tocilizumab. In general, the safety profile observed in patients with pJIA was consistent with the known safety profile of RoActemra with the exception of ISRs (see Table 1). A higher frequency of pJIA patients experienced ISRs following SC RoActemra injections compared to adult RA.

Infections
In the SC RoActemra study, the rate of infection in pJIA patients treated with SC RoActemra was comparable with pJIA patients treated with IV RoActemra.

Injection Site Reactions
A total of 28.8% (15/52) pJIA patients experienced ISRs to RoActemra SC. These ISRs occurred in a 44% of patients ≥30 kg compared to 14.8% of patients below 30 kg. The most common ISRs were injection site erythema, swelling, hematoma, pain and pruritis. All ISRs reported were non-serious Grade 1 events, and none of the ISRs required patient withdrawal from treatment or dose interruption.

Immunogenicity
In the SC Study 5.8% [3/52] developed positive neutralizing anti-tocilizumab antibodies without developing a serious or clinically significant hypersensitivity reaction. Of these 3 patients, 1 subsequently withdrew from the study. No correlation between antibody development and clinical response or adverse events was observed

Laboratory Abnormalities
During routine laboratory monitoring in the RoActemra all exposure population, a decrease in neutrophil count below 1×10^9/L occurred in 15.4% of patients treated with SC RoActemra. An elevation in ALT or AST ≥3 x ULN occurred in 9.6% and 3.8% patients treated with RoActemra SC, respectively. No patients treated with SC RoActemra experienced a decrease in platelet count to ≤50×10^3 / μL.

Lipid parameters
In the SC Study, 14.3% and 12.8% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively.

Subcutaneous use
GCA
The safety of subcutaneous RoActemra has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the RoActemra all exposure population was 138.5 patient years during the 12 month double blind, placebo controlled phase of the study. The overall safety profile observed in the RoActemra treatment groups was consistent with the known safety profile of RoActemra (see Table 1).

Infections
The rate of infection/serious infection events was balanced between the RoActemra weekly group (200.2/9.7 events per 100 patient years) vs. placebo plus 26 weeks prednisone taper (156.0/4.2 events per 100 patient years) and placebo plus 52 weeks taper (210.2/12.5 events per 100 patient years) groups.

Injection site reactions
In the RoActemra subcutaneous weekly group, a total of 6% (6/100) patients reported an adverse reaction occurring at the site of a subcutaneous injection. No injection site reaction was reported as a serious adverse event or required treatment discontinuation.

Immunogenicity
In the RoActemra subcutaneous weekly group, one patient (1.1%, 1/95) developed positive neutralizing anti-RoActemra antibodies, though not of the IgE isotype. This patient did not develop a hypersensitivity reaction or injection site reaction.

Haematological abnormalities:
Neutrophils
During routine laboratory monitoring in the Roactemra 12 month controlled clinical trial, a decrease in neutrophil count below 1×10^9/L occurred in 4% of patients in the RoActemra subcutaneous weekly group. This was not observed in either of the placebo plus prednisone taper groups.

Platelets
During routine laboratory monitoring in the RoActemra 12 month controlled clinical trial, one patient (1%, 1/100) in the RoActemra subcutaneous weekly group had a single transient occurence of decrease in platelet count to <100×10^3 / μL without associated bleeding events. A decrease in platelet count below 100×10^3 / μL was not observed in either of the placebo plus prednisone taper groups.

Hepatic transaminase elevations
During routine laboratory monitoring in the RoActemra 12 month controlled clinical trial, elevation in ALT ≥3 x ULN occurred in 3% of patients in the RoActemra subcutaneous weekly group compared

to 2% in the placebo plus 52 week prednisone taper group and none in the placebo plus 26 week prednisone taper group. An elevation in AST > 3 ULN occurred in 1% of patients in the RoActemra subcutaneous weekly group, compared to no patients in either of the placebo plus prednisone taper groups.

Lipid parameters
During routine laboratory monitoring in the RoActemra 12 month controlled clinical trial, 34% of patients experienced sustained elevations in total cholesterol > 6.2 mmol/L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) in the RoActemra subcutaneous weekly group.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are limited data available on overdose with RoActemra. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg administered intravenously. No adverse reactions were observed.

No serious adverse reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg, although dose limiting neutropenia was observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors; ATC code: L04AC07.

Mechanism of action
Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.

Pharmacodynamic effects
In clinical studies with RoActemra, rapid decreases in CRP, erythrocyte sedimentation rate (ESR), serum amyloid A (SAA) and fibrinogen were observed. Consistent with the effect on acute phase reactants, treatment with RoActemra was associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through RoActemra decreasing the IL-6 driven effects on hepcidin production to increase iron availability. In RoActemra -treated patients, decreases in the levels of CRP to within normal ranges were seen as early as week 2, with decreases maintained while on treatment.

In GCA clinical study WA28119, similar rapid decreases in CRP and ESR were observed along with slight increases in mean corpuscular haemoglobin concentration. In healthy subjects administered RoActemra in doses from 2 to 28 mg/kg intravenously and 81 to 162 mg subcutaneously, absolute neutrophil counts decreased to their lowest 2 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner.

Patients demonstrate a comparable (to healthy subjects) decrease of absolute neutrophil counts following RoActemra administration (see section 4.8).

RA
Intravenous use
Clinical efficacy
The efficacy of RoActemra in alleviating the signs and symptoms of RA was assessed in five randomised, double-blind, multi-centre studies. Studies I-V enrolled patients ≥ 18 years of age with active RA diagnosed according to the American College of Rheumatology (ACR) criteria and who had at least eight tender and six swollen joints at baseline.

In Study I, RoActemra was administered intravenously every four weeks as monotherapy. In Studies II, III and V, RoActemra was administered intravenously every four weeks in combination with MTX vs. placebo and MTX. In Study IV, RoActemra was administered intravenously every 4 weeks in combination with other DMARDs vs. placebo and other DMARDs. The primary endpoint for each of the five studies was the proportion of patients who achieved an ACR 20 response at week 24.

Study I evaluated 673 patients who had not been treated with MTX within six months prior to randomisation and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response. The majority (67%) of patients were MTX-naïve. Doses of 8 mg/kg of RoActemra were given every four weeks as monotherapy. The comparator group was weekly MTX (dose titrated from 7.5 mg to a maximum of 20 mg weekly over an eight week period).

Study II, a two year study with planned analyses at week 24, week 52 and week 104, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of RoActemra or placebo were given every four weeks as blinded therapy for 52 weeks in combination with stable MTX (10 mg to 25 mg weekly). After week 52, all patients could receive open-label treatment with RoActemra 8 mg/kg. Of the patients who completed the study who were originally randomised to placebo + MTX, 86% received open-label RoActemra 8 mg/kg in year 2. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At week 52 and week 104 the co-primary endpoints were prevention of joint damage and improvement in physical function.

Study III evaluated 623 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg RoActemra or placebo were given every four weeks, in combination with stable MTX (10 mg to 25 mg weekly).

Study IV evaluated 1,220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg RoActemra or placebo were given every four weeks in combination with stable DMARDs.

Study V evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomisation. Doses of 4 or 8 mg/kg RoActemra or placebo were given every four weeks in combination with stable MTX (10 mg to 25 mg weekly).

Clinical response
In all studies, patients treated with RoActemra 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 2). In study I, superiority of RoActemra 8 mg/kg was demonstrated against the active comparator MTX.
The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the open label extension studies I-V.

In patients treated with RoActemra 8 mg/kg, significant improvements were noted on all individual components of the ACR response including: tender and swollen joint counts; patients and physician

global assessment; disability index scores; pain assessment and CRP compared to patients receiving placebo plus MTX or other DMARDs in all studies.

Patients in studies I – V had a mean Disease Activity Score (DAS28) of 6.5–6.8 at baseline. Significant reduction in DAS28 from baseline (mean improvement) of 3.1–3.4 was observed in RoActemra-treated patients compared to control patients (1.3-2.1). The proportion of patients achieving a DAS28 clinical remission (DAS28 < 2.6) was significantly higher in patients receiving RoActemra (28–34%) compared to 1–12% of control patients at 24 weeks. In study II, 65% of patients achieved a DAS28 < 2.6 at week 104 compared to 48% at 52 weeks and 33% of patients at week 24.

In a pooled analysis of studies II, III and IV, the proportion of patients achieving an ACR 20, 50 and 70 response was significantly higher (59% vs. 50%, 37% vs. 27%, 18% vs. 11%, respectively) in the tocilizumab 8 mg/kg plus DMARD vs. the tocilizumab 4 mg/kg plus DMARD group (p< 0.03). Similarly the proportion of patients achieving a DAS 28 remission (DAS28 < 2.6) was significantly higher (31% vs. 16% respectively) in patients receiving RoActemra 8 mg/kg plus DMARD than in patients receiving RoActemra 4 mg/kg plus DMARD (p< 0.0001).

Table 2. ACR responses in placebo-/MTX-/DMARDs-controlled studies (% patients)

	Study I AMBITION		**Study II LITHE**		**Study III OPTION**		**Study IV TOWARD**		**Study V RADIATE**	
Week	**TCZ 8 mg/kg**	**MTX**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**	**TCZ 8 mg/kg + DMARD**	**PBO + DMARD**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**
	N = 286	**N = 284**	**N = 398**	**N = 393**	**N = 205**	**N = 204**	**N = 803**	**N = 413**	**N = 170**	**N = 158**
ACR 20										
24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
52			56%***	25%						
ACR 50										
24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%
52			36%***	10%						
ACR 70										
24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%
52			20%***	4%						

TCZ - Tocilizumab
MTX - Methotrexate
PBO - Placebo
DMARD - Disease modifying anti-rheumatic drug
** - *p< 0.01, TCZ vs. PBO + MTX/DMARD*
*** - *p< 0.0001, TCZ vs. PBO + MTX/DMARD*

Major clinical response
After 2 years of treatment with RoActemra plus MTX, 14% of patients achieved a major clinical response (maintenance of an ACR70 response for 24 weeks or more).

Radiographic response
In Study II, in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with

significantly less radiographic progression in patients receiving RoActemra compared to control (Table 3).

In the open-label extension of Study II the inhibition of progression of structural joint damage in RoActemra plus MTX-treated patients was maintained in the second year of treatment. The mean change from baseline at week 104 in total Sharp-Genant score was significantly lower for patients randomised to RoActemra 8 mg/kg plus MTX ($p<0.0001$) compared with patients who were randomised to placebo plus MTX.

Table 3. Radiographic mean changes over 52 weeks in Study II

	PBO + MTX (+ TCZ from week 24) N = 393	**TCZ 8 mg/kg + MTX N = 398**
Total Sharp-Genant score	1.13	0.29*
Erosion score	0.71	0.17*
JSN score	0.42	0.12**

PBO - *Placebo*
MTX - *Methotrexate*
TCZ - *Tocilizumab*
JSN - *Joint space narrowing*
* - *p≤ 0.0001, TCZ vs. PBO + MTX*
** - *p< 0.005, TCZ vs. PBO + MTX*

Following 1 year of treatment with RoActemra plus MTX, 85% of patients(n=348) had no progression of structural joint damage, as defined by a change in the Total Sharp Score of zero or less, compared with 67% of placebo plus MTX-treated patients(n=290) ($p \leq 0.001$). This remained consistent following 2 years of treatment (83%; n=353). Ninety three percent (93%; n=271) of patients had no progression between week 52 and week 104.

Health-related and quality of life outcomes
RoActemra -treated patients reported an improvement in all patient-reported outcomes (Health Assessment Questionnaire Disability Index - HAQ-DI), Short Form-36 and Functional Assessment of Chronic Illness Therapy questionnaires. Statistically significant improvements in HAQ-DI scores were observed in patients treated with RoActemra compared with patients treated with DMARDs. During the open-label period of Study II, the improvement in physical function has been maintained for up to 2 years. At Week 52, the mean change in HAQ-DI was -0.58 in the RoActemra 8 mg/kg plus MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at Week 104 in the RoActemra 8 mg/kg plus MTX group (-0.61).

Haemoglobin levels
Statistically significant improvements in haemoglobin levels were observed with RoActemra compared with DMARDs ($p< 0.0001$) at week 24. Mean haemoglobin levels increased by week 2 and remained within normal range through to week 24.

RoActemra versus adalimumab in monotherapy
Study VI (WA19924), a 24 week double-blinded study that compared RoActemra monotherapy with adalimumab monotherapy, evaluated 326 patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the RoActemra arm received an intravenous (IV) infusion of RoActemra (8 mg/kg) every 4 weeks (q4w) and a subcutaneous (SC) placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab SC injection (40 mg) q2w plus an IV placebo infusion q4w.

A statistically significant superior treatment effect was seen in favour of RoActemra over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 4).

Table 4: Efficacy Results for Study VI (WA19924)

	ADA + Placebo (IV) N = 162	**TCZ + Placebo (SC) N = 163**	p-value[(a)]
Primary Endpoint - Mean Change from baseline at Week 24			
DAS28 (adjusted mean)	**-1.8**	**-3.3**	
Difference in adjusted mean (95% CI)	**-1.5 (-1.8, -1.1)**		**<0.0001**
Secondary Endpoints - Percentage of Responders at Week 24 [(b)]			
DAS28 < 2.6, n (%)	17 (10.5)	65 (39.9)	<0.0001
DAS28 ≤ 3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001
ACR20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR70 response, n (%)	29 (17.9)	53 (32.5)	0.0023

[a] *p value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.*
[b] *Non-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure*

The overall clinical adverse event profile was similar between RoActemra and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (RoActemra 11.7% vs. adalimumab 9.9%). The types of adverse drug reactions in the RoActemra arm were consistent with the known safety profile of RoActemra and adverse drug reactions were reported at a similar frequency compared with Table 1. A higher incidence of infections and infestations was reported in the RoActemra arm (48% vs. 42%), with no difference in the incidence of serious infections (3.1%). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with RoActemra compared with adalimumab. Four (2.5%) patients in the RoActemra arm and two (1.2%) patients in the adalimumab arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the RoActemra arm and five (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/L (25 mg/dL) for patients in the RoActemra arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the tocilizumab arm was consistent with the known safety profile of RoActemra and no new or unexpected adverse drug reactions were observed (see Table 1).

RA
Subcutaneous use
Clinical efficacy
The efficacy of subcutaneous administered RoActemra in alleviating the signs and symptoms of RA and radiographic response, was assessed in two randomised, double-blind, controlled, multi-center studies. For study I (SC-I), patients were required to be >18 years of age with moderate to severe active RA diagnosed according to ACR criteria who had at least 4 tender and 4 swollen joints at baseline. All patients received background non-biologic DMARD(s). For study II (SC-II), patients were required to be > 18 years of age with moderate to severe active RA diagnosed according to ACR criteria who had at least 8 tender and 6 swollen joints at baseline.

Switching from 8 mg/kg intravenous once every 4 weeks to 162 mg subcutaneous once every week, will alter exposure in the patient. The extent varies with the patient's body weight (increased in light body weight patients and decreased in heavy body weight patients) but clinical outcome is consistent with that observed in intravenous treated patients.

Clinical response
Study SC-I evaluated patients with moderate to severe active RA who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where

approximately 20% had a history of inadequate response to at least one TNF inhibitor. In SC-I, 1262 patients were randomized 1:1 to receive RoActemra subcutaneous 162 mg every week or RoActemra intravenous 8 mg/kg every four weeks in combination with non-biologic DMARD(s). The primary endpoint in the study was the difference in the proportion of patients who achieved an ACR20 response at week 24. The results from study SC-I is shown in Table 5.

Table 5. ACR responses in study SC-I (% patients) at Week 24

	SC-I[a]	
	TCZ SC 162 mg every week + DMARD N=558	TCZ IV 8 mg/kg + DMARD N=537
ACR20 Week 24	69.4%	73.4%
Weighted difference (95% CI)	-4.0 (-9.2, 1.2)	
ACR50 Week 24	47.0%	48.6%
Weighted difference (95% CI)	-1.8 (-7.5, 4.0)	
ACR70 Week 24	24.0%	27.9%
Weighted difference (95% CI)	-3.8 (-9.0, 1.3)	

TCZ = tocilizumab

a = Per Protocol Population

Patients in study SC-I had a mean Disease Activity Score (DAS28) at baseline of 6.6 and 6.7 on the subcutaneous and intravenous arms, respectively. At week 24, a significant reduction in DAS28 from baseline (mean improvement) of 3.5 was observed on both treatment arms, and a comparable proportion of patients had achieved DAS28 clinical remission (DAS28 < 2.6) on the subcutaneous (38.4%) and IV (36.9%) arms.

Radiographic response

The radiographic response of subcutaneous administered RoActemra was assessed in a double-blind, controlled, multicenter study in patients with active RA (SC-II). Study SC-II evaluated patients with moderate to severe active RA who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where approximately 20% had a history of inadequate response to at least one TNF inhibitor. Patients were required to be >18 years of age with active RA diagnosed according to ACR criteria who had at least 8 tender and 6 swollen joints at baseline. In SC-II, 656 patients were randomized 2:1 to RoActemra subcutaneous 162 mg every other week or placebo, in combination with non-biologic DMARD(s).

In study SC-II, inhibition of structural joint damage was assessed radiographically and expressed as a change from baseline in the van der Heijde modified mean total Sharp score (mTSS). At week 24, inhibition of structural damage was shown, with significantly less radiographic progression in patients receiving RoActemra subcutaneous compared to placebo (mean mTSS of 0.62 vs. 1.23, p=0.0149 (van Elteren). These results are consistent with those observed in patients treated with intravenous RoActemra.

In study SC-II, at week 24 there was ACR20 of 60.9%, ACR50 of 39.8% and ACR70 of 19.7% for patients treated with RoActemra subcutaneous every other week versus placebo ACR20 of 31.5%, ACR50 of 12.3% and ACR70 of 5.0%. Patients had mean DAS28 at baseline of 6.7 on subcutaneous and 6.6 on placebo arms. At week 24, a significant reduction in DAS28 from baseline of 3.1 was observed on subcutaneous and 1.7 on placebo arm, and for DAS28 < 2.6, 32.0% was observed on subcutaneous and 4.0% on placebo arm.

Health-related and quality of life outcomes
In study SC-I, the mean decrease in HAQ-DI from baseline to week 24 was 0.6 on both the subcutaneous and intravenous arms. The proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was also comparable on the subcutaneous (65.2%) versus intravenous (67.4%) arms, with a weighted difference in proportions of -2.3% (95% CI - 8.1, 3.4). For SF-36, the mean change from baseline at week 24 in the mental component score was 6.22 for the subcutaneous arm and 6.54 for the intravenous arm, and for the physical component score was also similar with 9.49 for the subcutaneous arm and 9.65 for the intravenous arm.

In study SC-II, mean decrease in HAQ-DI from baseline to week 24 was significantly greater for patients treated with RoActemra subcutaneous every other week (0.4) versus placebo (0.3). Proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was higher for RoActemra subcutaneous every other week (58%) versus placebo (46.8%). SF-36 (mean change in mental and physical component scores) was significantly greater with RoActemra subcutaneous group (6.5 and 5.3) versus placebo (3.8 and 2.9).

sJIA
Subcutaneous Use
Clinical Efficacy
A 52-week, open-label, multi-centre, PK/PD and safety study (WA28118) was conducted in paediatric patients with sJIA, aged 1 to 17 years, to determine the appropriate SC dose of RoActemra that achieved comparable PK/PD and safety profiles to the IV regimen.

Eligible patients received RoActemra dosed according to body weight (BW), with patients weighing ≥30 kg (n=26) dosed with 162 mg of RoActemra every week (QW) and patients weighing below 30 kg (n=25) dosed with 162 mg of RoActemra every 10 days (Q10D; n=8) or every 2 weeks (Q2W; n=17) for 52 weeks. Of these 51 patients, 26 (51%) were naive to RoActemra and 25 (49%) had been receiving RoActemra IV and switched to RoActemra SC at baseline.

Exploratory efficacy results showed that RoActemra SC improved all exploratory efficacy parameters including Juvenile Arthritis Disease Activity Score (JADAS)-71, for TCZ naïve patients and maintained all exploratory efficacy parameters for patients who switched from RoActemra IV to RoActemra SC treatment over the entire course of the study for patients in both body weight groups (below 30 kg and ≥30 kg).

pJIA Patients
A 52-week, open-label, multicenter, PK-PD and safety study was conducted in paediatric patients with pJIA, aged 1 to 17 years old, to determine the appropriate subcutaneous dose of RoActemra that achieved comparable PK/PD and safety profiles to the IV regimen.

Eligible patients received tocilizumab dosed according to body weight (BW), with patients weighing ≥30 kg (n = 25) dosed with 162 mg of RoActemra every 2 weeks (Q2W) and patients weighing below 30 kg (n = 27) dosed with 162 mg of RoActemra every 3 weeks (Q3W) for 52 weeks. Of these 52 patients, 37 (71%) were naive to RoActemra and 15 (29%) had been receiving RoActemra IV and switched to RoActemra SC at baseline.

The RoActemra SC regimens of 162 mg Q3W for patients weighing below 30 kg and of 162 mg Q2W for patients weighing ≥ 30 kg respectively provide PK exposure and PD responses to support efficacy and safety outcomes similar to those achieved with the approved RoActemra IV regimens for pJIA.

Exploratory efficacy results showed that RoActemra SC improved median Juvenile Arthritis Disease Activity Score (JADAS)-71 for RoActemra naïve patients and maintained the median JADAS-71 for patients who switched from IV to SC RoActemra treatment over the entire course of the study for patients in both body weight groups (below 30 kg and ≥ 30 kg).

GCA
Subcutaneous Use
Clinical efficacy
Study WA28119 was a randomized, multi-center, double-blind placebo-controlled Phase III superiority study conducted to assess the efficacy and safety of RoActemra in patients with GCA.

Two hundred and fifty one (251) patients with new-onset or relapsing GCA were enrolled and assigned to one of four treatment arms. The study consisted of a 52-week blinded period (Part 1), followed by a 104-week open-label extension (Part 2). The purpose of Part 2 was to describe the long-term safety and maintenance of efficacy after 52 weeks of RoActemra therapy, to explore the rate of relapse and the requirement for RoActemra therapy beyond 52 weeks, and to gain insight into the potential long-term steroid-sparing effect of RoActemra.

Two subcutaneous doses of RoActemra (162 mg every week and 162 mg every other week) were compared to two different placebo control groups randomised 2:1:1:1.

All patients received background glucocorticoid (prednisone) therapy. Each of the RoActemra-treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen over 26 weeks, while the second placebo-treated group followed a pre-specified prednisone-taper regimen over 52 weeks, designed to be more in keeping with standard practice.

The duration of glucocorticoid therapy during screening and before RoActemra (or placebo) was initiated, was similar in all 4 treatment groups (see Table 6).
Table 6. Duration of Corticosteroid Therapy During Screening in Study WA28119

	Placebo + 26 weeks prednisone taper	**Placebo + 52 weeks prednisone taper**	**RoActemra 162mg SC weekly + 26 weeks prednisone taper**	**RoActemra 162 mg SC every other weekly + 26 weeks prednisone taper**
	N=50	**N=51**	**N=100**	**N=49**
Duration (days)				
Mean (SD)	35.7 (11.5)	36.3 (12.5)	35.6 (13.2)	37.4 (14.4)
Median	42.0	41.0	41.0	42.0
Min - Max	6 - 63	12 – 82	1 - 87	9 - 87

The primary efficacy endpoint assessed by the proportion of patients achieving steroid free sustained remission at week 52 on RoActemra plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper, was met (Table 7).

The key secondary efficacy endpoint also based on the proportion of patients achieving sustained remission at week 52, comparing tocilizumab plus 26 weeks prednisone taper with placebo plus 52 weeks prednisone taper, was also met (Table 7).

A statistically significant superior treatment effect was seen in favour of RoActemra over placebo in achieving steroid-free sustained remission at week 52 on RoActemra plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper and with placebo plus 52 weeks prednisone taper.

The percentage of patients achieving sustained remission at week 52, are shown in the Table 7.

Secondary Endpoints
The assessment of the time to first GCA flare showed a significantly lower risk of flare for the RoActemra subcutaneous weekly group compared to placebo plus 26 weeks prednisone and placebo plus 52 weeks prednisone taper groups and for the RoActemra subcutaneous every other weekly group compared to placebo plus 26 weeks prednisone (when compared at a 0.01 significance level). RoActemra subcutaneous weekly dose also showed a clinically meaningful decrease in the risk

for flare compared to placebo plus 26 weeks prednisone in patients who entered the trial with relapsing GCA as well as those with new-onset disease (Table 7).

Cumulative glucocorticoid dose

The cumulative prednisone dose at week 52 was significantly lower in the two RoActemra dose groups compared to the two placebo groups (Table 6). In a separate analysis of the patients who received escape prednisone to treat GCA flare during the first 52 weeks, the cumulative prednisone dose varied greatly. The median doses for escape patients in the RoActemra weekly and every other weekly groups were 3129.75 mg and 3847 mg, respectively. Both considerably lower than in the placebo plus 26 weeks and the placebo plus 52 weeks prednisone taper groups, 4023.5 mg and 5389.5 mg respectively.

Table 7. Efficacy results from Study WA28119

	Placebo + 26 weeks prednisone taper N=50	Placebo + 52 weeks prednisone taper N=51	RoActemra 162mg SC weekly + 26 weeks prednisone taper N=100	RoActemra 162 mg SC every other weekly + 26 weeks prednisone taper N=49
Primary Endpoint				
****Sustained remission (Tocilizumab groups vs Placebo+26)				
Responders at Week 52, n (%)	7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions (99.5% CI)	N/A	N/A	42%* (18.00, 66.00)	39.06%* (12.46 , 65.66)
Key Secondary Endpoint				
Sustained remission (Tocilizumab groups vs Placebo+52)				
Responders at Week 52, n (%)	7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions (99.5% CI)	N/A	N/A	38.35%* (17.89 , 58.81)	35.41%** (10.41 ,60.41)
Other Secondary Endpoints				
Time to first GCA flare[1] (Tocilizumab groups vs Placebo+26)	N/A	N/A	0.23* (0.11, 0.46)	0.28** (0.12, 0.66)
HR (99% CI)	N/A	N/A	0.39** (0.18, 0.82)	0.48 (0.20, 1.16)
Time to first GCA flare[1] (Tocilizumab groups vs Placebo+52)				
HR (99% CI)	N/A	N/A	0.23*** (0.09,0.61)	0.42 (0.14, 1.28)
Time to first GCA flare[1] (Relapsing patients; Tocilizumab groups vs Placebo +26) HR (99% CI)	N/A	N/A	0.36 (0.13, 1.00)	0.67 (0.21,2.10)
Time to first GCA flare[1] (Relapsing patients; Tocilizumab groups vs Placebo + 52) HR (99% CI)	N/A	N/A	0.25*** (0.09, 0.70)	0.20*** (0.05, 0.76)
Time to first GCA flare[1] (New-onset patients; Tocilizumab groups vs Placebo +26) HR (99% CI)	N/A	N/A	0.44 (0.14, 1.32)	0.35 (0.09, 1.42)
Time to first GCA flare[1] (New-onset patients; Tocilizumab groups vs Placebo + 52) HR (99% CI)				
Cumulative glucocorticoid dose (mg)				
median at Week 52 (Tocilizumab groups vs Placebo+26[2])	3296.00	N/A	1862.00*	1862.00*
median at Week 52 (Tocilizumab groups vs Placebo +52[2])	N/A	3817.50	1862.00*	1862.00*
Exploratory Endpoints				
Annualized relapse rate, Week 52[§]				
Mean (SD)	1.74 (2.18)	1.30 (1.84)	0.41 (0.78)	0.67 (1.10)

* p<0.0001
** p<0.005 (threshold for significance for primary and key secondary tests of superiority)
***Descriptive p value ≤0.005
****Flare: recurrence of GCA signs or symptoms and/or ESR ≥30 mm/h – Increase in the prednisone dose required
Remission: absence of flare and normalization of the CRP
Sustained remission: remission from week 12 to week 52 –Patients must adhere to the protocol-defined prednisone taper
[1] analysis of the time (in days) between clinical remission and first disease flare
[2] p-values are determined using a Van Elteren analysis for non-parametric data
[§] statistical analyses has not been performed
N/A= Not applicable
HR = Hazard Ratio
CI = Confidence Interval

Quality of Life Outcomes

In study WA28119, the SF-36 results were separated into the physical and mental component summary scores (PCS and MCS, respectively). The PCS mean change from baseline to week 52 was higher (showing more improvement) in the RoActemra weekly and every other weekly dose groups [4.10, 2.76, respectively] than in the two placebo groups [placebo plus 26 weeks; -0.28, placebo plus 52 weeks; -1.49], although only the comparison between RoActemra weekly plus 26 weeks prednisone taper group and placebo plus 52 weeks prednisone taper group (5.59, 99% CI: 8.6, 10.32) showed a statistically significant difference (p=0.0024). For MCS, the mean change from baseline to week 52 for both RoActemra weekly and every other weekly dose groups [7.28, 6.12, respectively] were higher than the placebo plus 52 weeks prednisone taper group [2.84] (although the differences were not statistically significant [weekly p=0.0252 for weekly, p=0.1468 for every other weekly]) and similar to the placebo plus 26 weeks prednisone taper group [6.67].

The Patient's Global Assessment of disease activity was assessed on a 0-100mm Visual Analogue Scale (VAS). The mean change in Patient's global VAS from baseline at week 52 was lower (showing greater improvement) in the RoActemra weekly and every other weekly dose groups [-19.0, -25.3, respectively] than in both placebo groups [placebo plus 26 weeks -3.4, placebo plus 52 weeks -7.2], although only the RoActemra every other weekly plus 26 weeks prednisone taper group showed a statistically significant difference compared to placebo [placebo plus 26 weeks taper p=0.0059, and placebo plus 52 weeks taper p=0.0081].

FACIT-Fatigue change from baseline to week 52 scores were calculated for all groups. The mean [SD] change scores were as follows: RoActemra weekly plus 26 weeks 5.61 [10.115], RoActemra every other weekly plus 26 weeks 1.81 [8.836], placebo plus 26 weeks 0.26 [10.702], and placebo plus 52 weeks -1.63 [6.753].

Change in EQ5D scores from baseline to week 52 were RoActemra weekly plus 26 weeks 0.10 [0.198], RoActemra every other weekly plus 26 weeks 0.05 [0.215], placebo plus 26 weeks 0.07 [0.293], and placebo plus 52 weeks -0.02 [0.159].

Higher scores signal improvement in both FACIT-Fatigue and EQ5D.

5.2 Pharmacokinetic properties

The pharmacokinetics of RoActemra is characterized by nonlinear elimination which is a combination of linear clearance and Michaelis-Menten elimination. The nonlinear part of RoActemra elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of RoActemra do not change with time. Due to the dependence of total clearance on RoActemra serum concentrations, the half-life of RoActemra is also concentration-dependent and varies depending on the serum concentration level. Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.

<u>RA</u>
<u>Intravenous use</u>
The pharmacokinetics of RoActemra were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with a one-hour infusion of 4 or 8 mg/kg RoActemra every 4 weeks for 24 weeks or with 162 mg tocilizumab given subcutaneously either once a week or every other week for 24 weeks.

The following parameters (predicted mean ± SD) were estimated for a dose of 8 mg/kg RoActemra given every 4 weeks: steady-state area under curve (AUC) = 38000 ± 13000 h•µg/mL, trough concentration (Cmin) = 15.9 ± 13.1 µg/mL and maximum concentration (Cmax) = 182 ± 50.4 µg/mL, and. the accumulation ratios for AUC and Cmax were small, 1.32 and 1.09, respectively. The accumulation ratio was higher for Cmin (2.49), which was expected based on the non-linear clearance contribution at lower concentrations. Steady-state was reached following the first administration for

Cmax and after 8 and 20 weeks for AUC and Cmin, respectively. RoActemra AUC, Cmin and Cmax increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, Cmin and Cmax of RoActemra were 50000 ± 16800 µg•h/mL, 24.4 ± 17.5 µg/mL, and 226 ± 50.3 µg/mL, respectively, which are higher than mean exposure values for the patient population (i.e. all body weights) reported above. The dose-response curve for tocilizumab flattens at higher exposure, resulting in smaller efficacy gains for each incremental increase in RoActemra concentration such that clinically meaningful increases in efficacy were not demonstrated in patients treated with > 800 mg of RoActemra. Therefore, RoActemra doses exceeding 800 mg per infusion are not recommended (see section 4.2).

Distribution
In RA patients the central volume of distribution was 3.72 L, the peripheral volume of distribution was 3.35 L resulting in a volume of distribution at steady state of 7.07 L.

Elimination
Following intravenous administration, RoActemra undergoes biphasic elimination from the circulation. The total clearance of RoActemra was concentration-dependent and is the sum of the linear and non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 9.5 mL/h. The concentration-dependent non-linear clearance plays a major role at low RoActemra concentrations. Once the non-linear clearance pathway is saturated, at higher RoActemra concentrations, clearance is mainly determined by the linear clearance.

The $t_{1/2}$ of RoActemra was concentration-dependent. At steady-state following a dose of 8 mg/kg every 4 weeks, the effective $t_{1/2}$ decreased with decreasing concentrations within a dosing interval from 18 days to 6 days.

Linearity
Pharmacokinetic parameters of RoActemra did not change with time. A more than dose-proportional increase in the AUC and C_{min} was observed for doses of 4 and 8 mg/kg every 4 weeks. C_{max} increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 3.2 and 30 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

Subcutaneous use
The pharmacokinetics of RoActemra were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with 162 mg subcutaneous every week, 162 mg subcutaneous every other week, and or 4 or 8 mg/kg intravenous every 4 weeks for 24 weeks.

The pharmacokinetic parameters of RoActemra did not change with time. For the 162 mg every week dose, the predicted mean (±SD) steady-state AUC_{1week}, C_{min} and C_{max} of RoActemra were 7970 ± 3432 µg•h/mL, 43.0 ± 19.8 µg/mL, and 49.8 ± 21.0 µg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 6.32, 6.30, and 5.27, respectively. Steady state was reached after 12 weeks for AUC, C_{min}, and C_{max}.

For the 162 every other week dose, the predicted mean (±SD) steady-state AUC_{2week}, C_{min}, and C_{max} of RoActemra were 3430 ± 2660 µg•h/mL, 5.7 ± 6.8 µg/mL, and 13.2 ± 8.8 µg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 2.67, 6.02, and 2.12, respectively. Steady state was reached after 12 weeks for AUC and C_{min}, and after 10 weeks for C_{max}.

Absorption
Following subcutaneous dosing in RA patients, the time to peak serum RoActemra concentrations t_{max} was 2.8 days. The bioavailability for the subcutaneous formulation was 79%.

Elimination
For subcutaneous administration, the effective $t_{1/2}$ is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state.

sJIA
Subcutaneous Use
The pharmacokinetics of RoActemra in sJIA patients was characterized by a population pharmacokinetic analysis which included 140 patients who were treated with 8 mg/kg IV every 2 weeks (patients weighing ≥30 kg), 12 mg/kg IV every 2 weeks (patients weighing below 30 kg), 162 mg SC every week (patients weighing ≥30 kg), 162 mg SC every 10 days or every 2 weeks (patients weighing below 30 kg).

Limited data are available regarding exposures following subcutaneous administration of RoActemra in sJIA patients below 2 years of age with a body weight less than 10 kg.
Patients with sJIA must have a minimum body weight of 10 kg when receiving RoActemra subcutaneously (see section 4.2).

Table 8. Predicted mean ± SD PK parameters at steady-state after SC dosing in sJIA

RoActemra PK Parameter	**162 mg QW ≥ 30 kg**	**162 mg Q2W below 30 kg**
C_{max} (µg/mL)	99.8 ± 46.2	134 ± 58.6
C_{min} (µg/mL)	79.2 ± 35.6	65.9 ± 31.3
C_{mean} (µg/mL)	91.3 ± 40.4	101 ± 43.2
Accumulation C_{max}	3.66	1.88
Accumulation C_{min}	4.39	3.21
Accumulation C_{mean} or AUC_{τ}*	4.28	2.27

*τ = 1 week or 2 weeks for the two SC regimens

After SC dosing, approximately 90% of the steady-state was reached by week 12 for both the 162 mg QW and Q2W regimens.

Absorption
Following SC dosing in sJIA patients, the absorption half-life was around 2 days, and the bioavailability for the SC formulation in sJIA patients was 95%.

Distribution
In paediatric patients with sJIA, the central volume of distribution was 1.87 L, the peripheral volume of distribution was 2.14 L resulting in a volume of distribution at steady state of 4.01 L

Elimination
The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 5.7 mL/h in paediatric patients with systemic juvenile idiopathic arthritis. Following subcutaneous administration, the effective $t_{1/2}$ of RoActemra in sJIA patients is up to 14 days for both the 162 mg QW and Q2W regimens during a dosing interval at steady state.

pJIA
Subcutaneous use
The pharmacokinetics of RoActemra in pJIA patients was characterized by a population pharmacokinetic analysis which included 237 patients who were treated with 8 mg/kg IV every 4 weeks (patients weighing ≥ 30 kg), 10 mg/kg IV every 4 weeks (patients weighing below 30 kg), 162 mg SC every 2 weeks (patients weighing ≥ 30 kg), or 162 mg SC every 3 weeks (patients weighing below 30 kg).

Table 9. Predicted mean ± SD PK parameters at steady-state after SC dosing in pJIA

RoActemra PK Parameter	**162 mg Q2W ≥ 30 kg**	**162 mg Q3W below 30 kg**
C_{max} (µg/mL)	29.4 ± 13.5	75.5 ± 24.1
C_{min} (µg/mL)	11.8 ± 7.08	18.4 ± 12.9
C_{avg} (µg/mL)	21.7 ± 10.4	45.5 ± 19.8
Accumulation C_{max}	1.72	1.32
Accumulation C_{min}	3.58	2.08
Accumulation C_{mean} or AUC_{τ} *	2.04	1.46

*τ = 2 week or 3 week for the two SC regimens

After IV dosing, approximately 90% of the steady-state was reached by Week 12 for the 10 mg/kg (BW < 30 kg), and by Week 16 for the 8 mg/kg (BW ≥ 30 kg) dose. After SC dosing, approximately 90% of the steady-state was reached by Week 12 for both the 162 mg SC Q2W and Q3W regimens.

Absorption

Following SC dosing in pJIA patients, the absorption half-life was around 2 days, and the bioavailability for the SC formulation in pJIA patients was 96%.

Distribution

In paediatric patients with pJIA, the central volume of distribution was 1.97 L, the peripheral volume of distribution was 2.03 L, resulting in a volume of distribution at steady state of 4.0 L.

Elimination

Population pharmacokinetic analysis for pJIA patients showed body size related impact on linear clearance so that body-weight based dosing should be taken into consideration (see Table 9).

After subcutaneous administration, the effective $t_{1/2}$ of RoActemra in pJIA patients is up to 10 days for patients < 30 kg (162 mg SC Q3W) and up to 7 days for patients >= 30 kg (162 mg SC Q2W) during a dosing interval at steady state. Following intravenous administration, tocilizumab undergoes biphasic elimination from the circulation. The total clearance of tocilizumab was concentration-dependent and is the sum of the linear and non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 6.25 mL/h. The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

GCA

Subcutaneous use

The PK of RoActemra in GCA patients were determined using a population PK model from an analysis dataset composed of 149 GCA patients treated with 162 mg subcutaneous every week or 162 mg subcutaneous every other week. The developed model had the same structure as the population PK model developed earlier based on data from RA patients (see Table 10).

Table 10. Predicted mean ± SD PK parameters at steady-state after subcutaneous dosing in GCA

	Subcutaneous	
Tocilizumab PK Parameter	**162 mg every other weekly**	**162 mg weekly**
C_{max} (µg/mL)	19.3 ± 12.8	73 ± 30.4
C_{min} (µg/mL)	11.1 ± 10.3	68.1± 29.5
C_{mean} (µg/mL)	16.2 ± 11.8	71.3 ± 30.1
Accumulation C_{max}	2.18	8.88
Accumulation C_{min}	5.61	9.59
Accumulation C_{mean} or AUC_{τ}	2.81	10.91

The steady-state profile following the RoActemra weekly dose was almost flat, with very little fluctuations between trough and peak values, while there were substantial fluctuations for the RoActemra every other weekly dose. Approximately 90% of the steady-state (AUC_{τ}) was reached by week 14 in the every other weekly and week 17 in the weekly dose groups.

Based on the current characterization of PK, RoActemra trough concentration at steady state are 50% higher in this population relative to average concentrations in a large dataset from the RA population. These differences occur due to unknown reasons. PK differences are not accompanied by marked differences in PD parameters and so the clinical relevance is unknown.

In GCA patients, higher exposure was observed in patients with lower body weight. For the 162 mg every week dosing regimen, the steady-state Cavg was 51% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. For the 162 mg every other week regimen, the steady-state Cavg was 129% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. There is limited data for patients above 100 kg (n=7).

Absorption
Following subcutaneous dosing in GCA patients, the absorption t½ was around 4 days. The bioavailability for the SC formulation was 0.8. The median values of T_{max} were 3 days after the RoActemra weekly dose and 4.5 days after the tocilizumab every other week dose.

Distribution
In GCA patients, the central volume of distribution was 4.09 L, the peripheral volume of distribution was 3.37 L, resulting in a volume of distribution at steady state of 7.46 L.

Elimination
The total clearance of RoActemra was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 6.7 mL/h in GCA patients,

In GCA patients, at steady state, the effective t ½ of RoActemra varied between 18.3 and 18.9 days for 162 mg weekly regimen, and between 4.2 and 7.9 days for 162 mg every other weekly regimen. At high serum concentrations, when total clearance of RoActemra is dominated by linear clearance, an effective t ½ of approximately 32 days was derived from the population parameter estimates.

Special populations
Renal impairment: No formal study of the effect of renal impairment on the pharmacokinetics of RoActemra has been conducted. Most of the patients in the RA and GCA studies population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance based on Cockcroft-Gault formula) did not impact the pharmacokinetics of RoActemra.

Approximately one-third of the patients in the GCA study had moderate renal impairment at baseline (estimated creatinine clearance of 30-59 mL/min). No impact on RoActemra exposure was noted in these patients.

No dose adjustment is required in patients with mild or moderate renal impairment.

Hepatic impairment: No formal study of the effect of hepatic impairment on the pharmacokinetics of RoActemra has been conducted.

Age, gender and ethnicity: Population pharmacokinetic analyses in RA and GCA patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of RoActemra.

Results of the population PK analysis for sJIA and pJIA patients confirmed that body size is the only covariate which has an appreciable impact on the pharmacokinetics of RoActemra including elimination and absorption so that body-weight based dosing should be taken into consideration (see Tables 8 and 9).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies were not performed because IgG1 monoclonal antibodies are not deemed to have intrinsic carcinogenic potential.

Available non-clinical data demonstrated the effect of IL-6 on malignant progression and apoptosis resistance to various cancer types. This data does not suggest a relevant risk for cancer initiation and progression under RoActemra treatment. Additionally, proliferative lesions were not observed in a 6-month chronic toxicity study in cynomolgus monkeys or in IL-6 deficient mice.

Available non-clinical data do not suggest an effect on fertility under RoActemra treatment. Effects on endocrine active and reproductive system organs were not observed in a chronic cynomolgus monkey toxicity study and reproductive performance was not affected in IL-6 deficient mice. RoActemra administered to cynomolgus monkeys during early gestation, was observed to have no direct or indirect harmful effect on pregnancy or embryonal-foetal development. However, a slight increase in abortion/embryonal-foetal death was observed with high systemic exposure (> 100 x human exposure) in the 50 mg/kg/day high-dose group compared to placebo and other low-dose groups. Although IL-6 does not seem to be a critical cytokine for foetal growth or the immunological control of the maternal/foetal interface, a relation of this finding to RoActemra cannot be excluded.

Treatment with a murine analogue did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

The non-clinical safety profile of RoActemra in the cynomolgus monkey does not suggest a difference between intravenous and subcutaneous routes of administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine monohydrochloride monohydrate
L-Arginine
L-Arginine hydrochloride
L-Methionine
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatability studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months.

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

0.9 mL solution in a pre-filled syringe (type I glass) with a staked-in needle. The syringe is closed by a rigid needle shield (elastomer seal with a polypropylene shell) and a plunger stopper (butyl rubber with a fluororesin coating).

Pack sizes of 4 pre-filled syringes **and multipacks containing 12 (3 packs of 4) pre-filled syringes. Not all pack sizes may be marketed.**

6.6 Special precautions for disposal and other handling

RoActemra is supplied in a single use pre-filled syringe fitted into a needle safety device. After removing the pre-filled syringe from the refrigerator the pre-filled syringe should be allowed to reach room temperature (18°C to 28°C) by waiting for 25 to 30 minutes, before injecting RoActemra . The syringe should not be shaken. After removing the cap the injection must be started within 5 minutes, to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of removing the cap, you must dispose of it in a puncture resistant container and use a new pre-filled syringe.
If following insertion of the needle you cannot depress the plunger, you must dispose of the pre-filled syringe in a puncture resistant container and use a new pre-filled syringe.

Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to slightly yellowish, or any part of the pre-filled syringe appears to be damaged.

Comprehensive instructions for the administration of RoActemra in a pre-filled syringe are given in the package leaflet.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/007
EU/1/08/492/008

9. DATE OF FIRST AUTHORISATION/DATE OF LATEST RENEWAL

Date of first authorisation: 16 January 2009
Date of last renewal: 25 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 162 mg of RoActemra (tocilizumab) in 0.9 mL.

RoActemra is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against soluble and membrane-bound interleukin 6 receptors.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (ACTPen).

A colourless to slightly yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RoActemra, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

RoActemra is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA and/or GCA. All patients treated with RoActemra should be given the Patient Alert Card. Suitability of the patient for subcutaneous home use should be assessed and patients should be instructed to inform a healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions (see section 4.4).

<u>Posology</u>

<u>RA</u>
The recommended posology is subcutaneous 162 mg once every week.

Limited information is available regarding switching patients from RoActemra intravenous formulation to RoActemra subcutaneous fixed dose-formulation. The once every week dosing interval should be followed.

Patients transitioning from intravenous to subcutaneous formulation should administer their first subcutaneous dose instead of the next scheduled intravenous dose under the supervision of a qualified healthcare professional.

GCA
The recommended posology is subcutaneous 162 mg once every week in combination with a tapering course of glucocorticoids. RoActemra can be used alone following discontinuation of glucocorticoids. RoActemra monotherapy should not be used for the treatment of acute relapses (see 4.4).

Based upon the chronic nature of GCA, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

RA and GCA
Dose adjustments due to laboratory abnormalities (see section 4.4).

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x Upper Limit of Normal (ULN)	Dose modify concomitant DMARDs (RA) or immunomodulatory agents (GCA) if appropriate. For persistent increases in this range, reduce RoActemra dose frequency to every other week injection or interrupt RoActemra until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised. Restart with weekly or every other week injection, as clinically appropriate.
> 3 to 5 x ULN	Interrupt RoActemra dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN. For persistent increases > 3 x ULN (confirmed by repeat testing, see 4.4.), discontinue RoActemra.
> 5 x ULN	Discontinue RoActemra.

- Low absolute neutrophil count (ANC)

In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/L.

Laboratory Value (cells x 10^9/ L)	Action
ANC > 1	Maintain dose.
ANC 0.5 to 1	Interrupt RoActemra dosing. When ANC increases > 1 x 10^9/ L resume RoActemra dosing every other week and increase to every week injection, as clinically appropriate.
ANC < 0.5	Discontinue RoActemra.

- Low platelet count

Laboratory Value (cells x 10^3/ μL)	Action
50 to 100	Interrupt RoActemra dosing. When platelet count > 100 x 10^3/ μL resume RoActemra dosing every other week and increase to every week injection as clinically appropriate.
< 50	Discontinue RoActemra.

Missed dose
If a patient misses a subcutaneous weekly injection of RoActemra within 7 days of the scheduled dose, he/she should be instructed to take the missed dose on the next scheduled day. If a patient misses a subcutaneous once every other week injection of RoActemra within 7 days of the scheduled dose, he/she should be instructed to take the missed dose immediately and the next dose on the next scheduled day.

Special populations

Elderly:
No dose adjustment is required in patients aged 65 years and older.

Renal impairment:
No dose adjustment is required in patients with mild or moderate renal impairment. RoActemra has not been studied in patients with severe renal impairment (see section 5.2). Renal function should be monitored closely in these patients.

Hepatic impairment:
RoActemra has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made.

Paediatric patients
The safety and efficacy of RoActemra subcutaneous formulation in children from birth to less than 1 year have not been established. No data are available

Method of administration

RoActemra is for subcutaneous use.
After proper training in injection technique, patients may self-inject with RoActemra if their physician determines that it is appropriate. The total content (0.9 mL) of the pre-filled pen should be administered as a subcutaneous injection. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

The pre-filled pen should not be shaken.

Comprehensive instructions for the administration of RoActemra in a pre-filled pen are given in the package leaflet, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

RoActemra subcutaneous formulation is not intended for intravenous administration.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections
Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra (see section 4.8, Undesirable effects). RoActemra treatment must not be initiated in patients with active infections (see section 4.3). Administration of RoActemra should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). Healthcare professionals should exercise caution when considering the use of RoActemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes and interstitial lung disease which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents such as RoActemra for moderate to severe RA or GCA as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. The effects of RoActemra on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Tuberculosis
As recommended for other biological treatments, all patients should be screened for latent tuberculosis (TB) infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoActemra. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised.

Patients should be advised to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade (fever) suggestive of a tuberculosis infection occur during or after therapy with RoActemra.

Viral reactivation
Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for RA. In clinical studies with RoActemra, patients who screened positive for hepatitis were excluded.

Complications of diverticulitis
Events of diverticular perforations as complications of diverticulitis have been reported uncommonly in patients treated with RoActemra (see section 4.8). RoActemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation.

Hypersensitivity reactions
Serious hypersensitivity reactions, including anaphylaxis have been reported in association with RoActemra (see section 4.8). Such reactions may be more severe, and potentially fatal in patients who have experienced hypersensitivity reactions during previous treatment with RoActemra even if they have received premedication with steroids and antihistamines. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of RoActemra should be stopped immediately, appropriate therapy initiated and RoActemra should be permanently discontinued.

Active hepatic disease and hepatic impairment
Treatment with RoActemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases, therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8).

Hepatic transaminase elevations
In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with RoActemra treatment, without progression to hepatic injury (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with RoActemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Caution should be exercised when considering initiation of RoActemra treatment in patients with elevated ALT or AST > 1.5 x ULN. In patients with baseline ALT or AST > 5 x ULN, treatment is not recommended.

In RA and GCA patients, ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see section 4.2. For ALT or AST elevations > 3–5 x ULN, RoActemra treatment should be interrupted.

Haematological abnormalities
Decreases in neutrophil and platelet counts have occurred following treatment with RoActemra 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

In patients not previously treated with RoActemra, initiation is not recommended in patients with an ANC below 2 x 10^9/L. Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/ μL). In patients who develop an ANC < 0.5 x 10^9/L or a platelet count < 50 x 10^3/μL, continued treatment is not recommended.

Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with RoActemra to date.

In RA and GCA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2.

Lipid parameters
Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with RoActemra (see section 4.8). In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents.

In RA and GCA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of RoActemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Neurological disorders
Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with RoActemra is currently unknown.

Malignancy
The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy.

Vaccinations
Live and live attenuated vaccines should not be given concurrently with RoActemra as clinical safety has not been established. In a randomized open-label study, adult RA patients treated with RoActemra and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus toxoid vaccines which was comparable to the response seen in patients on MTX only. It is recommended that all patients particularly elderly patients, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating RoActemra therapy. The interval between live vaccinations and initiation of RoActemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Cardiovascular risk
RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care.

Combination with TNF antagonists
There is no experience with the use of RoActemra with TNF antagonists or other biological treatments for RA patients. RoActemra is not recommended for use with other biological agents.

GCA
RoActemra monotherapy should not be used for the treatment of acute relapses as efficacy in this setting has not been established. Glucocorticoids should be given according to medical judgement and practice guidelines.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Concomitant administration of a single dose of 10 mg/kg RoActemra with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids on RoActemra clearance in RA patients. In GCA patients, no effect of cumulative corticosteroid dose on RoActemra exposure was observed.

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as RoActemra, is introduced.

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression. RoActemra normalises expression of these enzymes.

In a study in RA patients, levels of simvastatin (CYP3A4) were decreased by 57% one week following a single dose of RoActemra, to the level similar to, or slightly higher than, those observed in healthy subjects.

When starting or stopping therapy with RoActemra, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2 or 2C9 (e.g. methylprednisolone, dexamethasone, (with the possibility for oral glucocorticoid withdrawal syndrome), atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of RoActemra on CYP450 enzyme activity may persist for several weeks after stopping therapy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Pregnancy

There are no adequate data from the use of RoActemra in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose (see section 5.3). The potential risk for humans is unknown.

RoActemra should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is unknown whether RoActemra is excreted in human breast milk. The excretion of RoActemra in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with RoActemra should be made taking into account the benefit of breast-feeding to the child and the benefit of RoActemra therapy to the woman.

Fertility

Available non-clinical data do not suggest an effect on fertility under RoActemra treatment.

4.7 Effects on ability to drive and use machines

RoActemra has a minor influence on the ability to drive and use machines (see section 4.8, dizziness).

4.8 Undesirable effects

Summary of the safety profile

The safety profile comes from 4158 patients exposed to RoActemra in clinical trials; the majority of these patients were participating in RA studies (n=4009), while the remaining experience comes from GCA (n=149) studies. The safety profile of RoActemra across these indications remains similar and undifferentiated.

The most commonly reported Adverse Drug Reactions (ADRs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The most serious ADRs were serious infections, complications of diverticulitis, and hypersensitivity reactions.

Tabulated list of adverse reactions

ADRs from clinical trials and/or post marketing experience with RoActemra based on spontaneous case reports, literature cases and cases from non-interventional study programs are listed in Table 1 and are presented by MedDRA system organ class. The corresponding frequency category is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. List of ADRs occurring in patients treated with RoActemra

MedDRA System Organ Class	Frequency category with preferred term		
	Very Common	**Common**	**Uncommon**
Blood and lymphatic system disorders		Leukopenia, Neutropenia, Hypofibrionogenaemia	
Endocrine disorders			Hypothyroidism
Eye disorders		Conjunctivitis	
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer
General disorders and administration site conditions		Peripheral oedema Hypersensitivity reaction, Injection site reaction	
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis
Investigations		Hepatic transaminases increased, Weight increased, Total bilirubin increased*	
Metabolism and nutrition disorders	Hypercholesterolaemia*		Hypertriglyceridaemia
Nervous system disorders		Headache, Dizziness	
Renal and urinary disorders			Nephrolithiasis
Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea	
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria	
Vascular disorders		Hypertension	

***** Includes elevations collected as part of routine laboratory monitoring (see text below)

RA

Intravenous use

The safety of RoActemra has been studied in 4 placebo-controlled studies (studies II, III, IV and V), 1 MTX-controlled study (study I) and their extension periods (see section 5.1).

The double-blind controlled period was 6 months in four studies (studies I, III, IV and V) and was up to 2 years in one study (study II). In the double-blind controlled studies, 774 patients received RoActemra 4 mg/kg in combination with MTX, 1870 patients received RoActemra 8 mg/kg in combination with MTX or other DMARDs and 288 patients received RoActemra 8 mg/kg monotherapy.

The long-term exposure population includes all patients who received at least one dose of RoActemra either in the double-blind control period or open label extension phase in the studies. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year, 2806 received treatment for at least 2 years and 1222 for 3 years.

Description of selected adverse reactions

Infections
In the 6-month controlled studies the rate of all infections reported with RoActemra8 mg/kg plus DMARD treatment was 127 events per 100 patient years compared to 112 events per 100 patient years in the placebo plus DMARD group. In the long-term exposure population, the overall rate of infections with RoActemra was 108 events per 100 patient years exposure.

In 6-month controlled clinical studies, the rate of serious infections with RoActemra8 mg/kg plus DMARDs was 5.3 events per 100 patient years exposure compared to 3.9 events per 100 patient years exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 patient years of exposure in the RoActemra group and 1.5 events per 100 patient years of exposure in the MTX group.

In the long-term exposure population, the overall rate of serious infections (bacterial, viral and fungal) was 4.7 events per 100 patient years. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported.

Interstitial lung disease
Impaired lung function may increase the risk for developing infections. There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Gastrointestinal perforation
During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with RoActemra therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Reports of gastrointestinal perforation on RoActemrawere primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.

Infusion reactions
In the 6-month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the RoActemra 8 mg/kg plus DMARD group and 5.1% of patients in the placebo plus DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment limiting.

The rate of anaphylactic reactions (occurring in a total of 8/4,009 patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with RoActemra and requiring treatment discontinuation were reported in a total of 56 out of 4,009 patients (1.4%) treated with RoActemra during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of RoActemra (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with intravenous RoActemra (see section 4.4).

Immunogenicity
A total of 2,876 patients have been tested for anti-RoActemra antibodies in the 6-month controlled clinical trials. Of the 46 patients (1.6%) who developed anti-RoActemra antibodies, 6 had an associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. Thirty patients (1.1%) developed neutralising antibodies.

Haematological abnormalities:
Neutrophils
In the 6-month controlled trials decreases in neutrophil counts below 1 x 10^9/ L occurred in 3.4% of patients on RoActemra 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < 1 x 10^9/ L did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/ L were reported in 0.3% patients receiving RoActemra8 mg/kg plus DMARDs. Infections with neutropenia have been reported.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials.

Platelets
In the 6-month controlled trials decreases in platelet counts below 100 x 10^3/ μL occurred in 1.7% of patients on RoActemra 8 mg/kg plus DMARDs compared to < 1% on placebo plus DMARDs. These decreases occurred without associated bleeding events.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials.

Very rare reports of pancytopenia have occurred in the post marketing setting.

Hepatic transaminase elevations
During the 6-month controlled trials transient elevations in ALT/AST > 3 x ULN were observed in 2.1% of patients on RoActemra 8 mg/kg compared to 4.9% of patients on MTX and in 6.5% of patients who received 8 mg/kg RoActemra plus DMARDs compared to 1.5% of patients on placebo plus DMARDs.

The addition of potentially hepatotoxic drugs (e.g. MTX) to RoActemra monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 x ULN were observed in 0.7% of RoActemra monotherapy patients and 1.4% of RoActemra plus DMARD patients, the majority of whom were discontinued permanently from RoActemra treatment. These elevations were not associated with clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment. During the double-blind controlled period, the incidence of indirect bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, is 6.2% in patients treated with 8 mg/kg RoActemra+ DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of > 1 to 2 x ULN and 0.4% had an elevation of > 2 x ULN.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevation in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials.

Lipid parameters
During the 6-month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving RoActemra in clinical trials experienced sustained elevations in total cholesterol ≥ 6.2 mmol/ l, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/ L. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled trials.

Malignancies
The clinical data are insufficient to assess the potential incidence of malignancy following exposure to RoActemra. Long-term safety evaluations are ongoing.

Skin Reactions
Very rare reports of Stevens-Johnson Syndrome have occurred in the post marketing setting.

Subcutaneous use
RA
The safety of subcutaneous RoActemra in RA includes a double-blind, controlled, multicenter study, SC-I. SC-I was a non-inferiority study that compared the efficacy and safety of RoActemra162 mg administered every week versus 8 mg/kg intravenous in 1262 patients with RA. All patients received background non-biologic DMARD(s). The safety and immunogenicity observed for RoActemra administered subcutaneous was consistent with the known safety profile of intravenous RoActemra and no new or unexpected adverse drug reactions were observed (see Table 1). A higher frequency of injection site reactions was observed in the subcutaneous arms compared with placebo subcutaneous injections in the intravenous arms.

Injection site reactions
During the 6-month controlled period, in SC-I, the frequency of injection site reactions was 10.1% (64/631) and 2.4% (15/631) for the subcutaneous RoActemra and the subcutaneous placebo (intravenous group) weekly injections, respectively. These injection site reactions (including erythema, pruritus, pain and haematoma) were mild to moderate in severity. The majority was resolved without any treatment and none necessitated drug discontinuation.

Immunogenicity
In SC-I, a total of 625 patients treated with RoActemra 162mg weekly were tested for anti-RoActemra antibodies in the 6 month controlled period. Five patients (0.8%) developed positive anti-RoActemra antibodies; of these, all developed neutralizing anti-RoActemra antibodies. One patient was tested positive for IgE isotype (0.2%).

In SC-II, a total of 434 patients treated with RoActemra 162mg every other week were tested for anti-RoActemra antibodies in the 6 month controlled period. Seven patients (1.6%) developed positive anti-RoActemra antibodies; of these, six (1.4%) developed neutralizing anti-RoActemra antibodies. Four patients were tested positive for IgE isotype (0.9%).

No correlation of antibody development to clinical response or adverse events was observed.

Haematological abnormalities:
Neutrophils
During routine laboratory monitoring in the RoActemra 6 month controlled clinical trial SC-I, a decrease in neutrophil count below 1×10^9/L occurred in 2.9% of patients on the subcutaneous weekly dose.

There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

Platelets
During routine laboratory monitoring in the RoActemra 6 month clinical trial SC-I, none of the patients on the SC weekly dose had a decrease in platelet count to $\leq 50 \times 10^3$ / μL.

Hepatic transaminase elevations
During routine laboratory monitoring in the RoActemra 6-month controlled clinical trial SC-I, elevation in ALT or AST ≥3 x ULN occurred in 6.5% and 1.4% of patients, respectively on the subcutaneous weekly dose.

Lipid parameters
During routine laboratory monitoring in the RoActemra 6 month controlled clinical trial SC-I, 19% of patients experienced sustained elevations in total cholesterol > 6.2 mmol/L (240 mg/dL), with 9% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) on the subcutaneous weekly dose.

Subcutaneous use
GCA
The safety of subcutaneous RoActemra has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the RoActemra all exposure population was 138.5 patient years during the 12 month double blind, placebo controlled phase of the study. The overall safety profile observed in the RoActemra treatment groups was consistent with the known safety profile of RoActemra (see Table 1).

Infections
The rate of infection/serious infection events was balanced between the RoActemra weekly group (200.2/9.7 events per 100 patient years) vs. placebo plus 26 weeks prednisone taper (156.0/4.2 events per 100 patient years) and placebo plus 52 weeks taper (210.2/12.5 events per 100 patient years) groups.

Injection site reactions
In the RoActemra subcutaneous weekly group, a total of 6% (6/100) patients reported an adverse reaction occurring at the site of a subcutaneous injection. No injection site reaction was reported as a serious adverse event or required treatment discontinuation.

Immunogenicity
In the RoActemra subcutaneous weekly group, one patient (1.1%, 1/95) developed positive neutralizing anti-RoActemra antibodies, though not of the IgE isotype. This patient did not develop a hypersensitivity reaction or injection site reaction.

Haematological abnormalities:
Neutrophils
During routine laboratory monitoring in the Roactemra 12 month controlled clinical trial, a decrease in neutrophil count below 1×10^9/L occurred in 4% of patients in the RoActemra subcutaneous weekly group. This was not observed in either of the placebo plus prednisone taper groups.

Platelets
During routine laboratory monitoring in the RoActemra 12 month controlled clinical trial, one patient (1%, 1/100) in the RoActemra subcutaneous weekly group had a single transient occurence of decrease in platelet count to $<100 \times 10^3$ / μL without associated bleeding events. A decrease in platelet count below 100×10^3 / μL was not observed in either of the placebo plus prednisone taper groups.

Hepatic transaminase elevations
During routine laboratory monitoring in the RoActemra 12 month controlled clinical trial, elevation in ALT ≥3 x ULN occurred in 3% of patients in the RoActemra subcutaneous weekly group compared to 2% in the placebo plus 52 week prednisone taper group and none in the placebo plus 26 week prednisone taper group. An elevation in AST > 3 ULN occurred in 1% of patients in the RoActemra subcutaneous weekly group, compared to no patients in either of the placebo plus prednisone taper groups.

Lipid parameters
During routine laboratory monitoring in the RoActemra 12 month controlled clinical trial, 34% of patients experienced sustained elevations in total cholesterol > 6.2 mmol/L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) in the RoActemra subcutaneous weekly group.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are limited data available on overdose with RoActemra. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg administered intravenously. No adverse reactions were observed.

No serious adverse reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg, although dose limiting neutropenia was observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosupressants, Interleukin inhibitors; ATC code: L04AC07.

Mechanism of action
RoActemra binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). RoActemra has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.

Pharmacodynamic effects
In RA clinical studies with RoActemra, rapid decreases in CRP, erythrocyte sedimentation rate (ESR), serum amyloid A (SAA) and fibrinogen were observed. Consistent with the effect on acute phase reactants, treatment with RoActemra was associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through RoActemra decreasing the IL-6 driven effects on hepcidin production to increase iron availability. In RoActemra-treated patients, decreases in the levels of CRP to within normal ranges were seen as early as week 2, with decreases maintained while on treatment.

In GCA clinical study WA28119, similar rapid decreases in CRP and ESR were observed along with slight increases in mean corpuscular haemoglobin concentration. In healthy subjects administered RoActemra in doses from 2 to 28 mg/kg intravenously and 81 to 162 mg subcutaneously, absolute neutrophil counts decreased to their lowest 2 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. RA and GCA patients demonstrate a comparable (to healthy subjects) decrease of absolute neutrophil counts following RoActemra administration (see section 4.8).

RA
Intravenous use
Clinical efficacy
The efficacy of RoActemra in alleviating the signs and symptoms of RA was assessed in five randomised, double-blind, multi-centre studies. Studies I-V enrolled patients ≥ 18 years of age with active RA diagnosed according to the American College of Rheumatology (ACR) criteria and who had at least eight tender and six swollen joints at baseline.

In Study I, RoActemra was administered intravenously every four weeks as monotherapy. In Studies II, III and V, RoActemra was administered intravenously every four weeks in combination with MTX vs. placebo and MTX. In Study IV, RoActemra was administered intravenously every 4 weeks in combination with other DMARDs vs. placebo and other DMARDs. The primary endpoint for each of the five studies was the proportion of patients who achieved an ACR 20 response at week 24.

Study I evaluated 673 patients who had not been treated with MTX within six months prior to randomisation and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response. The majority (67%) of patients were MTX-naïve. Doses of 8 mg/kg of RoActemra were given every four weeks as monotherapy. The comparator group was weekly MTX (dose titrated from 7.5 mg to a maximum of 20 mg weekly over an eight week period).

Study II, a two year study with planned analyses at week 24, week 52 and week 104, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of RoActemra or placebo were given every four weeks as blinded therapy for 52 weeks in combination with stable MTX (10 mg to 25 mg weekly). After week 52, all patients could receive open-label treatment with RoActemra 8 mg/kg. Of the patients who completed the study who were originally randomised to placebo + MTX, 86% received open-label RoActemra 8 mg/kg in year 2. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At week 52 and week 104 the co-primary endpoints were prevention of joint damage and improvement in physical function.

Study III evaluated 623 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg RoActemra or placebo were given every four weeks, in combination with stable MTX (10 mg to 25 mg weekly).

Study IV evaluated 1,220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg RoActemra or placebo were given every four weeks in combination with stable DMARDs.

Study V evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomisation. Doses of 4 or 8 mg/kg RoActemra or placebo were given every four weeks in combination with stable MTX (10 mg to 25 mg weekly).

Clinical response

In all studies, patients treated with RoActemra 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 2). In study I, superiority of RoActemra 8 mg/kg was demonstrated against the active comparator MTX.

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the ongoing open label extension studies I-V.

In patients treated with RoActemra 8 mg/kg, significant improvements were noted on all individual components of the ACR response including: tender and swollen joint counts; patients and physician global assessment; disability index scores; pain assessment and CRP compared to patients receiving placebo plus MTX or other DMARDs in all studies.

Patients in studies I – V had a mean Disease Activity Score (DAS28) of 6.5–6.8 at baseline. Significant reduction in DAS28 from baseline (mean improvement) of 3.1–3.4 were observed in RoActemra-treated patients compared to control patients (1.3-2.1). The proportion of patients achieving a DAS28 clinical remission (DAS28 < 2.6) was significantly higher in patients receiving RoActemra (28–34%) compared to 1–12% of control patients at 24 weeks. In study II, 65% of patients achieved a DAS28 < 2.6 at week 104 compared to 48% at 52 weeks and 33% of patients at week 24.

In a pooled analysis of studies II, III and IV, the proportion of patients achieving an ACR 20, 50 and 70 response was significantly higher (59% vs. 50%, 37% vs. 27%, 18% vs. 11%, respectively) in the RoActemra 8 mg/kg plus DMARD vs. the RoActemra 4 mg/kg plus DMARD group (p< 0.03). Similarly the proportion of patients achieving a DAS 28 remission (DAS28 < 2.6) was significantly higher (31% vs. 16% respectively) in patients receiving RoActemra 8 mg/kg plus DMARD than in patients receiving RoActemra 4 mg/kg plus DMARD (p< 0.0001).

Table 2. ACR responses in placebo-/MTX-/DMARDs-controlled studies (% patients)

	Study I AMBITION		**Study II LITHE**		**Study III OPTION**		**Study IV TOWARD**		**Study V RADIATE**	
Week	**TCZ 8 mg/kg**	**MTX**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**	**TCZ 8 mg/kg + DMARD**	**PBO + DMARD**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**
	N = 286	**N = 284**	**N = 398**	**N = 393**	**N = 205**	**N = 204**	**N = 803**	**N = 413**	**N = 170**	**N = 158**
ACR 20										
24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
52			56%***	25%						
ACR 50										
24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%
52			36%***	10%						
ACR 70										
24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%
52			20%***	4%						

TCZ - Tocilizumab
MTX - Methotrexate
PBO - Placebo
DMARD - Disease modifying anti-rheumatic drug
** *- p< 0.01, TCZ vs. PBO + MTX/DMARD*
*** *- p< 0.0001, TCZ vs. PBO + MTX/DMARD*

Major clinical response
After 2 years of treatment with RoActemra plus MTX, 14% of patients achieved a major clinical response (maintenance of an ACR70 response for 24 weeks or more).

Radiographic response
In Study II, in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with significantly less radiographic progression in patients receiving RoActemra compared to control (Table 3).

In the open-label extension of Study II the inhibition of progression of structural joint damage in RoActemra plus MTX-treated patients was maintained in the second year of treatment. The mean change from baseline at week 104 in total Sharp-Genant score was significantly lower for patients randomised to RoActemra 8 mg/kg plus MTX (p<0.0001) compared with patients who were randomised to placebo plus MTX.

Table 3. Radiographic mean changes over 52 weeks in Study II

	PBO + MTX (+ TCZ from week 24) N = 393	**TCZ 8 mg/kg + MTX N = 398**
Total Sharp-Genant score	1.13	0.29*
Erosion score	0.71	0.17*
JSN score	0.42	0.12**

PBO - Placebo
MTX - Methotrexate
TCZ - Tocilizumab
JSN - Joint space narrowing
* - *p≤ 0.0001, TCZ vs. PBO + MTX*
** - *p< 0.005, TCZ vs. PBO + MTX*

Following 1 year of treatment with RoActemra plus MTX, 85% of patients(n=348) had no progression of structural joint damage, as defined by a change in the Total Sharp Score of zero or less, compared with 67% of placebo plus MTX-treated patients(n=290) ($p \leq 0.001$). This remained consistent following 2 years of treatment (83%; n=353). Ninety three percent (93%; n=271) of patients had no progression between week 52 and week 104.

Health-related and quality of life outcomes
RoActemra-treated patients reported an improvement in all patient-reported outcomes (Health Assessment Questionnaire Disability Index - HAQ-DI), Short Form-36 and Functional Assessment of Chronic Illness Therapy questionnaires. Statistically significant improvements in HAQ-DI scores were observed in patients treated with RoActemra compared with patients treated with DMARDs. During the open-label period of Study II, the improvement in physical function has been maintained for up to 2 years. At Week 52, the mean change in HAQ-DI was -0.58 in the RoActemra 8 mg/kg plus MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at Week 104 in the RoActemra 8 mg/kg plus MTX group (-0.61).

Haemoglobin levels
Statistically significant improvements in haemoglobin levels were observed with RoActemra compared with DMARDs ($p< 0.0001$) at week 24. Mean haemoglobin levels increased by week 2 and remained within normal range through to week 24.

Tocilizumab versus adalimumab in monotherapy
Study VI (WA19924), a 24 week double-blinded study that compared RoActemra monotherapy with adalimumab monotherapy, evaluated 326 patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the RoActemra arm received an intravenous (IV) infusion of RoActemra (8 mg/kg) every 4 weeks (q4w) and a subcutaneous (SC) placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab SC injection (40 mg) q2w plus an IV placebo infusion q4w. A statistically significant superior treatment effect was seen in favour of RoActemra over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 4).

Table 4: Efficacy Results for Study VI (WA19924)

	ADA + Placebo (IV) N = 162	**TCZ + Placebo (SC) N = 163**	p-value[(a)]
Primary Endpoint - Mean Change from baseline at Week 24			
DAS28 (adjusted mean)	**-1.8**	**-3.3**	
Difference in adjusted mean (95% CI)	**-1.5 (-1.8, -1.1)**		**<0.0001**
Secondary Endpoints - Percentage of Responders at Week 24 [(b)]			
DAS28 < 2.6, n (%)	17 (10.5)	65 (39.9)	<0.0001
DAS28 ≤ 3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001
ACR20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR70 response, n (%)	29 (17.9)	53 (32.5)	0.0023

[a] *p value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.*
[b] *Non-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure*

The overall clinical adverse event profile was similar between RoActemra and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (RoActemra 11.7% vs. adalimumab 9.9%). The types of adverse drug reactions in the RoActemra arm were consistent with the known safety profile of RoActemra and adverse drug reactions were reported at a similar frequency compared with Table 1. A higher incidence of infections and infestations was reported in the RoActemra arm (48% vs. 42%), with no difference in the incidence of serious infections (3.1%). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with RoActemra compared with adalimumab. Four (2.5%) patients in the RoActemra arm and two (1.2%) patients in the adalimumab arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the RoActemra arm and five (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/L (25 mg/dL) for patients in the RoActemra arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the RoActemra arm was consistent with the known safety profile of RoActemra and no new or unexpected adverse drug reactions were observed (see Table 1).

Subcutaneous use

Clinical efficacy

The efficacy of subcutaneous administered RoActemra in alleviating the signs and symptoms of RA and radiographic response, was assessed in two randomised, double-blind, controlled, multi-center studies. For study I (SC-I), patients were required to be >18 years of age with moderate to severe active RA diagnosed according to ACR criteria who had at least 4 tender and 4 swollen joints at baseline. All patients received background non-biologic DMARD(s). For study II (SC-II), patients were required to be > 18 years of age with moderate to severe active RA diagnosed according to ACR criteria who had at least 8 tender and 6 swollen joints at baseline.

Switching from 8 mg/kg intravenous once every 4 weeks to 162 mg subcutaneous once every week, will alter exposure in the patient. The extent varies with the patient's body weight (increased in light body weight patients and decreased in heavy body weight patients) but clinical outcome is consistent with that observed in intravenous treated patients.

Clinical response

Study SC-I evaluated patients with moderate to severe active RA who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where approximately 20% had a history of inadequate response to at least one TNF inhibitor. In SC-I, 1262 patients were randomized 1:1 to receive RoActemra subcutaneous 162 mg every week or RoActemra intravenous 8 mg/kg every four weeks in combination with non-biologic DMARD(s). The primary endpoint in the study was the difference in the proportion of patients who achieved an ACR20 response at week 24. The results from study SC-I is shown in Table 5.

Table 5. ACR responses in study SC-I (% patients) at Week 24

	SC-I[a]	
	TCZ SC 162 mg every week + DMARD N=558	TCZ IV 8 mg/kg + DMARD N=537
ACR20 Week 24	69.4%	73.4%
Weighted difference (95% CI)	-4.0 (-9.2, 1.2)	
ACR50 Week 24	47.0%	48.6%
Weighted difference (95% CI)	-1.8 (-7.5, 4.0)	
ACR70 Week 24	24.0%	27.9%
Weighted difference (95% CI)	-3.8 (-9.0, 1.3)	

TCZ = tocilizumab

a = Per Protocol Population

Patients in study SC-I had a mean Disease Activity Score (DAS28) at baseline of 6.6 and 6.7 on the subcutaneous and intravenous arms, respectively. At week 24, a significant reduction in DAS28 from baseline (mean improvement) of 3.5 was observed on both treatment arms, and a comparable proportion of patients had achieved DAS28 clinical remission (DAS28 < 2.6) on the subcutaneous (38.4%) and IV (36.9%) arms.

Radiographic response

The radiographic response of subcutaneous administered RoActemra was assessed in a double-blind, controlled, multicenter study in patients with active RA (SC-II). Study SC-II evaluated patients with moderate to severe active RA who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where approximately 20% had a history of inadequate response to at least one TNF inhibitor. Patients were required to be >18 years of age with active RA diagnosed according to ACR criteria who had at least 8 tender and 6 swollen joints at baseline. In SC-II, 656 patients were randomized 2:1 to RoActemra subcutaneous 162 mg every other week or placebo, in combination with non-biologic DMARD(s).

In study SC-II, inhibition of structural joint damage was assessed radiographically and expressed as a change from baseline in the van der Heijde modified mean total Sharp score (mTSS). At week 24, inhibition of structural damage was shown, with significantly less radiographic progression in patients receiving RoActemra subcutaneous compared to placebo (mean mTSS of 0.62 vs. 1.23, p=0.0149 (van Elteren). These results are consistent with those observed in patients treated with intravenous RoActemra.

In study SC-II, at week 24 there was ACR20 of 60.9%, ACR50 of 39.8% and ACR70 of 19.7% for patients treated with RoActemra subcutaneous every other week versus placebo ACR20 of 31.5%, ACR50 of 12.3% and ACR70 of 5.0%. Patients had mean DAS28 at baseline of 6.7 on subcutaneous and 6.6 on placebo arms. At week 24, a significant reduction in DAS28 from baseline of 3.1 was

observed on subcutaneous and 1.7 on placebo arm, and for DAS28 < 2.6, 32.0% was observed on subcutaneous and 4.0% on placebo arm.

Health-related and quality of life outcomes
In study SC-I, the mean decrease in HAQ-DI from baseline to week 24 was 0.6 on both the subcutaneous and intravenous arms. The proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was also comparable on the subcutaneous (65.2%) versus intravenous (67.4%) arms, with a weighted difference in proportions of -2.3% (95% CI - 8.1, 3.4). For SF-36, the mean change from baseline at week 24 in the mental component score was 6.22 for the subcutaneous arm and 6.54 for the intravenous arm, and for the physical component score was also similar with 9.49 for the subcutaneous arm and 9.65 for the intravenous arm.

In study SC-II, mean decrease in HAQ-DI from baseline to week 24 was significantly greater for patients treated with RoActemra subcutaneous every other week (0.4) versus placebo (0.3). Proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was higher for RoActemra subcutaneous every other week (58%) versus placebo (46.8%). SF-36 (mean change in mental and physical component scores) was significantly greater with RoActemra subcutaneous group (6.5 and 5.3) versus placebo (3.8 and 2.9).

GCA
Subcutaneous Use
Clinical efficacy
Study WA28119 was a randomized, multi-center, double-blind placebo-controlled Phase III superiority study conducted to assess the efficacy and safety of RoActemra in patients with GCA.

Two hundred and fifty one (251) patients with new-onset or relapsing GCA were enrolled and assigned to one of four treatment arms. The study consisted of a 52-week blinded period (Part 1), followed by a 104-week open-label extension (Part 2). The purpose of Part 2 was to describe the long-term safety and maintenance of efficacy after 52 weeks of RoActemra therapy, to explore the rate of relapse and the requirement for RoActemra therapy beyond 52 weeks, and to gain insight into the potential long-term steroid-sparing effect of RoActemra.

Two subcutaneous doses of RoActemra (162 mg every week and 162 mg every other week) were compared to two different placebo control groups randomised 2:1:1:1.

All patients received background glucocorticoid (prednisone) therapy. Each of the RoActemra-treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen over 26 weeks, while the second placebo-treated group followed a pre-specified prednisone-taper regimen over 52 weeks, designed to be more in keeping with standard practice.

The duration of glucocorticoid therapy during screening and before RoActemra (or placebo) was initiated, was similar in all 4 treatment groups (see Table 6).

Table 6. Duration of Corticosteroid Therapy During Screening in Study WA28119

	Placebo + 26 weeks prednisone taper N=50	Placebo + 52 weeks prednisone taper N=51	RoActemra 162mg SC weekly + 26 weeks prednisone taper N=100	RoActemra 162 mg SC every other weekly + 26 weeks prednisone taper N=49
Duration (days)				
Mean (SD)	35.7 (11.5)	36.3 (12.5)	35.6 (13.2)	37.4 (14.4)
Median	42.0	41.0	41.0	42.0
Min - Max	6 - 63	12 – 82	1 - 87	9 - 87

The primary efficacy endpoint assessed by the proportion of patients achieving steroid free sustained remission at week 52 on RoActemra plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper, was met (Table 7).

The key secondary efficacy endpoint also based on the proportion of patients achieving sustained remission at week 52, comparing tocilizumab plus 26 weeks prednisone taper with placebo plus 52 weeks prednisone taper, was also met (Table 7).

A statistically significant superior treatment effect was seen in favour of RoActemra over placebo in achieving steroid-free sustained remission at week 52 on RoActemra plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper and with placebo plus 52 weeks prednisone taper.

The percentage of patients achieving sustained remission at week 52, are shown in the Table 7.

Secondary Endpoints
The assessment of the time to first GCA flare showed a significantly lower risk of flare for the RoActemra subcutaneous weekly group compared to placebo plus 26 weeks prednisone and placebo plus 52 weeks prednisone taper groups and for the RoActemra subcutaneous every other weekly group compared to placebo plus 26 weeks prednisone (when compared at a 0.01 significance level). RoActemra subcutaneous weekly dose also showed a clinically meaningful decrease in the risk for flare compared to placebo plus 26 weeks prednisone in patients who entered the trial with relapsing GCA as well as those with new-onset disease (Table 7).

Cumulative glucocorticoid dose
The cumulative prednisone dose at week 52 was significantly lower in the two RoActemra dose groups compared to the two placebo groups (Table 6). In a separate analysis of the patients who received escape prednisone to treat GCA flare during the first 52 weeks, the cumulative prednisone dose varied greatly. The median doses for escape patients in the RoActemra weekly and every other weekly groups were 3129.75 mg and 3847 mg, respectively. Both considerably lower than in the placebo plus 26 weeks and the placebo plus 52 weeks prednisone taper groups, 4023.5 mg and 5389.5 mg respectively.

Table 7. Efficacy results from Study WA28119

	Placebo + 26 weeks prednisone taper N=50	Placebo + 52 weeks prednisone taper N=51	RoActemra 162mg SC weekly + 26 weeks prednisone taper N=100	RoActemra 162 mg SC every other weekly + 26 weeks prednisone taper N=49
Primary Endpoint				
****Sustained remission (Tocilizumab groups vs Placebo+26)				
Responders at Week 52, n (%)	7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions (99.5% CI)	N/A	N/A	42%* (18.00, 66.00)	39.06%* (12.46 , 65.66)
Key Secondary Endpoint				
Sustained remission (Tocilizumab groups vs Placebo+52)				
Responders at Week 52, n (%)	7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions (99.5% CI)	N/A	N/A	38.35%* (17.89 , 58.81)	35.41%** (10.41 ,60.41)
Other Secondary Endpoints				
Time to first GCA flare[1] (Tocilizumab groups vs Placebo+26)	N/A	N/A	0.23* (0.11, 0.46)	0.28** (0.12, 0.66)
HR (99% CI)	N/A	N/A	0.39** (0.18, 0.82)	0.48 (0.20, 1.16)
Time to first GCA flare[1] (Tocilizumab groups vs Placebo+52)				
HR (99% CI)	N/A	N/A	0.23*** (0.09,0.61)	0.42 (0.14, 1.28)
Time to first GCA flare[1] (Relapsing patients; Tocilizumab groups vs Placebo +26) HR (99% CI)	N/A	N/A	0.36 (0.13, 1.00)	0.67 (0.21,2.10)
Time to first GCA flare[1] (Relapsing patients; Tocilizumab groups vs Placebo + 52) HR (99% CI)	N/A	N/A	0.25*** (0.09, 0.70)	0.20*** (0.05, 0.76)
Time to first GCA flare[1] (New-onset patients; Tocilizumab groups vs Placebo +26) HR (99% CI)	N/A	N/A	0.44 (0.14, 1.32)	0.35 (0.09, 1.42)
Time to first GCA flare[1] (New-onset patients; Tocilizumab groups vs Placebo + 52) HR (99% CI)				
Cumulative glucocorticoid dose (mg)				
median at Week 52 (Tocilizumab groups vs Placebo+26[2])	3296.00	N/A	1862.00*	1862.00*
median at Week 52 (Tocilizumab groups vs Placebo +52[2])	N/A	3817.50	1862.00*	1862.00*
Exploratory Endpoints				
Annualized relapse rate, Week 52[§]				
Mean (SD)	1.74 (2.18)	1.30 (1.84)	0.41 (0.78)	0.67 (1.10)

* p<0.0001
** p<0.005 (threshold for significance for primary and key secondary tests of superiority)
***Descriptive p value ≤0.005
****Flare: recurrence of GCA signs or symptoms and/or ESR ≥30 mm/h** – Increase in the prednisone dose required
Remission: absence of flare and normalization of the CRP
Sustained remission: remission from week 12 to week 52 –Patients must adhere to the protocol-defined prednisone taper
[1] analysis of the time (in days) between clinical remission and first disease flare
[2] p-values are determined using a Van Elteren analysis for non-parametric data
[§] statistical analyses has not been performed
N/A= Not applicable
HR = Hazard Ratio
CI = Confidence Interval

Quality of Life Outcomes

In study WA28119, the SF-36 results were separated into the physical and mental component summary scores (PCS and MCS, respectively). The PCS mean change from baseline to week 52 was higher (showing more improvement) in the RoActemra weekly and every other weekly dose groups [4.10, 2.76, respectively] than in the two placebo groups [placebo plus 26 weeks; -0.28, placebo plus 52 weeks; -1.49], although only the comparison between RoActemra weekly plus 26 weeks prednisone taper group and placebo plus 52 weeks prednisone taper group (5.59, 99% CI: 8.6, 10.32) showed a statistically significant difference (p=0.0024). For MCS, the mean change from baseline to week 52 for both RoActemra weekly and every other weekly dose groups [7.28, 6.12, respectively] were higher than the placebo plus 52 weeks prednisone taper group [2.84] (although the differences were not statistically significant [weekly p=0.0252 for weekly, p=0.1468 for every other weekly]) and similar to the placebo plus 26 weeks prednisone taper group [6.67].

The Patient's Global Assessment of disease activity was assessed on a 0-100mm Visual Analogue Scale (VAS). The mean change in Patient's global VAS from baseline at week 52 was lower (showing greater improvement) in the RoActemra weekly and every other weekly dose groups [-19.0, -25.3, respectively] than in both placebo groups [placebo plus 26 weeks -3.4, placebo plus 52 weeks -7.2], although only the RoActemra every other weekly plus 26 weeks prednisone taper group showed a statistically significant difference compared to placebo [placebo plus 26 weeks taper p=0.0059, and placebo plus 52 weeks taper p=0.0081].

FACIT-Fatigue change from baseline to week 52 scores were calculated for all groups. The mean [SD] change scores were as follows: RoActemra weekly plus 26 weeks 5.61 [10.115], RoActemra every other weekly plus 26 weeks 1.81 [8.836], placebo plus 26 weeks 0.26 [10.702], and placebo plus 52 weeks -1.63 [6.753].

Change in EQ5D scores from baseline to week 52 were RoActemra weekly plus 26 weeks 0.10 [0.198], RoActemra every other weekly plus 26 weeks 0.05 [0.215], placebo plus 26 weeks 0.07 [0.293], and placebo plus 52 weeks -0.02 [0.159].

Higher scores signal improvement in both FACIT-Fatigue and EQ5D.

5.2 Pharmacokinetic properties

The pharmacokinetics of RoActemra is characterized by nonlinear elimination which is a combination of linear clearance and Michaelis-Menten elimination. The nonlinear part of RoActemra elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of RoActemra do not change with time. Due to the dependence of total clearance on RoActemra serum concentrations, the half-life of RoActemra is also concentration-dependent and varies depending on the serum concentration level. Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.

<u>RA</u>
<u>Intravenous use</u>
The pharmacokinetics of RoActemra were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with a one-hour infusion of 4 or 8 mg/kg RoActemra every 4 weeks for 24 weeks or with 162 mg RoActemra given subcutaneously either once a week or every other week for 24 weeks.

The following parameters (predicted mean ± SD) were estimated for a dose of 8 mg/kg RoActemra given every 4 weeks: steady-state area under curve (AUC) = 38000 ± 13000 h μg/mL, trough concentration (Cmin) = 15.9 ± 13.1 μg/mL and maximum concentration (Cmax) = 182 ± 50.4 μg/mL, and. the accumulation ratios for AUC and Cmax were small, 1.32 and 1.09, respectively. The accumulation ratio was higher for Cmin (2.49), which was expected based on the non-linear clearance contribution at lower concentrations. Steady-state was reached following the first administration for

Cmax and after 8 and 20 weeks for AUC and Cmin, respectively. RoActemra AUC, Cmin and Cmax increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, Cmin and Cmax of RoActemra were 50000 ± 16800 µg•h/mL, 24.4 ± 17.5 µg/mL, and 226 ± 50.3 µg/mL, respectively, which are higher than mean exposure values for the patient population (i.e. all body weights) reported above. The dose-response curve for RoActemra flattens at higher exposure, resulting in smaller efficacy gains for each incremental increase in RoActemra concentration such that clinically meaningful increases in efficacy were not demonstrated in patients treated with > 800 mg of RoActemra. Therefore, RoActemra doses exceeding 800 mg per infusion are not recommended (see section 4.2).

Distribution
In RA patients the central volume of distribution was 3.72, the peripheral volume of distribution was 3.35 resulting in a volume of distribution at steady state of 7.07.

Elimination
Following intravenous administration, RoActemra undergoes biphasic elimination from the circulation. The total clearance of RoActemra was concentration-dependent and is the sum of the linear and non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 9.5 mL/h. The concentration-dependent non-linear clearance plays a major role at low RoActemra concentrations. Once the non-linear clearance pathway is saturated, at higher RoActemra concentrations, clearance is mainly determined by the linear clearance.
The $t_{1/2}$ of RoActemra was concentration-dependent. At steady-state following a dose of 8 mg/kg every 4 weeks, the effective $t_{1/2}$ decreased with decreasing concentrations within a dosing interval from 18 days to 6 days.

Linearity
Pharmacokinetic parameters of RoActemra did not change with time. A more than dose-proportional increase in the AUC and C_{min} was observed for doses of 4 and 8 mg/kg every 4 weeks. C_{max} increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 3.2 and 30 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

Subcutaneous use
The pharmacokinetics of RoActemra were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with 162 mg subcutaneous every week, 162 mg subcutaneous every other week, and or 4 or 8 mg/kg intravenous every 4 weeks for 24 weeks.

The pharmacokinetic parameters of RoActemra did not change with time. For the 162 mg every week dose, the predicted mean (±SD) steady-state AUC1week, C_{min} and C_{max} of RoActemra were 7970 ± 3432 µg•h/mL, 43.0 ± 19.8 µg/mL, and 49.8 ± 21.0 µg /mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 6.32, 6.30, and 5.27, respectively. Steady state was reached after 12 weeks for AUC, C_{min}, and C_{max}.

For the 162 every other week dose, the predicted mean (±SD) steady-state AUC2week, C_{min}, and Cmax of RoActemra were 3430 ± 2660 µg•h/mL, 5.7 ± 6.8 µg/mL, and 13.2 ± 8.8 µg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 2.67, 6.02, and 2.12, respectively. Steady state was reached after 12 weeks for AUC and C_{min}, and after 10 weeks for C_{max}.

Absorption
Following subcutaneous dosing in RA patients, the time to peak serum RoActemra concentrations t_{max} was 2.8 days. The bioavailability for the subcutaneous formulation was 79%.

Elimination
For subcutaneous administration, the concentration-dependent apparent $t_{1/2}$ is up to 12 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state.

GCA

Subcutaneous use

The PK of RoActemra in GCA patients were determined using a population PK model from an analysis dataset composed of 149 GCA patients treated with 162 mg subcutaneous every week or 162 mg subcutaneous every other week. The developed model had the same structure as the population PK model developed earlier based on data from RA patients (see Table 8).

Table 8. Predicted mean ± SD PK parameters at steady-state after subcutaneous dosing in GCA

	Subcutaneous	
Tocilizumab PK Parameter	**162 mg every other weekly**	**162 mg weekly**
C_{max} (μg/mL)	19.3 ± 12.8	73 ± 30.4
C_{trough} (μg/mL)	11.1 ± 10.3	68.1± 29.5
C_{mean} (μg/mL)	16.2 ± 11.8	71.3 ± 30.1
Accumulation C_{max}	2.18	8.88
Accumulation C_{trough}	5.61	9.59
Accumulation C_{mean} or AUC_{τ}	2.81	10.91

The steady-state profile following the RoActemra weekly dose was almost flat, with very little fluctuations between trough and peak values, while there were substantial fluctuations for the RoActemra every other weekly dose. Approximately 90% of the steady-state (AUC_{τ}) was reached by week 14 in the every other weekly and week 17 in the weekly dose groups.

Based on the current characterization of PK, RoActemra trough concentration at steady state are 50% higher in this population relative to average concentrations in a large dataset from the RA population. These differences occur due to unknown reasons. PK differences are not accompanied by marked differences in PD parameters and so the clinical relevance is unknown.

In GCA patients, higher exposure was observed in patients with lower body weight. For the 162 mg every week dosing regimen, the steady-state Cavg was 51% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. For the 162 mg every other week regimen, the steady-state Cavg was 129% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. There is limited data for patients above 100 kg (n=7).

Absorption

Following subcutaneous dosing in GCA patients, the absorption t½ was around 4 days. The bioavailability for the SC formulation was 0.8. The median values of T_{max} were 3 days after the RoActemra weekly dose and 4.5 days after the tocilizumab every other week dose.

Distribution

In GCA patients, the central volume of distribution was 4.09 L, the peripheral volume of distribution was 3.37 L, resulting in a volume of distribution at steady state of 7.46 L.

Elimination

The total clearance of RoActemra was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 6.7 mL/h in GCA patients,

In GCA patients, at steady state, the effective t ½ of RoActemra varied between 18.3 and 18.9 days for 162 mg weekly regimen, and between 4.2 and 7.9 days for 162 mg every other weekly regimen. At high serum concentrations, when total clearance of RoActemra is dominated by linear clearance, an effective t ½ of approximately 32 days was derived from the population parameter estimates.

Special populations
Renal impairment: No formal study of the effect of renal impairment on the pharmacokinetics of RoActemra has been conducted. Most of the patients in the RA and GCA studies population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance based on Cockcroft-Gault formula) did not impact the pharmacokinetics of RoActemra.

Approximately one-third of the patients in the GCA study had moderate renal impairment at baseline (estimated creatinine clearance of 30-59 mL/min). No impact on RoActemra exposure was noted in these patients.

No dose adjustment is required in patients with mild or moderate renal impairment.

Hepatic impairment: No formal study of the effect of hepatic impairment on the pharmacokinetics of RoActemra has been conducted.

Age, gender and ethnicity: Population pharmacokinetic analyses in RA and GCA patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of RoActemra.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies were not performed because IgG1 monoclonal antibodies are not deemed to have intrinsic carcinogenic potential.

Available non-clinical data demonstrated the effect of IL-6 on malignant progression and apoptosis resistance to various cancer types. This data does not suggest a relevant risk for cancer initiation and progression under RoActemra treatment. Additionally, proliferative lesions were not observed in a 6-month chronic toxicity study in cynomolgus monkeys or in IL-6 deficient mice.

Available non-clinical data do not suggest an effect on fertility under RoActemra treatment. Effects on endocrine active and reproductive system organs were not observed in a chronic cynomolgus monkey toxicity study and reproductive performance was not affected in IL-6 deficient mice. RoActemra administered to cynomolgus monkeys during early gestation, was observed to have no direct or indirect harmful effect on pregnancy or embryonal-foetal development. However, a slight increase in abortion/embryonal-foetal death was observed with high systemic exposure (> 100 x human exposure) in the 50 mg/kg/day high-dose group compared to placebo and other low-dose groups. Although IL-6 does not seem to be a critical cytokine for foetal growth or the immunological control of the maternal/foetal interface, a relation of this finding to RoActemra cannot be excluded.

Treatment with a murine analogue did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

The non-clinical safety profile of RoActemra in the cynomolgus monkey does not suggest a difference between intravenous and subcutaneous routes of administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine monohydrochloride monohydrate
L-Arginine
L-Arginine hydrochloride
L-Methionine
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months.

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

0.9 mL solution in a pre-filled syringe (type I glass) with a staked-in needle containing 162 mg RoActemra assembled into a pre-filled pen. The syringe is closed by a rigid needle shield (elastomer seal with a polypropylene shell) and a plunger stopper (butyl rubber with a fluororesin coating).

Pack sizes of 4 pre-filled pens **and multipacks containing 12 (3 packs of 4) pre-filled pens. Not all pack sizes may be marketed.**

6.6 Special precautions for disposal and other handling

RoActemra is supplied in a single use pre-filled pen. After removing the pre-filled pen from the refrigerator the pre-filled pen should be allowed to reach room temperature (18°C to 28°C) by waiting for 45 minutes, before injecting RoActemra. The pen should not be shaken. After removing the cap the injection must be started within 3 minutes, to prevent the medicine from drying out and blocking the needle. If the pre-filled pen is not used within 3 minutes of removing the cap, you must dispose of it in a puncture resistant container and use a new pre-filled pen.

If following pressing the activation button the purple indicator does not move, you must dispose of the pre-filled pen in a puncture resistant container. **Do not** try to re-use the pre-filled pen. Do not repeat the injection with another pre-filled pen. Call your healthcare provider for help.

Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to slightly yellowish, or any part of the pre-filled pen appears to be damaged.

Comprehensive instructions for the administration of RoActemra in a pre-filled pen are given in the package leaflet.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/009
EU/1/08/492/010

9. DATE OF FIRST AUTHORISATION/DATE OF LATEST RENEWAL

Date of first authorisation: 16 January 2009
Date of last renewal: 25 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Chugai Pharma Manufacturing Co., Ltd.
16-3 Kiyohara Kogyodanchi
Utsunomiya City
Tochigi, 321-3231
Japan

Genentech Inc.
One Antibody Way
Oceanside
CA 92056
USA

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA, sJIA, pJIA and GCA, targeting all physicians who are expected to prescribe/use RoActemra containing the following:

- Physician Information Pack
- Nurse Information Pack
- Patient Information Pack

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational material.

The Physician Information pack should contain the following key elements:

- The Summary of Product Characteristics
- Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
- Risk of serious infections
    - The product must not be given to patients with active or suspected infection
    - The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Serious injection/infusion reaction and their management
- Serious hypersensitivity reactions and their management
- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
- Reporting of serious adverse drug reactions
- The Patient Information Packs (to be given to patients by healthcare professionals)
- Diagnosis of Macrophage Activation Syndrome in sJIA patients
- Recommendations for dose interruptions in sJIA and pJIA patients

The Nurse Information Pack should contain the following key elements:

- Prevention of medical errors and injection/infusion reactions
    - Preparation of injection/infusion
    - Infusion rate
- Monitoring of the patient for injection/infusion reactions
- Reporting of serious adverse reactions

The Patient Information Pack should contain the following key elements:

- Package leaflet (with instructions for use for SC)
- Patient alert card

- to address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear.
- to address the risk that patients using RoActemra may develop complications of diverticulitis which can become serious if not treated.
- to address the risk of allergic reactions.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 20 mg/mL concentrate for solution for infusion
Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 80 mg tocilizumab.

3. LIST OF EXCIPIENTS

Polysorbate 80, sucrose, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
80 mg/4 mL
1 vial of 4 mL
4 vials of 4 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after dilution
The diluted product should be used immediately
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/001
EU/1/08/492/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 20 mg/mL concentrate for solution for infusion
Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 200 mg tocilizumab.

3. LIST OF EXCIPIENTS

Polysorbate 80, sucrose, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
200 mg/10 mL
1 vial of 10 mL
4 vials of 10 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after dilution
The diluted product should be used immediately
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton, in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/003
EU/1/08/492/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 20 mg/mL concentrate for solution for infusion
Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 400 mg tocilizumab.

3. LIST OF EXCIPIENTS

Polysorbate 80, sucrose, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
400 mg/20 mL
1 vial of 20 mL
4 vials of 20 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after dilution
The diluted product should be used immediately
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton, in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/005
EU/1/08/492/006

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled syringe

Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe contains 162 mg tocilizumab

3. LIST OF EXCIPIENTS

L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
4 pre-filled syringes
162 mg/0.9 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the syringe to sit at room temperature outside the box for 25 to 30 minutes before use

8. EXPIRY DATE

EXP

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30 °C

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

roactemra 162 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON (WITH BLUE BOX) - Multipack

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled syringe

Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe contains 162 mg tocilizumab

3. LIST OF EXCIPIENTS

L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
Multipack: 12 (3 packs of 4) pre-filled syringes.
162 mg/0.9 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the syringe to sit at room temperature outside the box for 25 to 30 minutes before use

8. EXPIRY DATE

EXP

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30 °C

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C–8°C)
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/008

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

roactemra 162 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON (WITHOUT BLUE BOX) - Multipack

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled syringe

Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe contains 162 mg tocilizumab

3. LIST OF EXCIPIENTS

L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
4 pre-filled syringes. Component of a multipack, can't be sold separately.
162 mg/0.9 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the syringe to sit at room temperature outside the box for 25 to 30 minutes before use

8. EXPIRY DATE

EXP

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30 °C

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/008

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

roactemra 162 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled pen

Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled pen contains 162 mg tocilizumab

3. LIST OF EXCIPIENTS

L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen, ACTPen®
4 pre-filled pens
162 mg/0.9 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the pre-filled pen to sit at room temperature outside the box for 45 minutes before use

8. EXPIRY DATE

EXP

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30 °C

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C–8°C)
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/009

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

roactemra 162 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON (WITH BLUE BOX) - Multipack

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled pen

Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled pen contains 162 mg tocilizumab

3. LIST OF EXCIPIENTS

L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen, ACTPen®
Multipack: 12 (3 packs of 4) pre-filled pens.
162 mg/0.9 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the pre-filled pen to sit at room temperature outside the box for 45 minutes before use

8. EXPIRY DATE

EXP

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30 °C

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C–8°C)
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/010

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

roactemra 162 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON (WITHOUT BLUE BOX) - Multipack

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled pen

Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled pen contains 162 mg tocilizumab

3. LIST OF EXCIPIENTS

L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen, ACTPen®
4 pre-filled pens. Component of a multipack, can't be sold separately.
162 mg/0.9 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the pre-filled pen to sit at room temperature outside the box for 45 minutes before use

8. EXPIRY DATE

EXP

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30 °C

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C–8°C)
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/010

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

roactemra 162 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RoActemra 20 mg/mL sterile concentrate
Tocilizumab
IV

2. METHOD OF ADMINISTRATION

IV infusion

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 mg/4 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RoActemra 20 mg/mL sterile concentrate
Tocilizumab
IV

2. METHOD OF ADMINISTRATION

IV infusion

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg/10 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RoActemra 20 mg/mL sterile concentrate
Tocilizumab
IV

2. METHOD OF ADMINISTRATION

IV infusion

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

400 mg/20 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RoActemra 162 mg injection
Tocilizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

162 mg/0.9 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RoActemra 162 mg injection
Tocilizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

162 mg/0.9 mL

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

RoActemra 20 mg/mL concentrate for solution for infusion
Tocilizumab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, you will be given a **Patient Alert Card**, which contains important safety information that you need to be aware of before and during treatment with RoActemra.

What is in this leaflet:
1. What RoActemra is and what it is used for
2. What you need to know before you are given RoActemra
3. How RoActemra is given
4. Possible side effects
5. How to store RoActemra
6. Contents of the pack and other information

1. What RoActemra is and what it is used for

RoActemra contains the active substance tocilizumab, which is a protein made from specific immune cells (monoclonal antibody), that blocks the action of a specific protein (cytokine) called interleukin-6. This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body. RoActemra helps to reduce symptoms such as pain and swelling in your joints and can also improve your performance of daily tasks. RoActemra has been shown to slow the damage to the cartilage and bone of the joints caused by the disease and to improve your ability to do normal daily activities.

- **RoActemra is used to treat adults** with moderate to severe active rheumatoid arthritis (RA), an autoimmune disease, if previous therapies did not work well enough. RoActemra is usually given in combination with methotrexate. However, RoActemra can be given alone if your doctor determines that methotrexate is inappropriate.

- RoActemra can also be used to treat adults who have not had previous methotrexate treatment if they have severe, active and progressive rheumatoid arthritis.

- **RoActemra is used to treat children with sJIA**. RoActemra is used for children aged 2 years and over who have ***active systemic juvenile idiopathic arthritis*** (***sJIA***), an inflammatory disease that causes pain and swelling in one or more joints as well as fever and rash. RoActemra is used to improve the symptoms of sJIA and can be given in combination with methotrexate or alone.

- **RoActemra is used to treat children with pJIA**. RoActemra is used for children aged 2 years and over with active ***polyarticular juvenile idiopathic arthritis*** (***pJIA***), an inflammatory disease that causes pain and swelling in one or more joints. RoActemra is used to improve the symptoms of pJIA and can be given in combination with methotrexate or alone.

- **RoActemra is used to treat adults and children** aged 2 years and over with severe or life-threatening **cytokine release syndrome (CRS)**, a side-effect in patients treated with chimeric antigen receptor (CAR) T-cell therapies used to treat certain types of cancer.

2. What you need to know before you are given RoActemra

You are not to be given RoActemra
- if you are **allergic** to tocilizumab or any of the other ingredients of this medicine (listed in Section 6).
- if you have an active, severe infection.

If any of these applies to you, tell the doctor or nurse giving you the infusion.

Warnings and precautions
Talk to your doctor or nurse before you are given RoActemra.

- If you experience **allergic reactions** such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips or skin rash during or after the infusion, then **tell your doctor immediately.**

- If you have any kind of **infection**, short- or long-term, or if you often get infections. **Tell your doctor immediately** if you feel unwell. RoActemra can reduce your body's ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection.

- If you have had **tuberculosis**, tell your doctor. Your doctor will check for signs and symptoms of tuberculosis before starting RoActemra. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

- If you have had **intestinal ulcers** or **diverticulitis**, tell your doctor. Symptoms would include abdominal pain and unexplained changes in bowel habits with a fever.

- If you have **liver disease**, tell your doctor. Before you use RoActemra, your doctor may do a blood test to measure your liver function.

- **If any patient has recently been vaccinated** (either adult or child), or is planning a vaccination, tell your doctor. All patients, especially children, should be up-to-date with all their vaccinations before they start treatment with RoActemra. Certain types of vaccines should not be used while receiving RoActemra.

- If you have **cancer**, tell your doctor. Your doctor will have to decide if you can still be given RoActemra.

- If you have **cardiovascular risk factors** such as raised blood pressure and raised cholesterol levels, tell your doctor. These factors need to be monitored while receiving RoActemra.

- If you have moderate to severe **kidney function problems**, your doctor will monitor you.

- If you have **persistent headaches**.

Your doctor will perform blood tests before you are given RoActemra, and during your treatment, to determine if you have a low white blood cell count, low platelet count or high liver enzymes.

Children and adolescents
RoActemra is not recommended for use in children under 2 years of age.

If a child has a history of ***macrophage activation syndrome***, (activation and uncontrolled proliferation of specific blood cells), tell your doctor. Your doctor will have to decide if they can still be given RoActemra.

Other medicines and RoActemra
Tell your doctor if you are taking any other medicines (or your child is, if they are the patient), or have recently taken any. This includes medicines obtained without a prescription. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. If you are using medicines containing any of the following active substances, **tell your doctor**:

- methylprednisolone, dexamethasone, used to reduce inflammation
- simvastatin or atorvastatin, used to reduce **cholesterol levels**
- calcium channel blockers (e.g. amlodipine), used to treat **raised blood pressure**
- theophylline, used to treat **asthma**
- warfarin or phenprocoumon, used as a **blood thinning agents**
- phenytoin, used to treat **convulsions**
- ciclosporin, used to **suppress your immune system** during organ transplants
- benzodiazepines (e.g. temazepam), used to **relieve anxiety.**

Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA, sJIA or pJIA.

Pregnancy, breast-feeding and fertility
RoActemra is not to be used in pregnancy unless clearly necessary. Talk to your doctor if you are pregnant, may be pregnant, or intend to become pregnant.

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Stop breast-feeding if you are to be given RoActemra, and talk to your doctor. Leave a gap of at least 3 months after your last treatment before you start breast-feeding. It is not known whether RoActemra is passed into breast milk.

The data available so far does not suggest any effect on fertility from this treatment.

Driving and using machines
This medicine can cause dizziness. If you feel dizzy, do not drive or use machines.

RoActemra contains sodium
This medicine contains 26.55 mg sodium per maximum dose of 1200 mg. Take this into account if you are on a low-sodium diet. However, doses below 1025 mg of this medicine contain less than 23 mg sodium, so they are virtually sodium free.

3. How RoActemra is given

This medicine is subject to restricted medical prescription by your doctor.

RoActemra will be given to **you as a drip into a vein, by a doctor or a nurse.** They will dilute the solution, set up the intravenous infusion and monitor you during and after the treatment.

Adult patients with RA
The usual dose of RoActemra is 8 mg per kg of body weight. Depending on your response, your doctor may decrease your dose to 4 mg/kg then increase back to 8 mg/kg when appropriate.

Adults will be given RoActemra once every 4 weeks through a drip in the vein (intravenous infusion) over one hour.

Children with sJIA (aged 2 and over)
The usual dose of RoActemra depends on your weight.
- If you weigh less than 30 kg: the dose is **12 mg for every kilogram of body weight**
- If you weigh 30 kg or more, the dose is **8 mg for every kilogram of body weight**

The dose is calculated based on your body weight at each administration.

Children with sJIA will be given RoActemra once every 2 weeks through a drip in the vein (intravenous infusion) over one hour.

Children with pJIA (aged 2 and over)
The usual dose of RoActemra depends on your weight.
- If you weigh less than 30 kg: the dose is **10mg for every kilogram of body weight**
- If you weigh 30 kg or more: the dose is **8 mg for every kilogram of body weight**

The dose is calculated based on your body weight at each administration.

Children with pJIA will be given RoActemra once every 4 weeks through a drip in the vein (intravenous infusion) over one hour.

Patients with CRS
The usual dose of RoActemra is **8 mg for every kg of body weight if you weigh 30 kg or more**.
The dose is **12 mg for every kg of body weight if you weigh less than 30 kg**.
RoActemra can be given alone or in combination with corticosteroids.

If you are given more RoActemra than you should
Since RoActemra is given by a doctor or nurse, it is unlikely that you will be given too much. However, if you are worried, talk to your doctor.

If you miss a dose of RoActemra
Since RoActemra is given by a doctor or nurse, it is unlikely that you will miss a dose. However, if you are worried, talk to your doctor or nurse.

If you stop being given RoActemra
You should not stop using RoActemra without discussing with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, RoActemra can cause side effects, although not everybody gets them. Side effects could occur at least up to 3 months after your last dose of RoActemra.

Possible serious side effects: tell a doctor straight away.
These are common: they may affect up to 1 in every 10 users

Signs of serious infections
- fever and chills
- mouth or skin blisters
- stomach ache

If you notice any of these, tell your doctor **as soon as possible.**

Very common side effects:
These may affect more than 1 in every 10 users
- upper respiratory tract infections with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache
- high blood fat (cholesterol) levels.

Common side effects:
These may affect up to 1 in every 10 users
- lung infection (pneumonia)
- shingles (herpes zoster)
- cold sores (oral herpes simplex), blisters
- skin infection (cellulitis) sometimes with fever and chills
- rash and itching, hives
- allergic (hypersensitivity) reactions
- eye infection (conjunctivitis)
- headache, dizziness, high blood pressure
- mouth ulcers, stomach pain
- fluid retention (oedema) in the lower legs, weight increase
- cough, shortness of breath
- low white blood cell counts shown by blood tests (neutropenia, leucopenia)
- abnormal liver function tests (increased transaminases)
- increased bilirubin shown by blood tests
- low fibrinogen levels in the blood (a protein involved in blood clotting).

Uncommon side effects:
These may affect up to 1 in every 100 users
- diverticulitis (fever, nausea, diarrhoea, constipation, stomach pain)
- red swollen areas in the mouth
- high blood fat (triglycerides)
- stomach ulcer
- kidney stones
- underactive thyroid.

Very rare side effects:
These may affect up to 1 in every 10,000 users
- low counts for white blood cells, red blood cells and platelets in blood tests.
- stevens-johnson syndrome (skin rash, which may lead to severe blistering and peeling of the skin)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

Children with sJIA
In general, side effects in sJIA patients were of a similar type to those in adults with RA. Some side effects were seen more often: inflamed nose and throat, diarrhoea, lower white blood cell counts and higher liver enzymes.

Children with pJIA
In general, side effects in pJIA patients were of a similar type to those in adults with RA. Some side effects were seen more often: inflamed nose and throat, headache, feeling sick (nausea) and lower white blood cell counts.

5. How to store RoActemra

Keep RoActemra out of the sight and reach of children.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Do not use this medicine after the expiry date which is stated on the carton.

6. Contents of the pack and other information

What RoActemra contains

- The active substance is tocilizumab.
  Each 4 mL vial contains 80 mg tocilizumab (20 mg/mL).
  Each 10 mL vial contains 200 mg tocilizumab (20 mg/mL).
  Each 20 mL vial contains 400 mg tocilizumab (20 mg/mL).

- The other ingredients are sucrose, polysorbate 80, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections.

What RoActemra looks like and contents of the pack
RoActemra is a concentrate for solution for infusion. The concentrate is a clear to opalescent, colourless to pale yellow liquid.
RoActemra is supplied as vials containing 4 mL, 10 mL and 20 mL concentrate for solution for infusion. Pack size of 1 and 4 vials. Not all pack sizes may be marketed.

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This leaflet was last revised

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Instructions for dilution prior to administration
Parenteral medicinal products should be inspected visually for particulate matter or discoloration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted.

RA and CRS adult patients (≥ 30 kg)
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (0.4 mL/kg) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

Use in the paediatric population

sJIA, pJIA and CRS patients ≥ 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.4 mL/kg**) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

sJIA and CRS patients < 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 50 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.6 mL/kg**) should be withdrawn from the vial and placed in the 50 mL infusion bag. This should be a final volume of 50 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

pJIA patients < 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 50 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.5 mL/kg**) should be withdrawn from the vial and placed in the 50 mL infusion bag. This should be a final volume of 50 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

RoActemra is for single-use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

RoActemra 162 mg solution for injection in pre-filled syringe
Tocilizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it onto others. It may harm them even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, you will be given a **Patient Alert Card**, which contains important safety information that you need to be aware of before and during treatment with RoActemra.

What is in this leaflet:
1. What RoActemra is and what it is used for
2. What you need to know before you use RoActemra
3. How to use RoActemra
4. Possible side effects
5. How to store RoActemra
6. Contents of the pack and other information

1. What RoActemra is and what it is used for

RoActemra contains the active substance tocilizumab, which is a protein made from specific immune cells (monoclonal antibody), that blocks the action of a specific protein (cytokine) called interleukin-6. This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body. RoActemra is used to treat:

- **adults with moderate to severe active rheumatoid arthritis (RA)**, an autoimmune disease, if previous therapies did not work well enough.

- **adults with severe, active and progressive rheumatoid arthritis (RA),** who have not had previous treatment with methotrexate.

  RoActemra helps to reduce RA symptoms such as pain and swelling in your joints, and can also improve your performance of daily tasks. RoActemra has been shown to slow the damage to the cartilage and bone of the joints caused by the disease and to improve your ability to do normal daily activities.

  RoActemra is usually given in combination with another medicine for RA called methotrexate. However, RoActemra can be given alone if your doctor determines that methotrexate is inappropriate.

- **adults with a disease of the arteries called giant cell arteritis** (**GCA**), caused by inflammation of the body's largest arteries, especially those that supply blood to the head and neck. Symptoms include headache, fatigue and jaw pain. Effects can include strokes and blindness.

  RoActemra can reduce pain and swelling in the arteries and veins in your head, neck and arms.

GCA is often treated with medicines called steroids. They are usually effective, but can have side effects if used at high doses for a long time. Reducing the steroid dose can also lead to a flare-up of the GCA. Adding RoActemra to the treatment means that steroids can be used for a shorter time, while still controlling GCA.

- **children and adolescents, aged 1 year and over, with active *systemic juvenile idiopathic arthritis (sJIA)*,** an inflammatory disease that causes pain and swelling in one or more joints as well as fever and rash.

  RoActemra is used to improve the symptoms of sJIA. It can be given in combination with methotrexate or alone.

- **children and adolescents, aged 2 years and over, with active *polyarticular juvenile idiopathic arthritis* (*pJIA*).** This is an inflammatory disease that causes pain and swelling in one or more joints.

  RoActemra is used to improve the symptoms of pJIA. It can be given in combination with methotrexate or alone**.**

2. What you need to know before you use RoActemra

Do not use RoActemra
- if you or a child patient you look after are allergic to tocilizumab or any of the other ingredients of this medicine (listed in section 6).
- if you or a child patient you look after have an active, severe infection.

If either of these applies to you, tell a doctor. Do not use RoActemra.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using RoActemra.

- If you experience **allergic reactions** such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue, face or skin itching, hives or rash during or after the injection, then **tell your doctor immediately.**

- Do not take the next dose until you have informed your doctor AND your doctor has told you to take the next dose if you have experienced any allergic reaction symptoms after RoActemra administration.

- If you have any kind of **infection**, short- or long-term, or if you often get infections. **Tell your doctor immediately** if you feel unwell. RoActemra can reduce your body's ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection.

- If you have had **tuberculosis**, tell your doctor. Your doctor will check for signs and symptoms of tuberculosis before starting RoActemra. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever) or any other infection appear during or after therapy tell your doctor immediately.

- If you have had **intestinal ulcers** or **diverticulitis**, tell your doctor. Symptoms would include abdominal pain and unexplained changes in bowel habits with a fever.

- If you have **liver disease**, tell your doctor. Before you use RoActemra, your doctor may do a blood test to measure your liver function.

- **If any patient has recently been vaccinated,** or is planning a vaccination**,** tell your doctor. All patients should be up-to-date with all their vaccinations before they start treatment with RoActemra. Certain types of vaccines should not be given while receiving RoActemra.

- If you have **cancer**, tell your doctor. Your doctor will have to decide if you can still be given RoActemra.

- If you have **cardiovascular risk factors** such as raised blood pressure and raised cholesterol levels, tell your doctor. These factors need to be monitored while receiving RoActemra.

- If you have moderate to severe **kidney function problems**, your doctor will monitor you.

- If you have **persistent headaches**.

Your doctor will perform a blood test before you receive RoActemra, to determine if you have a low white blood cell count, low platelet count or high liver enzymes.

Children and adolescents
RoActemra subcutaneous injection is not recommended for use in children under 1 year of age. RoActemra must not be given to children weighing less than 10 kg.

If a child has a history of ***macrophage activation syndrome*** (activation and uncontrolled proliferation of specific blood cells), tell your doctor. Your doctor will have to decide if they can still be given RoActemra.

Other medicines and RoActemra
Tell your doctor if you are taking any other medicines, or have recently taken any. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. If you are using medicines containing any of the following active substances, **tell your doctor:**
- methylprednisolone, dexamethasone, used to reduce inflammation
- simvastatin or atorvastatin, used to reduce cholesterol levels
- calcium channel blockers (e.g. amlodipine), used to treat raised blood pressure
- theophylline, used to treat asthma
- warfarin or phenprocoumon, used as a blood thinning agents
- phenytoin, used to treat convulsions
- ciclosporin, used to suppress your immune system during organ transplants
- benzodiazepines (e.g. temazepam), used to relieve anxiety

Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA, sJIA, pJIA or GCA.

Pregnancy, breast-feeding and fertility

RoActemra is not to be used in pregnancy unless clearly necessary. Talk to your doctor if you are pregnant, may be pregnant, or intend to become pregnant.

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Stop breast-feeding if you are to be given RoActemra, and talk to your doctor. Leave a gap of at least 3 months after your last treatment before you start breast-feeding. It is not known whether RoActemra is passed into breast milk.

Driving and using machines
This medicine can cause dizziness. If you feel dizzy, do not drive or use machines.

3. How to use RoActemra

Always use this medicine exactly as your doctor, pharmacist or nurse has told you. You should check with your doctor, pharmacist or nurse if you are not sure.

The treatment will be prescribed and started by healthcare professionals experienced in the diagnosis and treatment of RA, sJIA, pJIA or GCA.

The recommended dose
The dose for RA and GCA adults is 162 mg (the content of 1 pre-filled syringe) given once a week.

Children and adolescents with sJIA (aged 1 year and over)
The usual dose of RoActemra depends on the patient's weight.
- If the patient weighs **less than 30 kg**: the dose is 162 mg (the content of 1 pre-filled syringe) once every 2 weeks
- If the patient weighs **30 kg or more**: the dose is 162 mg (the content of 1 pre-filled syringe) once every week

Children and adolescents with pJIA (aged 2 and over)
The usual dose of RoActemra depends on the patient's weight.
- If the patient weighs **less than 30 kg**: the dose is 162 mg (the content of 1 pre-filled syringe), **once every 3 weeks**
- If the patient weighs **30 kg or more**: the dose is 162 mg (the content of 1 pre-filled syringe), **once every 2 weeks.**

RoActemra is given by injection under the skin (*subcutaneously*). At the start, your doctor or nurse may inject RoActemra. However, your doctor may decide that you may inject RoActemra yourself. In this case you will get training on how to inject RoActemra yourself. Parents and carers will get training on how to inject RoActemra for patients who cannot inject themselves, such as children.

Talk to your doctor if you have any questions about giving yourself or a child patient you look after an injection. You will find detailed "Instructions for administration" at the end of this leaflet.

If you use more RoActemra than you should
Because RoActemra is given in one pre-filled syringe, it is unlikely that you will receive too much. However, if you are worried, talk to your doctor, pharmacist or nurse.

If an adult with RA or GCA or a child or adolescent with sJIA misses or forgets a dose
It is very important to use RoActemra exactly as prescribed by your doctor. Keep track of your next dose.
- If you miss your weekly dose within 7 days, take your dose on the next scheduled day.
- If you miss your once every 2 weeks dose within 7 days, inject a dose as soon as you remember and take your next dose at your regular scheduled time.
- If you miss your dose by more than 7 days, or you are not sure when to inject RoActemra, call your doctor or pharmacist.

If a child or adolescent with pJIA misses or forgets a dose
It is very important to use RoActemra exactly as prescribed by the doctor. Keep track of the next dose.
- If a dose is missed within 7 days, inject a dose as soon as you remember and give the next dose at the regular scheduled time.

- If a dose is missed by more than 7 days, or you are not sure when to inject RoActemra, call the doctor or pharmacist.

If you stop using RoActemra
You should not stop using RoActemra without discussing with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, RoActemra can cause side effects, although not everybody gets them.
Side effects could occur 3 months or more after your last dose of RoActemra.

Possible serious side effects: tell a doctor straight away.
These are common: they may affect up to 1 in every 10 users

Allergic reactions during or after injection:
- difficulty with breathing, chest tightness or light-headedness
- rash, itching, hives, swelling of the lips, tongue or face

If you notice any of these, tell your doctor **immediately**.

Signs of serious infections:
- fever and chills
- mouth or skin blisters
- stomach ache

If you notice any of these, tell your doctor **as soon as possible**.

Very common side effects:
These may affect 1 in 10 patients or more
- upper respiratory tract infections with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache,
- high blood fat (*cholesterol*) levels
- injection site reactions.

Common side effects:
These may affect up to 1 in 10 patients
- lung infection (pneumonia)
- shingles (herpes zoster)
- cold sores (oral herpes simplex), blisters
- skin infection (cellulitis) sometimes with fever and chills
- rash and itching, hives
- allergic (hypersensitivity) reactions
- eye infection (conjunctivitis)
- headache, dizziness, high blood pressure
- mouth ulceration, stomach pain
- fluid retention (oedema) in the lower legs, weight increase
- cough, shortness of breath
- low white blood cell counts shown by blood tests (neutropenia, leucopenia)
- abnormal liver function tests (increased transaminases)
- increased bilirubin shown by blood tests
- low fibrinogen levels in the blood (a protein involved in blood clotting).

Uncommon side effects:
These may affect up to 1 in every 100 patients
- diverticulitis (fever, nausea, diarrhoea, constipation, stomach pain)
- red swollen areas in the mouth
- high blood fat (triglycerides)
- stomach ulcer
- kidney stones
- underactive thyroid.

Very rare side effects:
These may affect up to1in every 10,000 patients
- Stevens-Johnson syndrome (skin rash, which may lead to severe blistering and peeling of the skin)

Side effects in children and adolescents with sJIA or pJIA
Side effects in children and adolescents with sJIA or pJIA are generally similar to those in adults. Some side effects are seen more often in children and adolescents: inflamed nose and throat, headache, feeling sick (nausea) and lower white blood cell counts.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store RoActemra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled syringe label and carton (EXP). The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the pre-filled syringes in the outer carton in order to protect from light and moisture.

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30°C.

Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to yellowish, or any part of the pre-filled syringe appears to be damaged.

The syringe should not be shaken. After removing the cap the injection must be started within 5 minutes to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of cap removal, you must dispose of it in a puncture resistant container and use a new pre-filled syringe.

If following insertion of the needle, you cannot depress the plunger, you must dispose of the pre-filled syringe in a puncture resistant container and use a new pre-filled syringe.

6. Contents of the pack and other information

What RoActemra contains

- The active substance is tocilizumab.
  Each pre-filled syringe contains 162 mg tocilizumab in 0.9 mL.

- The other ingredients are L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80 and Water for injections.

What RoActemra looks like and contents of the pack
RoActemra is a solution for injection. The solution is colourless to slightly yellowish.

RoActemra is supplied as a 0.9 mL pre-filled syringe containing 162 mg tocilizumab solution for injection.

Each pack contains 4 pre-filled syringes **with multipacks containing 12 (3 packs of 4) pre-filled syringes. Not all pack sizes may be marketed.**

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This leaflet was last revised

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu/.

What do I need to know to use my RoActemra pre-filled syringe safely?

It is important to read, understand and follow these instructions so that you or your caregiver uses the RoActemra syringe correctly. These instructions do not replace training from your healthcare provider. Your healthcare provider should show you how to prepare and inject properly before you use the RoActemra syringe for the first time. Ask your healthcare provider any questions you may have. Do not attempt to administer an injection until you are sure that you understand how to use the RoActemra syringe.

Please also read the Patient Leaflet that comes with the RoActemra syringe for the most important information you need to know about the medicine. It is important to remain under your healthcare provider's care while using RoActemra.

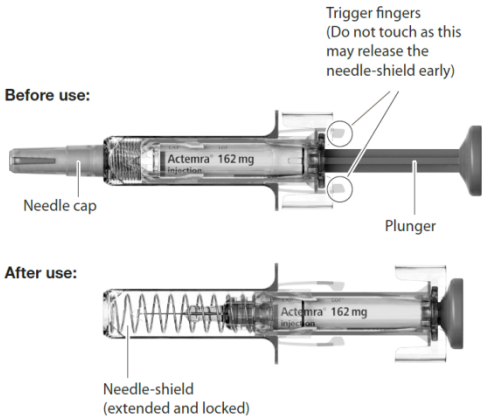
Important Information:

- Do not use the syringe if it appears to be damaged
- Do not use if medicine is cloudy, hazy, discolored or contains particles
- Do not try to take apart the syringe at any time
- Do not remove the needle-cap until you are ready to inject
- Do not inject through clothing covering the skin
- Never re-use the same syringe
- Do not touch the syringe trigger fingers as this may damage the syringe

Storage

Keep the RoActemra syringe and all medicines out of the sight and reach of children. Always store the syringe in a refrigerator at a temperature of 2°C - 8°C. Protect the syringe from freezing and from light. Keep the pre-filled syringes in the outer carton to protect it from light and keep them dry.

Pre-filled Syringe parts



You will need the following to give your injection:
Included in the box:

- Pre-filled Syringe

Not included in the box:

- Alcohol pad
- Sterile cotton ball or gauze
- Puncture-resistant container or sharps container for safe disposal of needle-cap and used syringe

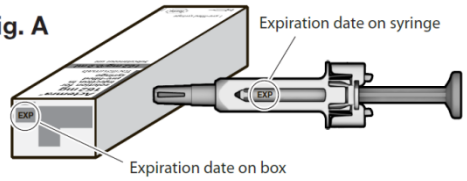
A place to prepare your supplies:

- **Find a well-lit, clean, flat surface such as a table**

Step 1. Visually check the syringe

- Take the box containing the syringe out of the refrigerator and open the box. Do not touch the trigger fingers on the syringe as this may damage the syringe.
- Remove the syringe from the box and visually examine the syringe, as well as the medicine in the syringe. This is important to ensure that the syringe and medicine are safe to use.
- Check the expiration date on the box and syringe (See Fig. A) to make sure that it has not passed (expired). Do not use the syringe if the expiration date has passed. This is important to ensure that the syringe and medicine are safe to use.

Fig. A



Dispose of the syringe and do not use if:

- the medicine is cloudy
- the medicine contains particles
- the medicine is any color besides colorless to yellowish
- any part of the syringe appears to be damaged

Step 2. Allow the syringe to adjust to room temperature

- Do not remove the needle-cap on your syringe until Step 5. Early removal of the needle-cap can cause the medication to dry out and block the needle.

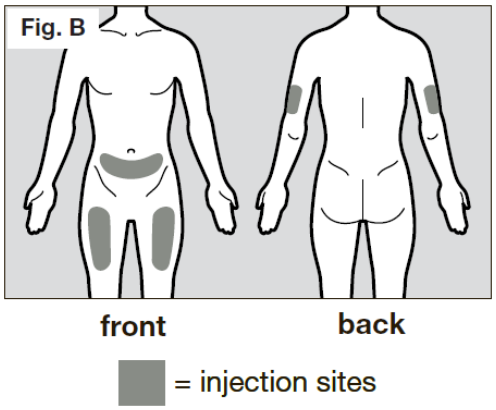
- Place the syringe on a clean flat surface and allow the syringe to come to room temperature (18°C – 28°C) for about 25-30 minutes to warm up. Not allowing the syringe to come to room temperature could result in an uncomfortable injection and it may be difficult to depress the plunger.
- Do not warm up the syringe in any other way.

Step 3. Clean your hands

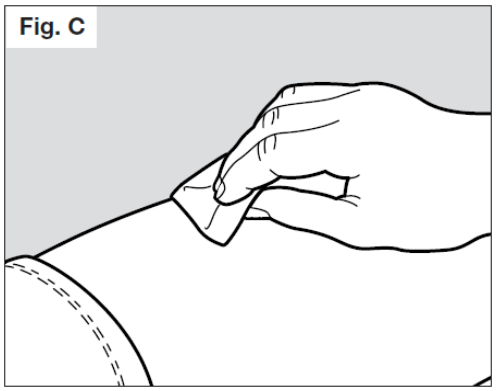
- Wash your hands with soap and water.

Step 4. Choose and prepare an injection site

- The recommended injection sites are the front and middle of your thighs and the lower part of the abdomen below the navel (belly button) except for the five centimeter area directly around the navel. (See Fig. B)
- If a caregiver is giving the injection, the outer area of the upper arms may also be used. (See Fig. B)



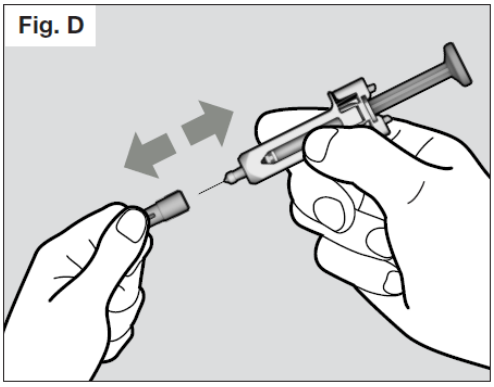
- You should use a different place each time you give yourself an injection, at least three centimeters from the area you used for your previous injection.
- Do not inject into areas that could be bothered by a belt or waistband. Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.
- Clean the chosen injection site area using the alcohol pad (See Fig. C), to reduce the risk of infection.



- Let the skin dry for approximately 10 seconds.
- Be sure not to touch the cleaned area prior to the injection. Do not fan or blow on the clean area.

Step 5. Remove needle-cap

- Do not hold the syringe by the plunger while removing the needle-cap.
- Hold the needle-shield of the syringe firmly with one hand and pull off the needle-cap with the other hand. (See Fig. D) If you cannot remove the needle cap you should request the help of a caregiver or contact your healthcare provider.



- Do not touch the needle or let it touch any surface.

- You may see a drop of liquid at the end of the needle. This is normal.
- Throw away the needle-cap in the puncture resistant container or sharps container.

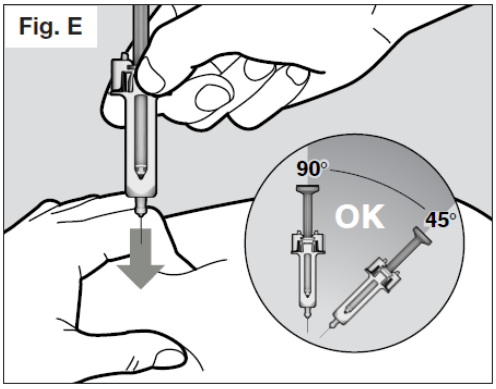
NOTE: Once the needle-cap is removed, the syringe must be used immediately.

- If it is not used within 5 minutes of cap removal, the syringe must be disposed of in the puncture resistant container or sharps container and a new syringe must be used. If the needle cap is removed for more than 5 minutes, it may be more difficult to perform an injection as the medicine can dry out and block the needle.

- Never reattach the needle-cap after removal.

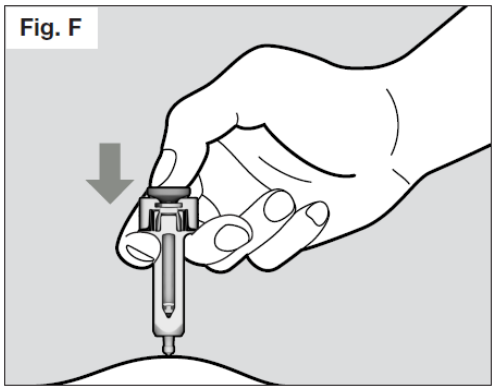
Step 6. Give the injection

- Hold the syringe comfortably in your hand.
- To be sure the needle can be inserted correctly under the skin, pinch a fold of loose skin at the clean injection site with your free hand. Pinching the skin is important to ensure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could result in an uncomfortable injection.
- Do not hold or push on the plunger while inserting the needle into the skin.
- Insert the needle all the way into the pinched skin at an angle between 45° to 90° with a quick, firm action. (See Fig. E).

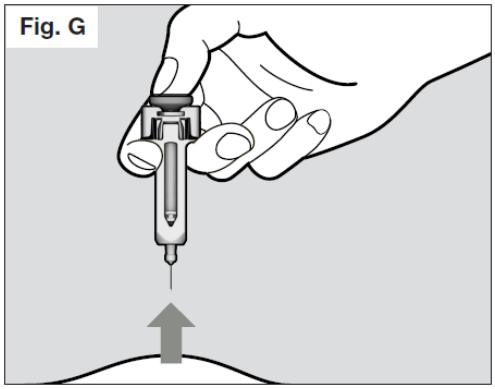


It is important to choose the correct angle to ensure the medication is delivered under the skin (into fatty tissue), otherwise the injection could be painful and the medication may not work.

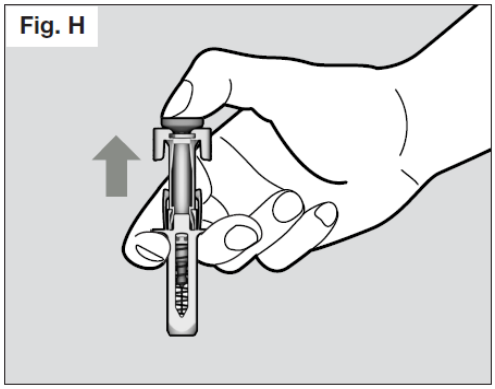
- Then keep the syringe in position and let go of the pinch of skin.
- Slowly inject all of the medicine by gently pushing the plunger all the way down. (See Fig. F). You must press the plunger all the way down to ensure that you get the full dose of medication and to ensure the trigger fingers are completely pushed to the side. If the plunger is not fully depressed the needle shield will not extend to cover the needle when it is removed. If the needle is not covered proceed carefully, and place the syringe into the puncture resistant container to avoid injury with the needle.



- Once the plunger is pushed all the way down, keep pressing down on the plunger to be sure all of the medicine is injected before taking the needle out of the skin.
- Keep pressing down on the plunger while you take the needle out of the skin at the same angle as inserted. (See Fig. G)
- If following insertion of the needle, you cannot press down the plunger, you must dispose of the pre-filled syringe in a puncture resistant container and use a new pre-filled syringe (starting again at Step 2). If you still experience difficulty, you should consult your healthcare provider.



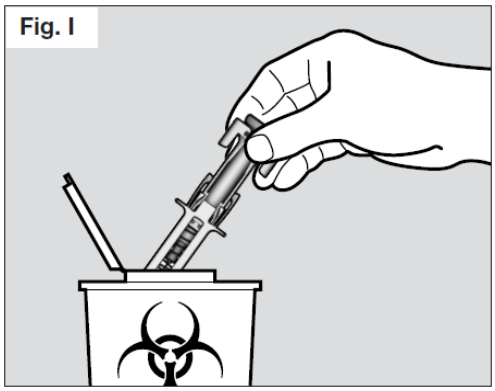
- Once the needle is removed completely from the skin, you can release the plunger, allowing the needle-shield to protect the needle. (See Fig. H)



- If you see drops of blood at the injection site, you can press a sterile cotton ball or gauze over the injection site for approximately 10 seconds.
- Do not rub the injection site.

Step 7. Dispose of the syringe

- Do not try to re-cap your syringe.
- Throw away used syringes in a puncture-resistant container or sharps container. Ask your healthcare provider or pharmacist for information about where you can get a "sharps" container or what other types of puncture-resistant containers you can use to safely dispose of your used syringes, if you do not have one. (See Fig. I)



Check with your healthcare provider for instructions about the right way to throw away used syringes. There may be local or state laws about how to throw away used syringes.

Do not throw away used syringes or the puncture resistant container in household trash and do not recycle them.

- Dispose of the full container as instructed by your healthcare provider or pharmacist.
- Always keep the puncture-resistant container out of the sight and reach of children.

Patient advice regarding hypersensitivity reactions (also known as anaphylaxis, if severe)

If you develop symptoms such as, but not limited to skin rash, itching, chills, swelling of face, lips, tongue or throat, chest pain, wheezing, difficulty breathing or swallowing or feeling dizzy or faint at any time while not at the clinic during or following an RoACTEMRA injection you should seek emergency care immediately.

Patient advice regarding early recognition and treatment to limit risk of a serious infection

Be alert for the first signs of infection such as:

- body aches, fever, chills
- cough, chest discomfort/tightness, shortness of breath
- redness, heat, unusual swelling of skin or joint
- abdominal pain/tenderness and/or change in bowel function

Call your doctor and seek medical attention without delay if you think you might be developing an infection.

If you have any concerns or questions about your syringe, contact your healthcare provider or pharmacist for assistance.

Package leaflet: Information for the user

RoActemra 162 mg solution for injection in pre-filled pen（ACTPen•）
Tocilizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it onto others. It may harm them even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, you will be given a **Patient Alert Card**, which contains important safety information that you need to be aware of before and during treatment with RoActemra.

What is in this leaflet:
1. What RoActemra is and what it is used for
2. What you need to know before you use RoActemra
3. How to use RoActemra
4. Possible side effects
5. How to store RoActemra
6. Contents of the pack and other information

1. What RoActemra is and what it is used for

RoActemra contains the active substance tocilizumab, which is a protein made from specific immune cells (monoclonal antibody), that blocks the action of a specific protein (cytokine) called interleukin-6. This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body. RoActemra is used to treat:

- **adults with moderate to severe active rheumatoid arthritis (RA)**, an autoimmune disease, if previous therapies did not work well enough.

- **adults** with **severe, active and progressive rheumatoid arthritis (RA),** who have not had previous treatment with methotrexate..

RoActemra helps to reduce symptoms such as pain and swelling in your joints and can also improve your performance of daily tasks. RoActemra has been shown to slow the damage to the cartilage and bone of the joints caused by the disease and to improve your ability to do normal daily activities.

RoActemra is usually given in combination with another medicine for RA called methotrexate. However, RoActemra can be given alone if your doctor determines that methotrexate is inappropriate.

- **adults with a disease of the arteries called giant cell arteritis** (**GCA**), caused by inflammation of the body's largest arteries, especially those that supply blood to the head and neck. Symptoms include headache, fatigue and jaw pain. Effects can include strokes and blindness.

RoActemra can reduce pain and swelling in the arteries and veins in your head, neck and arms.

GCA is often treated with medicines called steroids. They are usually effective, but can have side effects if used at high doses for a long time. Reducing the steroid dose can also lead to a flare-up of the GCA. Adding RoActemra to the treatment means that steroids can be used for a shorter time, while still controlling GCA.

2. What you need to know before you use RoActemra

Do not use RoActemra

- if you are allergic to tocilizumab or any of the other ingredients of this medicine (listed in section 6).
- if you have an active, severe infection.

If either of these applies to you, tell a doctor. Do not use RoActemra.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using RoActemra.

- If you experience **allergic reactions** such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue, face or skin itching, hives or rash during or after the injection, then **tell your doctor immediately.**

- Do not take the next dose until you have informed your doctor AND your doctor has told you to take the next dose if you have experienced any allergic reaction symptoms after RoActemra administration.

- If you have any kind of **infection**, short- or long-term, or if you often get infections. **Tell your doctor immediately** if you feel unwell. RoActemra can reduce your body's ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection.

- If you have had **tuberculosis**, tell your doctor. Your doctor will check for signs and symptoms of tuberculosis before starting RoActemra. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever) or any other infection appear during or after therapy tell your doctor immediately.

- If you have had **intestinal ulcers** or **diverticulitis**, tell your doctor. Symptoms would include abdominal pain and unexplained changes in bowel habits with a fever.

- If you have **liver disease**, tell your doctor. Before you use RoActemra, your doctor may do a blood test to measure your liver function.

- **If any patient has recently been vaccinated,** or is planning a vaccination**,** tell your doctor. All patients should be up-to-date with all their vaccinations before they start treatment with RoActemra. Certain types of vaccines should not be given while receiving RoActemra.

- If you have **cancer**, tell your doctor. Your doctor will have to decide if you can still be given RoActemra.

- If you have **cardiovascular risk factors** such as raised blood pressure and raised cholesterol levels, tell your doctor. These factors need to be monitored while receiving RoActemra.

- If you have moderate to severe **kidney function problems**, your doctor will monitor you.

- If you have **persistent headaches**.

Your doctor will perform a blood test before you receive RoActemra, to determine if you have a low white blood cell count, low platelet count or high liver enzymes.

Children and adolescents
RoActemra subcutaneous injection is not recommended for use in children under 18 years of age.

Other medicines and RoActemra
Tell your doctor if you are taking any other medicines, or have recently taken any. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. If you are using medicines containing any of the following active substances, **tell your doctor:**
- methylprednisolone, dexamethasone, used to reduce inflammation
- simvastatin or atorvastatin, used to reduce cholesterol levels
- calcium channel blockers (e.g. amlodipine), used to treat raised blood pressure
- theophylline, used to treat asthma
- warfarin or phenprocoumon, used as a blood thinning agents
- phenytoin, used to treat convulsions
- ciclosporin, used to suppress your immune system during organ transplants
- benzodiazepines (e.g. temazepam), used to relieve anxiety

Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA or GCA.

Pregnancy, breast-feeding and fertility

RoActemra is not to be used in pregnancy unless clearly necessary. Talk to your doctor if you are pregnant, may be pregnant, or intend to become pregnant.

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Stop breast-feeding if you are to be given RoActemra, and talk to your doctor. Leave a gap of at least 3 months after your last treatment before you start breast-feeding. It is not known whether RoActemra is passed into breast milk.

Driving and using machines
This medicine can cause dizziness. If you feel dizzy, do not drive or use machines.

3. How to use RoActemra

Always use this medicine exactly as your doctor, pharmacist or nurse has told you. You should check with your doctor, pharmacist or nurse if you are not sure.

The treatment will be prescribed and started by healthcare professionals experienced in the diagnosis and treatment of RA or GCA.

The recommended dose
The dose for all adults is 162 mg (the content of 1 pre-filled pen) given once a week.

RoActemra is given by injection under the skin (*subcutaneously*). At the start, your doctor or nurse may inject RoActemra (ACTPen®). However, your doctor may decide that you may inject RoActemra yourself. In this case you will get training on how to inject RoActemra yourself.

Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed “Instructions for administration” at the end of this leaflet.

If you use more RoActemra than you should
Because RoActemra is given in one pre-filled pen, it is unlikely that you will receive too much. However, if you are worried, talk to your doctor, pharmacist or nurse.

If you forget to use RoActemra
It is very important to use RoActemra exactly as prescribed by your doctor. Keep track of your next dose. If you miss your weekly dose within 7 days, take your dose on the next scheduled day. If you miss your once every other weekly dose within 7 days, inject a dose as soon as you remember and take your next dose at your regular scheduled time. If you miss your weekly or once every other weekly dose more than 7 days or are not sure when to inject RoActemra, call your doctor or pharmacist.

If you stop using RoActemra
You should not stop using RoActemra without discussing with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, RoActemra can cause side effects, although not everybody gets them.
Side effects could occur 3 months or more after your last dose of RoActemra.

Possible serious side effects: tell a doctor straight away.
These are common: they may affect up to 1 in every 10 users

Allergic reactions during or after injection:
- difficulty with breathing, chest tightness or light-headedness
- rash, itching, hives, swelling of the lips, tongue or face

If you notice any of these, tell your doctor **immediately**.

Signs of serious infections:
- fever and chills
- mouth or skin blisters
- stomach ache

If you notice any of these, tell your doctor **as soon as possible**.

Very common side effects:
These may affect 1 in 10 patients or more
- upper respiratory tract infections with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache
- high blood fat (*cholesterol*) levels.

Common side effects:
These may affect up to 1 in 10 patients
- lung infection (pneumonia)
- shingles (herpes zoster)
- cold sores (oral herpes simplex), blisters
- skin infection (cellulitis) sometimes with fever and chills
- rash and itching, hives
- allergic (hypersensitivity) reactions
- eye infection (conjunctivitis)
- headache, dizziness, high blood pressure
- mouth ulceration, stomach pain
- fluid retention (oedema) in the lower legs, weight increase

- cough, shortness of breath
- low white blood cell counts shown by blood tests (neutropenia, leucopenia)
- abnormal liver function tests (increased transaminases)
- increased bilirubin shown by blood tests
- injection site reactions
- low fibrinogen levels in the blood (a protein involved in blood clotting).

Uncommon side effects:
These may affect up to 1 in every 100 patients
- diverticulitis (fever, nausea, diarrhoea, constipation, stomach pain)
- red swollen areas in the mouth
- high blood fat (triglycerides)
- stomach ulcer
- kidney stones
- underactive thyroid.

Very rare side effects:
These may affect up to1in every 10,000 patients
- Stevens-Johnson Syndrome (skin rash, which may lead to severe blistering and peeling of the skin)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store RoActemra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled pen label and carton (EXP). The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the pre-filled pens in the outer carton in order to protect from light and moisture.

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30°C.

Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to yellowish, or any part of the pre-filled pen appears to be damaged.

The pen should not be shaken. After removing the cap the injection must be started within 3 minutes to prevent the medicine from drying out and blocking the needle. If the pre-filled pen is not used within 3 minutes of cap removal, you must dispose of it in a puncture resistant container and use a new pre-filled pen.

If following pressing the activation button the purple indicator does not move, you must dispose of the pre-filled pen in a puncture resistant container. **Do not** try to re-use the pre-filled pen. Do not repeat the injection with another pre-filled pen. Call your healthcare provider for help.

6. Contents of the pack and other information

What RoActemra contains

- The active substance is tocilizumab.
  Each pre-filled pen contains 162 mg tocilizumab in 0.9 mL.

- The other ingredients are L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80 and Water for injections.

What RoActemra looks like and contents of the pack
RoActemra is a solution for injection. The solution is colourless to slightly yellowish.

RoActemra is supplied as a 0.9 mL pre-filled pen containing 162 mg tocilizumab solution for injection.

Each pack contains 4 pre-filled pens **with multipacks containing 12 (3 packs of 4) pre-filled pens. Not all pack sizes may be marketed.**

Marketing Authorisation Holder
Roche Registration GmbH
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79639 Grenzach-Wyhlen
Germany

Manufacturer
Roche Pharma AG
Emil-Barell-Str. 1
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu/.

What you need to know to use your RoActemra pre-filled pen (ACTPen) safely.

Read and follow the Instructions for Use that come with your RoACTEMRA pre-filled pen before you start using it and each time you get a prescription refill. Before you use the RoACTEMRA pre-filled pen for the first time, make sure your healthcare provider shows you the right way to use it.

Important: Keep your unused pre-filled pens in the original carton and keep in the refrigerator at 2˚C to 8˚C (36˚F to 46˚F). **Do not** freeze.

- **Do not remove the pre-filled pen cap until you are ready to inject RoACTEMRA.**
- **Do not try to take apart the pre-filled pen at any time.**
- **Do not reuse the same pre-filled pen.**
- **Do not use the pre-filled pen through clothing.**
- **Do not leave the pre-filled pen unattended.**
- **Keep out of the reach of children.**

Parts of your RoACTEMRA pre-filled pen **(See Figure A).**

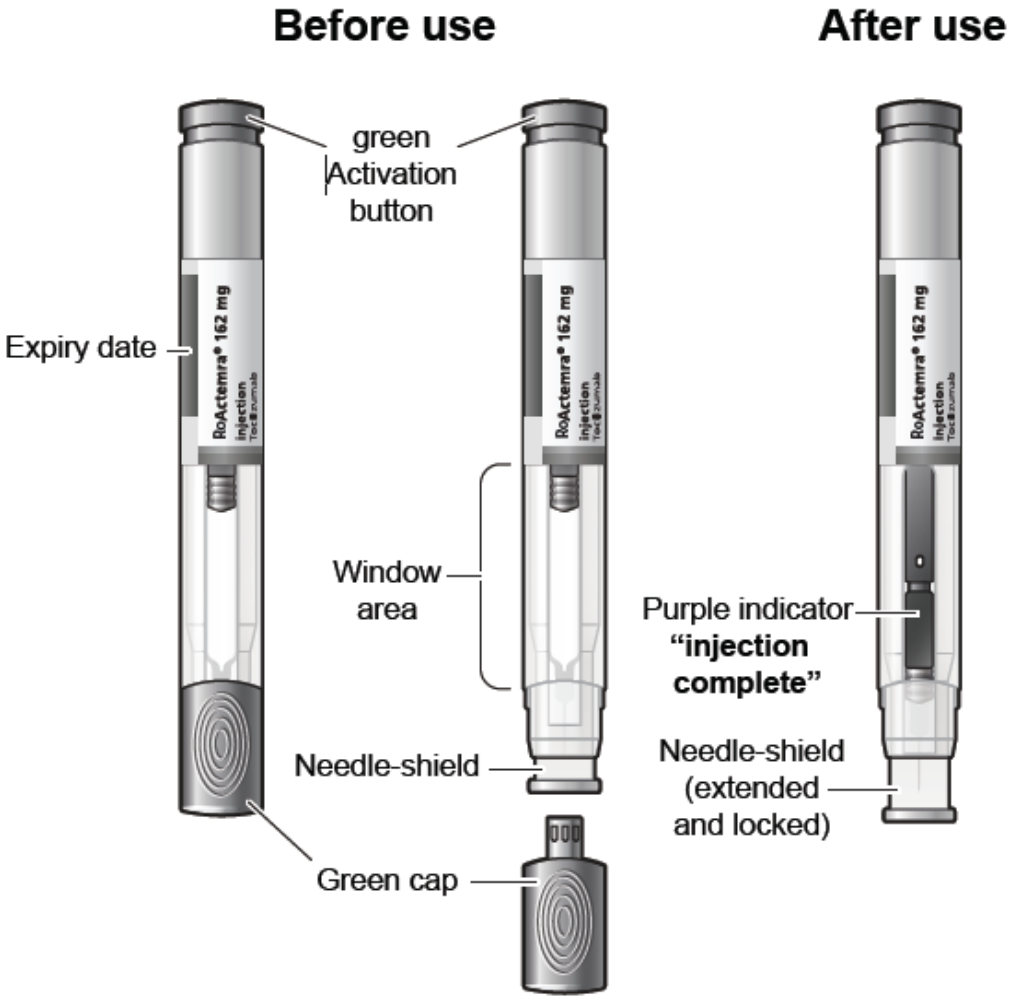


Figure A

Supplies needed for an injection using your RoACTEMRA pre-filled pen (See Figure B):

- 1 RoACTEMRA pre-filled pen
- 1 Alcohol pad
- 1 Sterile cotton ball or gauze
- 1 Puncture-resistant container or sharps container for safe disposal of pre-filled pen cap and used pre-filled pen (see **Step 4 "Dispose of the pre-filled pen")**

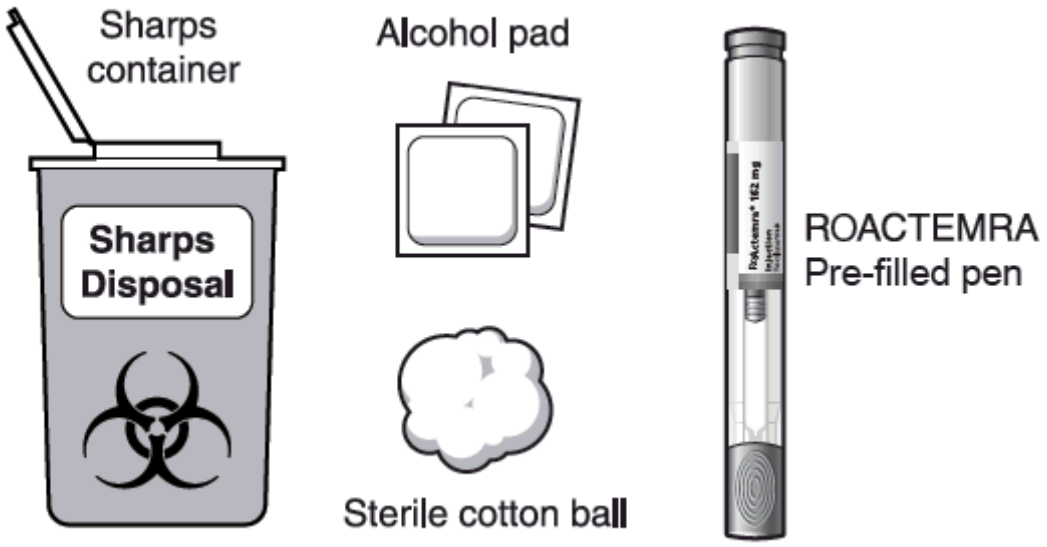


Figure B

Step 1. Preparing for a RoACTEMRA Injection

Find a comfortable space with a clean, flat, working surface.

- Take the box containing the pre-filled pen out of the refrigerator.
- If you are opening the box for the first time, check to make sure that it is properly sealed. **Do not** use the pre-filled pen if the box looks like it has already been opened.
- Check that the pre-filled pen box is not damaged. **Do not** use RoActemra pre-filled pen if the box looks damaged.
- **Check the expiration date on the pre-filled pen box**. **Do not** use the pre-filled pen if the expiration date has passed because it may not be safe to use.
- Open the box, and remove 1 single-use RoACTEMRA pre-filled pen from the box.
- Return any remaining pre-filled pens in the box to the refrigerator.
- **Check the expiration date on the RoACTEMRA pre-filled pen (See Figure A). Do not** use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed, safely dispose of the pre-filled pen in a sharps container and get a new one.
- **Check the pre-filled pen to make sure it is not damaged.** Do not use the pre-filled pen if it appears to be damaged or if you have accidentally dropped the pre-filled pen.
- Place the pre-filled pen on a clean, flat surface and let the pre-filled pen warm up for 45 minutes to allow it to reach room temperature. If the pre-filled pen does not reach room temperature, this could cause your injection to feel uncomfortable and it could take longer to inject.
    - **Do not** speed up the warming process in any way, such as using the microwave or placing the pre-filled pen in warm water.

- **Do not** leave the pre-filled pen to warm up in direct sunlight.

Do not remove the green cap while allowing your RoACTEMRA pre-filled pen to reach room temperature.

- Hold your RoACTEMRA pre-filled pen with the green cap pointing down **(See Figure C).**

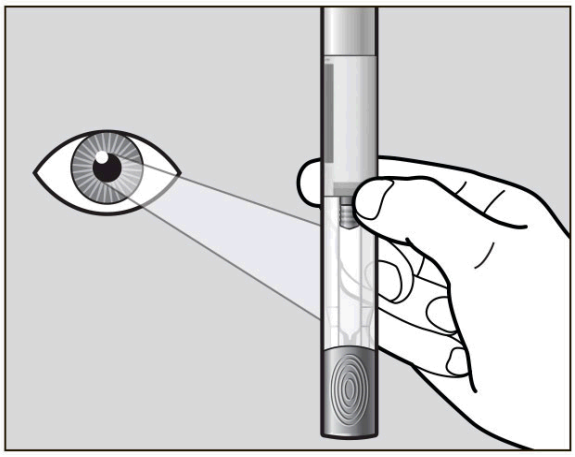


Figure C

- Look in the clear Window area. Check the liquid in the RoACTEMRA pre-filled pen **(See Figure C)**. It should be clear and colorless to pale yellow. **Do not** inject RoACTEMRA if the liquid is cloudy, discolored, or has lumps or particles in it because it may not be safe to use. Safely dispose of the pre-filled pen in a sharps container and get a new one.
- Wash your hands well with soap and water.

Step 2. Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh or your abdomen except for the 2-inch (5cm) area around your navel are the recommended injection sites **(See Figure D).**
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. Do not attempt to use the upper arm area by yourself **(See Figure D).**

Rotate Injection Site

- Choose a different injection site for each new injection at least 1 inch (2.5cm) from the last area you injected.
- Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.

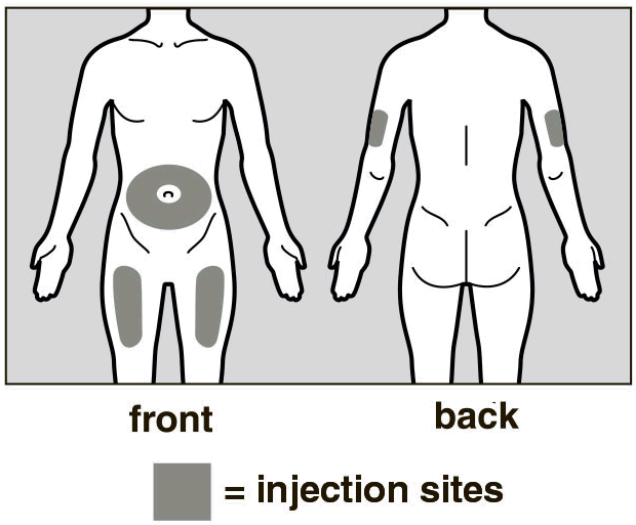


Figure D

Prepare the Injection Site

- Wipe the injection site with an alcohol pad in a circular motion and let it air dry to reduce the chance of getting an infection. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

Step 3. Inject RoACTEMRA

- Hold the RoACTEMRA pre-filled pen firmly with one hand. Twist and pull off the green cap with the other hand **(See Figure E).** The green cap contains a loose fitting metal tube.
- If you cannot remove the green cap you should ask a caregiver for help or contact your healthcare provider.

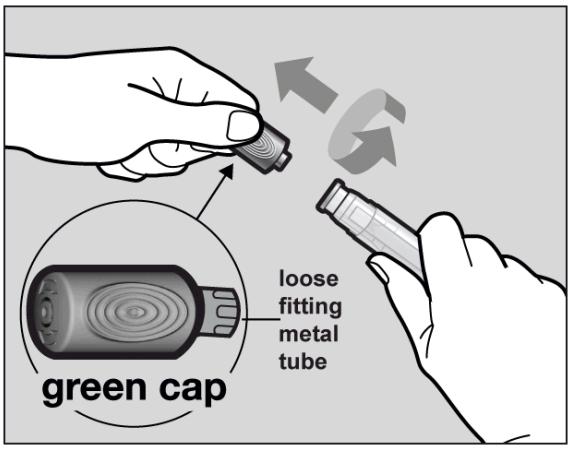


Figure E

Important: Do not touch the needle shield which is located at the tip of the pre-filled pen below the Window area (see Figure A), to avoid accidental needle stick injury.

- Throw away the green cap in a sharps container.
- After you remove the green cap, the pre-filled pen is ready for use. If the pre-filled pen is not used within 3 minutes of the cap removal, the pre-filled pen should be disposed of in the sharps container and a new pre-filled pen should be used.
- Never reattach the green cap after removal.

- Hold the pre-filled pen comfortably in 1 hand by the upper part, so that you can see the Window area of the pre-filled pen **(See Figure F).**

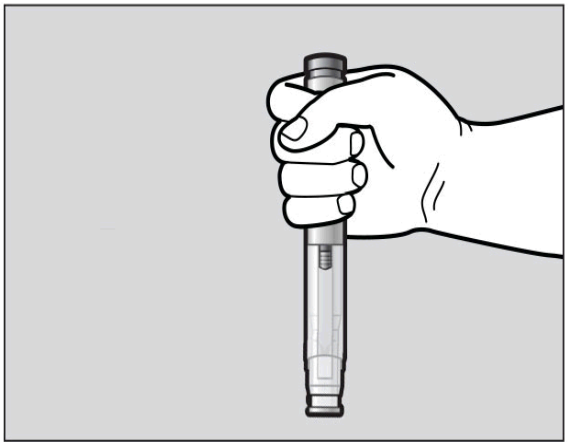


Figure F

- Use your other hand to gently pinch the area of skin you cleaned, to prepare a firm injection site **(See Figure G).** The pre-filled pen requires a firm injection site to properly activate.
- Pinching the skin is important to make sure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could cause the injection to feel uncomfortable.

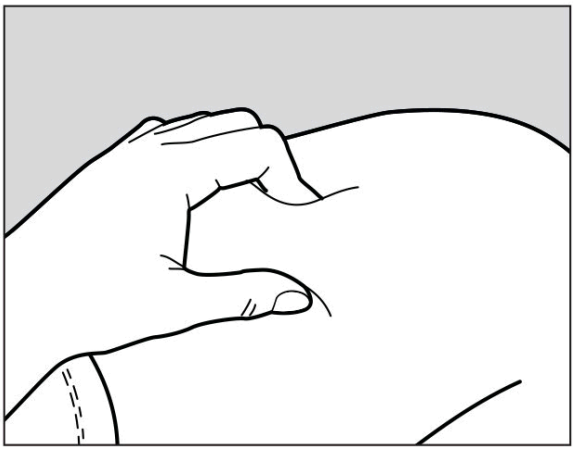


Figure G

- **Do not** press the green activation button yet.
- Place the needle-shield of the pre-filled pen against your pinched skin at a 90° angle **(See Figure H).**
- It is important to use the correct angle to make sure the medicine is delivered under the skin (into fatty tissue), or the injection could be painful and the medicine may not work.

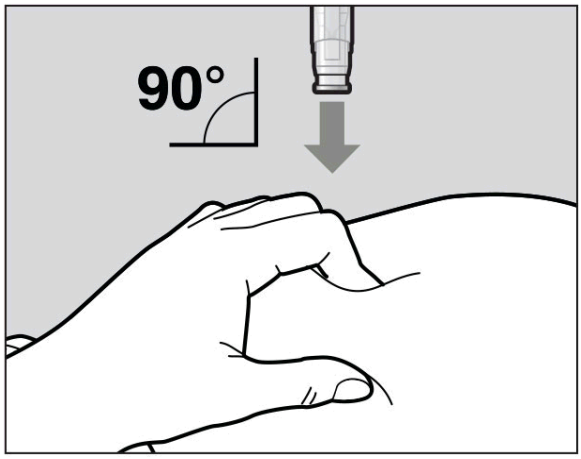


Figure H

- To use the pre-filled pen, you first have to unlock the green Activation button.
- To unlock it, press the pre-filled pen firmly against your pinched skin until the needle-shield is completely pushed in **(See Figure I)**.

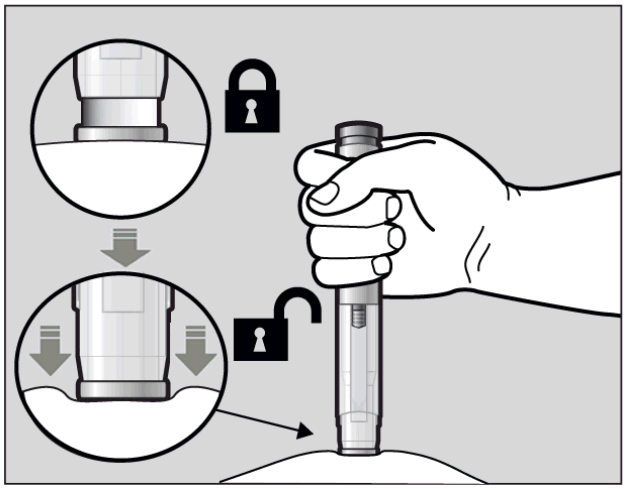


Figure I

- Continue to keep the needle-shield pushed in.
- If you don’t keep the needle-shield completely pushed against the skin, the green Activation button will not work.
- Continue to pinch the skin while you keep the pre-filled pen in place.
- Press the green Activation button to start the injection. A “click” sound indicates the start of the injection. Keep the green button pressed in and continue holding the pre-filled pen pressed firmly against your skin **(See Figure J).** If you cannot start the injection you should ask for help from a caregiver or contact your healthcare provider.

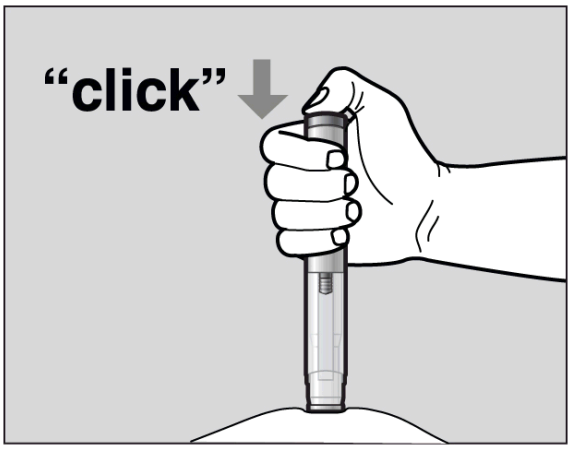


Figure J

- The purple indicator will move along the Window area during the injection **(See Figure K).**
- Watch the purple indicator until it stops moving to be sure the full dose of medication is injected.

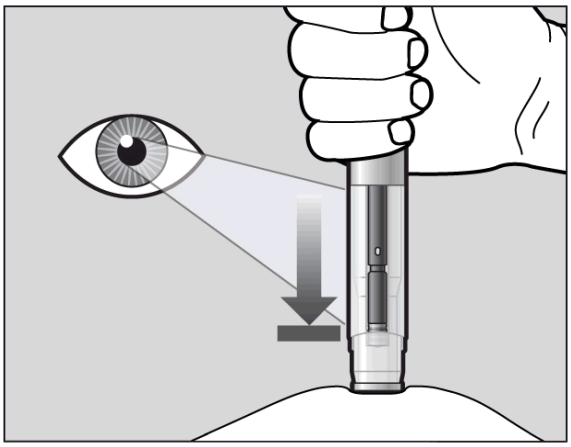


Figure K

- The injection may take up to **10 seconds**.
- You may hear a second “click” during the injection but you should continue to hold the pre-filled pen firmly against your skin until the purple indicator stops moving.
- When the purple indicator has stopped moving, release the green button. Lift the pre-filled pen straight off of the injection site at a 90° angle to remove the needle from the skin. The needle-shield will then move out and lock into place covering the needle **(See Figure L)**.

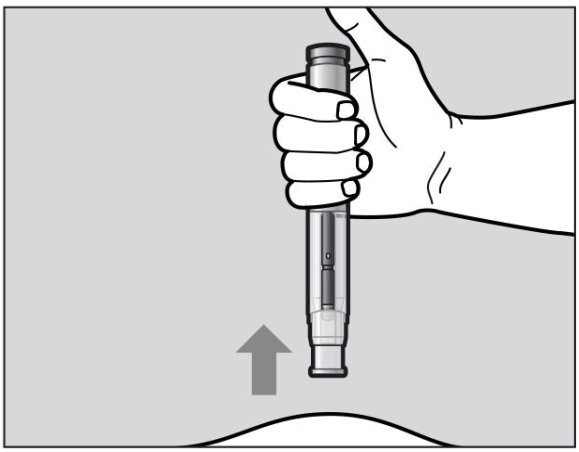


Figure L

- Check the Window area to see that it is filled with the purple indicator **(See Figure L).**
- If the Window area is not filled by the purple indicator then:
    - The needle-shield may not have locked. **Do not** touch the needle-shield of the pre-filled pen, because you may stick yourself with the needle. If the needle is not covered, carefully place the pre-filled pen into the sharps container to avoid any injury with the needle.
    - You may not have received your full dose of RoACTEMRA. **Do not** try to re-use the pre-filled pen. Do not repeat the injection with another pre-filled pen. Call your healthcare provider for help.

After the Injection

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

Step 4. Dispose of the pre-filled pen

- The RoACTEMRA pre-filled pen should not be reused.
- Put the used pre-filled pen into your sharps container (see **"How do I dispose of used pre-filled pens?")**
- **Do not** put the cap back on the pre-filled pen.
- **If your injection is given by another person, this person must also be careful when removing the pre-filled pen and disposing of it to prevent accidental needle stick injury and passing infection.**

How do I dispose of used pre-filled pens?

- Put your used RoACTEMRA pre-filled pen and green cap in a sharps disposal container right away after use **(See Figure M).**
- **Do not throw away (dispose of) the pre-filled pen and the green cap in your household trash and do not recycle them.**



Figure M

- Dispose of the full container as instructed by your healthcare provider or pharmacist.
- Always keep the puncture-resistant container out of the sight and reach of children.

Keep the RoACTEMRA pre-filled pen and disposal container out of the reach of children.

Record your Injection

- Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any questions or concerns about the injection so you can ask your healthcare provider.

If you have any questions or concerns about your RoACTEMRA pre-filled pen, talk to your healthcare provider familiar with RoACTEMRA.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for tocilizumab, the scientific conclusions of CHMP are as follows:

The MAH provided a comprehensive cumulative review of cases of hypofibrinogenaemia and related terms, including data from the literature, clinical development and post-marketing, in association with tocilizumab. Based on this review, the PRAC considered that a causal relationship between tocilizumab and hypofibrinogenaemia is established warranting the addition of hypofibrinogenaemia as an adverse drug reaction in section 4.8 of the SmPC (frequency 'common'). The package leaflet should be updated accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for tocilizumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing tocilizumab is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.

1.6.5　企業中核データシート（CDS）

CORE DATA SHEET [redacted]

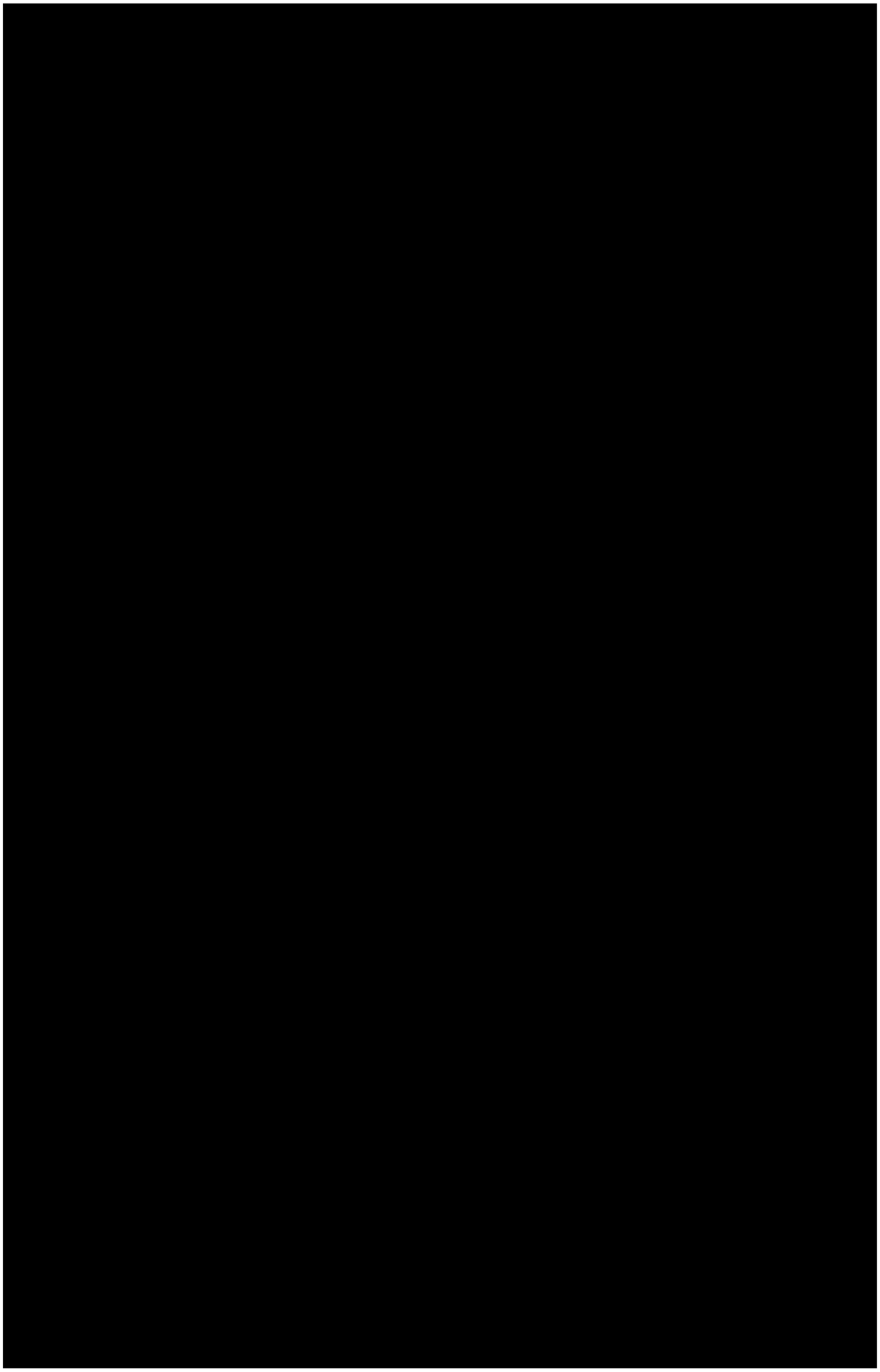
ACTEMRA®, ROACTEMRA®

Tocilizumab

[redacted]

[redacted]

[redacted]



アクテムラ点滴静注用80 mg，同200 mg，同400 mg（トシリズマブ（遺伝子組換え））

［サイトカイン放出症候群］

第1部　（モジュール1）：

申請書等行政情報及び添付文書に関する情報

1.7 同種同効品一覧表

最新の添付文書を参照すること。

中外製薬株式会社

目次

頁

1.7 同種同効品一覧表 3

1.7　同種同効品一覧表

表1.7- 1 同種同効品一覧表

販売名	アクテムラ点滴静注用80 mg、アクテムラ点滴静注用200 mg、アクテムラ点滴静注用400 mg	ソル・メドロール静注用40 mg、ソル・メドロール静注用125 mg、ソル・メドロール静注用500 mg、ソル・メドロール静注用1000 mg
一般名	トシリズマブ（遺伝子組換え）（JAN）	メチルプレドニゾロンコハク酸エステルナトリウム（JAN）
会社名	製造販売元：中外製薬株式会社	製造販売元：ファイザー株式会社
効能又は効果	○既存治療で効果不十分な下記疾患 関節リウマチ（関節の構造的損傷の防止を含む）、多関節に活動性を有する若年性特発性関節炎、全身型若年性特発性関節炎 ○キャッスルマン病に伴う諸症状及び検査所見（C 反応性タンパク高値、フィブリノーゲン高値、赤血球沈降速度亢進、ヘモグロビン低値、アルブミン低値、全身倦怠感）の改善。ただし、リンパ節の摘除が適応とならない患者に限る。 ○腫瘍特異的 T 細胞輸注療法に伴うサイトカイン放出症候群	[ソル・メドロール静注用40mg、125mg、500mg、1000mg] ○急性循環不全（出血性ショック、感染性ショック） ○腎臓移植に伴う免疫反応の抑制 ○受傷後8時間以内の急性脊髄損傷患者（運動機能障害及び感覚機能障害を有する場合）における神経機能障害の改善 ○ネフローゼ症候群 ○多発性硬化症の急性増悪 ○治療抵抗性の下記リウマチ性疾患 全身性血管炎（顕微鏡的多発血管炎、ヴェゲナ肉芽腫症、結節性多発動脈炎、Churg-Strauss 症候群、大動脈炎症候群等）、全身性エリテマトーデス、多発性筋炎、皮膚筋炎、強皮症、混合性結合組織病、及び難治性リウマチ性疾患 [ソル・メドロール静注用40mg、125mg] ○気管支喘息 [ソル・メドロール静注用40mg、125mg、500mg] ○以下の悪性腫瘍に対する他の抗悪性腫瘍剤との併用療法 再発又は難治性の悪性リンパ腫
添付文書改訂日	－	2016年9月改訂（第9版）

※※2016年９月改訂（第９版）
※2015年５月改訂

副腎皮質ホルモン剤

日本標準商品分類番号
８７２４５６

処方箋医薬品注)

ソル・メドロール®静注用40mg
ソル・メドロール®静注用125mg
ソル・メドロール®静注用500mg
ソル・メドロール®静注用1000mg

Solu-Medrol® for Intravenous Use 40mg・125mg・500mg・1000mg

注射用メチルプレドニゾロンコハク酸エステルナトリウム

	40mg	125mg	500mg	1000mg
承認番号	22000AMX00322	22000AMX00321	22000AMX00311	22000AMX00384
薬価収載	2008年６月			
販売開始	2008年９月	2008年８月	2008年８月	2008年７月
効能追加	2014年８月			
国際誕生	1959年４月			

貯　　法：室温保存
使用期限：最終年月を外箱等に記載

注)注意－医師等の処方箋により使用すること

【警　告】[1)]

1. 本剤を含むがん化学療法は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本療法が適切と判断される症例についてのみ実施すること。適応患者の選択にあたっては、各併用薬剤の添付文書を参照して十分注意すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。
2. 血清クレアチニンの高値（>2.0 mg/dL）を示す敗血症症候群及び感染性ショックの患者で本剤の大量投与により死亡率を増加させたとの報告がある。投与に際しては患者の選択、用法・用量に特に留意すること。

【禁　忌】

1. 次の患者には投与しないこと
本剤の成分に対し過敏症の既往歴のある患者
2. 次の薬剤を投与しないこと
生ワクチン又は弱毒生ワクチン［「相互作用」の項参照］

【原則禁忌（次の患者には投与しないことを原則とするが、特に必要とする場合には慎重に投与すること）】

1. 有効な抗菌剤の存在しない感染症、全身の真菌症の患者［免疫機能を抑制し、宿主防御能を低下させるので、感染症を悪化させるおそれがある。］
2. 腎機能低下及び慢性腎不全のある重症感染症の患者［「警告」の項参照］
3. 急性心筋梗塞を起こした患者［心破裂を起こしたとの報告がある。］

【組成・性状】

1. 組成

１バイアル中：

販売名 / 成分	ソル・メドロール静注用40mg	ソル・メドロール静注用125mg	ソル・メドロール静注用500mg	ソル・メドロール静注用1000mg
有効成分	メチルプレドニゾロンコハク酸エステルナトリウム（メチルプレドニゾロン相当量）			
	53.0 mg（40 mg）	165.7 mg（125 mg）	663.0 mg（500 mg）	1326.0 mg（1000 mg）
添加物	乳糖水和物 25.0 mg 無水リン酸一水素ナトリウム リン酸二水素ナトリウム一水和物 pH調節剤	－ 無水リン酸一水素ナトリウム リン酸二水素ナトリウム一水和物 pH調節剤	－ 無水リン酸一水素ナトリウム リン酸二水素ナトリウム一水和物 pH調節剤	－ 無水リン酸一水素ナトリウム リン酸二水素ナトリウム一水和物 pH調節剤

各製剤には溶解用液が添付されている（「包装」の項参照）。

2. 性状

本剤は白色の塊又は粉末で、添付溶解用液で溶かした注射液は、無色～微黄色澄明で、その溶液のpH及び浸透圧比は次のとおりである。

	ソル・メドロール静注用40mg	ソル・メドロール静注用125mg	ソル・メドロール静注用500mg	ソル・メドロール静注用1000mg
pH	7.0～8.0			
浸透圧比	約２	約１		

（浸透圧比：生理食塩液対比）

【効能・効果】

［ソル・メドロール静注用40mg、125mg、500mg、1000mg］
○急性循環不全（出血性ショック、感染性ショック）
○腎臓移植に伴う免疫反応の抑制
○受傷後８時間以内の急性脊髄損傷患者（運動機能障害及び感覚機能障害を有する場合）における神経機能障害の改善
○ネフローゼ症候群
○多発性硬化症の急性増悪
○治療抵抗性の下記リウマチ性疾患
全身性血管炎（顕微鏡的多発血管炎、ヴェゲナ肉芽腫症、結節性多発動脈炎、Churg-Strauss症候群、大動脈炎症候群等）、全身性エリテマトーデス、多発性筋炎、皮膚筋炎、強皮症、混合性結合組織病、及び難治性リウマチ性疾患
［ソル・メドロール静注用40mg、125mg］
○気管支喘息
［ソル・メドロール静注用40mg、125mg、500mg］
○以下の悪性腫瘍に対する他の抗悪性腫瘍剤との併用療法
再発又は難治性の悪性リンパ腫

［効能・効果に関連する使用上の注意］
○ネフローゼ症候群、治療抵抗性のリウマチ性疾患
原則として、経口副腎皮質ホルモン剤（プレドニゾロン等）による適切な治療で十分な効果がみられない場合に使用すること。
○気管支喘息
本剤の投与にあたっては、最新のガイドライン[2~4)]を参考に、本剤の投与が適切と判断される患者に使用すること。

【用法・用量】

［ソル・メドロール静注用40mg、125mg、500mg、1000mg］
○急性循環不全：
出血性ショック
通常、メチルプレドニゾロンとして１回125～2000 mgを緩徐に静注又は点滴静注する。症状が改善しない場合には、適宜追加投与する。

感染性ショック

通常、成人にはメチルプレドニゾロンとして１回1000 mgを緩徐に静注又は点滴静注する。症状が改善しない場合には、1000 mgを追加投与する。なお、年齢、症状により適宜増減する。

○腎臓移植に伴う免疫反応の抑制：

通常、成人にはメチルプレドニゾロンとして１日40～1000 mgを緩徐に静注又は点滴静注する。なお、年齢、症状により適宜増減する。

○受傷後８時間以内の急性脊髄損傷患者（運動機能障害及び感覚機能障害を有する場合）における神経機能障害の改善：

受傷後８時間以内に、メチルプレドニゾロンとして30 mg/kgを15分間かけて点滴静注し、その後45分間休薬し、5.4 mg/kg/時間を23時間点滴静注する。

○ネフローゼ症候群：

1. 通常、成人にはメチルプレドニゾロンとして１日500～1000 mgを緩徐に静注又は点滴静注する。
2. 通常、小児にはメチルプレドニゾロンとして１日30 mg/kg（最大1000 mg）を緩徐に静注又は点滴静注する。

○多発性硬化症の急性増悪：

通常、成人にはメチルプレドニゾロンとして１日500～1000 mgを緩徐に静注又は点滴静注する。

○治療抵抗性のリウマチ性疾患：

1. 通常、成人にはメチルプレドニゾロンとして１日500～1000 mgを緩徐に静注又は点滴静注する。
2. 通常、小児にはメチルプレドニゾロンとして１日30 mg/kgを緩徐に静注又は点滴静注する。なお、症状や患者の反応に応じて適宜増減するが、１日1000 mgを超えないこと。

［ソル・メドロール静注用40mg、125mg］

○気管支喘息：

1. 通常、成人にはメチルプレドニゾロンとして初回量40～125 mgを緩徐に静注又は点滴静注する。その後、症状に応じて、40～80 mgを４～６時間ごとに緩徐に追加投与する。
2. 通常、小児にはメチルプレドニゾロンとして1.0～1.5 mg/kgを緩徐に静注又は点滴静注する。その後、症状に応じて、1.0～1.5 mg/kgを４～６時間ごとに緩徐に追加投与する。

［ソル・メドロール静注用40mg、125mg、500mg］

○再発又は難治性の悪性リンパ腫に対する他の抗悪性腫瘍剤との併用療法の場合：

他の抗悪性腫瘍剤との併用において、本剤の投与量及び投与方法はメチルプレドニゾロンとして250～500 mgを１日１回５日間、緩徐に静注又は点滴静注する。これを１コースとして、３～４週ごとに繰り返す。

［用法・用量に関連する使用上の注意］

○ネフローゼ症候群

本剤を投与する際は、本剤の投与回数や投与スケジュールについて、国内外のガイドライン等[5,6]の最新の情報を参考にすること。

○多発性硬化症の急性増悪

本剤を投与する際は、本剤の投与回数等について、国内外のガイドライン[7]等の最新の情報を参考にすること。

○再発又は難治性の悪性リンパ腫に対する他の抗悪性腫瘍剤との併用療法においては、関連文献（「抗がん剤報告書：シスプラチン（悪性リンパ腫）」等）及び併用薬剤の添付文書を熟読すること。

【使用上の注意】

1.慎重投与（次の患者には慎重に投与すること）

⑴消化性潰瘍、憩室炎、腸吻合術後初期の患者［消化管粘膜保護作用を減弱させ、また、組織の修復を阻害するので、症状を悪化させるおそれがある。］

⑵糖尿病の患者［糖新生を促進させ、また、細胞のインスリンに対する感受性を低下させるので、症状を悪化させるおそれがある。］

⑶感染症の患者［免疫機能を抑制し、宿主防御能を低下させ、症状を悪化させるおそれがある。また、炎症反応を抑制し、徴候を隠蔽するおそれがあるので、感染症に対する適切な処置を行うこと。］

⑷結核性疾患の患者［免疫機能を抑制し、宿主防御能を低下させ、症状を悪化又は顕性化させるおそれがあるので、適宜抗結核療法を併用すること。］

⑸単純疱疹性角膜炎の患者［角膜に穿孔が生じるおそれがある。］

⑹骨粗鬆症の患者［骨基質の合成を阻害し、骨形成を抑制するので、症状を悪化させるおそれがある。］

⑺精神病の患者［中枢神経刺激作用により、症状を悪化させるおそれがある。］

⑻後嚢白内障の患者［水晶体嚢の透過性を変化させ、症状を悪化させるおそれがある。］

⑼緑内障の患者［眼圧を上昇させ、症状を悪化させるおそれがある。］

⑽腎不全、高血圧症、うっ血性心不全の患者［ナトリウム貯留作用により、症状を悪化させるおそれがある。］

⑾電解質異常のある患者［電解質代謝に影響を与えるので、症状を悪化させるおそれがある。］

⑿甲状腺機能低下のある患者、肝硬変の患者［代謝が阻害され、副作用があらわれるおそれがある。］

⒀脂肪肝、脂肪塞栓症の患者［脂質代謝に影響を与えるので、症状を悪化させるおそれがある。］

⒁血栓症の患者［血液凝固促進作用により、症状を悪化させるおそれがある。］

⒂重症筋無力症の患者［使用当初、一時症状を悪化させるおそれがある。］

⒃気管支喘息の患者［「重要な基本的注意」の項参照］

⒄乳製品に対して過敏症の既往歴のある患者［「重要な基本的注意」の項参照］

⒅潰瘍性大腸炎（切迫穿孔、膿瘍、他の化膿性感染症の疑いがある場合）の患者［炎症反応を抑制するので、これらの疑いがある場合、その徴候を隠蔽するおそれがある。］

⒆高齢者［「高齢者への投与」の項参照］

2.重要な基本的注意

⑴急性脊髄損傷における神経機能障害の改善の場合は、受傷後８時間以内に投与を開始すること。投与に際しては、用法・用量に記載の体重換算用量を厳守すること。

⑵本剤の高用量を急速静注（500 mgを超える用量を10分未満で投与）することにより、**心停止、循環性虚脱、不整脈等**があらわれたとの報告があるので、本剤の高用量を使用する場合にはこれらの副作用の出現に十分注意の上緩徐に投与すること。異常が認められた場合には、心臓蘇生法、輸液、昇圧剤、抗不整脈剤等の適切な救急処置を行うこと。

1)急性循環不全（出血性ショック、感染性ショック）及び腎臓移植に伴う免疫反応の抑制の場合において、例えば投与量が250 mgを超えるときには、少なくとも30分間以上かけて投与することが望ましい。

2)急性脊髄損傷における神経機能障害の改善の場合は、受傷後８時間以内に30 mg/kgを15分かけて点滴静注するため、心電図モニターによる十分な観察を行うとともに、これらの副作用に対する適切な処置（除細動器の使用等）についてもあらかじめ考慮しておくこと。

⑶本剤の投与により、**誘発感染症、循環器障害、続発性副腎皮質機能不全、消化性潰瘍、糖尿病、精神障害等の重篤な副作用**があらわれることがあるので、本剤の投与にあたっては、以下の点に注意すること。また、投与中は副作用の出現に対し、常に十分な配慮と観察を行うこと。

1)感染性ショックの場合は発生初期において、直ちに投与を開始することが望ましく、用法・用量どおり使用しても効果が認められないときは投与を中止すること。なお、副腎皮質ホルモン剤は感染症を悪化させることがあるので、本剤投与中及びショック離脱後も十分な量の抗菌剤の投与等の感染症に対する適切な処置を行うこと。

2)ショック状態の患者には、ショックが改善すれば、直ちに投与を中止すること。

3)腎臓移植に伴う免疫反応の抑制の場合は、副腎皮質ホルモン剤を連用することがあるので、連用中並びに連用後は以下の点に注意すること。
①連用中は副作用の出現に対し、常に十分な配慮と観察を行い、また、患者をストレスから避けるようにし、事故、手術等の場合には増量するなど適切な処置を行うこと。
②連用後に投与を急に中止すると、ときに発熱、頭痛、食欲不振、脱力感、筋肉痛、関節痛、ショック等の離脱症状があらわれることがあるので、投与を中止する場合には、徐々に減量するなど慎重に行うこと。離脱症状があらわれた場合には、直ちに再投与又は増量すること。

⑷副腎皮質ホルモン剤を投与されたB型肝炎ウイルスキャリアの患者において、B型肝炎ウイルスの増殖による肝炎があらわれることがある。本剤の投与期間中及び投与終了後は継続して肝機能検査値や肝炎ウイルスマーカーのモニタリングを行うなど、B型肝炎ウイルス増殖の徴候や症状の発現に注意すること。異常が認められた場合には、本剤の減量を考慮し、抗ウイルス剤を投与するなど適切な処置を行うこと。なお、投与開始前にHBs抗原陰性の患者において、B型肝炎ウイルスによる肝炎を発症した症例が報告されている。

⑸本剤投与により、気管支喘息患者の喘息発作を悪化させることがあるので、薬物、食物、添加物等に過敏な喘息患者（アスピリン喘息の既往を有する患者等）には特に注意が必要である。

※※⑹ソル・メドロール静注用40 mgには、添加物として、牛の乳由来の乳糖を使用している。乳製品に対して過敏症の既往歴のある患者に投与すると、アナフィラキシーがあらわれることがあるので、牛の乳由来の乳糖を含有しない他の製剤の使用を考慮すること。

⑺特に、本剤投与中に水痘又は麻疹に感染すると、致命的な経過をたどることがあるので、次の注意が必要である。
1)本剤投与前に水痘又は麻疹の既往や予防接種の有無を確認すること。
2)水痘又は麻疹の既往のない患者においては、水痘又は麻疹への感染を極力防ぐよう常に十分な配慮と観察を行うこと。感染が疑われる場合や感染した場合には、直ちに受診するよう指導し、適切な処置を講ずること。
3)水痘又は麻疹の既往や予防接種を受けたことがある患者であっても、本剤投与中は、水痘又は麻疹を発症する可能性があるので留意すること。

※⑻強皮症患者における強皮症腎クリーゼの発現率は、副腎皮質ホルモン剤投与患者で高いとの報告がある。本剤を強皮症患者に投与する場合は、血圧及び腎機能を慎重にモニターし、強皮症腎クリーゼの徴候や症状の出現に注意すること。また、異常が認められた場合には適切な処置を行うこと。

3. 相互作用

本剤は主として薬物代謝酵素CYP3A4で代謝される。

⑴併用禁忌（併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
生ワクチン又は弱毒生ワクチン （乾燥BCGワクチン等）	ワクチン株の異常増殖又は毒性の復帰があらわれるおそれがある。	免疫抑制が生じる量の副腎皮質ホルモン剤の投与を受けている患者

⑵併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
シクロスポリン	双方の血中濃度が上昇するおそれがある。また、痙攣が起こるおそれがある。 必要に応じて本剤又はシクロスポリンを減量するなど用量に注意すること。	相互に代謝が阻害される。
エリスロマイシン イトラコナゾール ミコナゾール キヌプリスチン ダルホプリスチン エストロゲン（経口避妊薬を含む） アプレピタント	本剤の作用が増強するおそれがある。必要に応じて本剤又はこれらの薬剤を減量するなど用量に注意すること。	これらの薬剤が代謝酵素（CYP3A4）を阻害することにより、本剤の代謝が阻害される。
抗凝血剤 パルナパリンナトリウム ワルファリンカリウム等	抗凝血剤の作用を増強又は減弱させるおそれがある。 必要に応じて本剤又は抗凝血剤の用量を調節すること。	本剤は血液凝固能を高め、抗凝血剤の効果に拮抗する可能性がある。 また一方、本剤の消化器系の副作用により、抗凝血剤の出血の危険性が増大する可能性がある。
非脱分極性筋弛緩剤 ベクロニウム臭化物 パンクロニウム臭化物等	非脱分極性筋弛緩剤の作用を増強又は減弱させるおそれがある。 また、併用により短期間でミオパチーがあらわれ、四肢麻痺に至るおそれがある。 必要に応じて本剤又は非脱分極性筋弛緩剤の用量を調節すること。	機序不明
※ 非ステロイド性解熱鎮痛消炎剤 サザピリン ジクロフェナク等	消化器系の副作用（消化性潰瘍、消化管出血等）を起こすおそれが高くなる。 必要に応じて本剤又は非ステロイド性解熱鎮痛消炎剤を減量するなど用量に注意すること。	ともに消化器系の副作用を起こすおそれがある。
カリウム排泄型利尿剤 トリクロルメチアジド ヒドロクロロチアジド フロセミド等	低カリウム血症があらわれるおそれがある。 必要に応じて本剤又はカリウム排泄型利尿剤を減量するなど用量に注意すること。	カリウム排泄が促進される。
ジゴキシン	ジゴキシン中毒があらわれるおそれがある。 必要に応じて本剤又はジゴキシンを減量するなど用量に注意すること。	カリウム排泄による血中カリウム値低下により、ジゴキシンの作用が増強する。
※ サリチル酸誘導体 サザピリン アスピリン等	サリチル酸中毒（めまい、耳鳴、悪心・嘔吐、過呼吸、高熱、意識障害等の症状）を起こすおそれがある。 必要に応じて本剤又はサリチル酸誘導体の用量を調節すること。 サリチル酸中毒があらわれた場合には、サリチル酸誘導体の投与を中止するなど適切な処置を行うこと。	本剤はサリチル酸誘導体の代謝・排泄を促進すると考えられているので、本剤の急な減量又は中止により、血清中のサリチル酸誘導体の濃度が増加すると考えられる。
※ バルビツール酸誘導体 フェノバルビタール等 フェニトイン リファンピシン カルバマゼピン	本剤の作用が減弱するおそれがある。 必要に応じて本剤又はこれらの薬剤の用量を調節すること。	本剤の代謝が促進される。
※ 経口糖尿病用剤 アカルボース トルブタミド等 インスリン製剤	これらの薬剤の効果が減弱されるおそれがある。 必要に応じて本剤又はこれらの薬剤の用量を調節すること。	本剤の糖新生促進作用等により、血糖値を上昇させる。

4. 副作用

○急性循環不全（出血性ショック、感染性ショック）

調査症例数4,022例中、副作用発現症例は33例（0.82%）であり、副作用発現件数は延べ33件であった。その主なものは、低血圧10件（0.25%）等であった。（承認時までの調査及び市販後の使用成績調査の集計）

○腎臓移植に伴う免疫反応の抑制

調査症例数1,378例中、副作用発現症例は339例（24.6%）であり、副作用発現件数は延べ441件であった。その主なものは、糖尿169件（12.3%）、感染112件（8.13%）、胃腸出血39件（2.83%）、肝機能異常28件（2.03%）等であった。（承認時までの調査及び市販後の使用成績調査の集計）

○急性脊髄損傷における神経機能障害の改善

調査症例数1,060例中、副作用発現症例は333例（31.4%）であり、副作用発現件数は延べ552件であった。その主なものは、血糖上昇234件（22.1%）、糖尿84件（7.92%）等であった。（承認時までの調査及び市販後の使用成績調査の集計）

○ネフローゼ症候群、気管支喘息、再発又は難治性の悪性リンパ腫に対する他の抗悪性腫瘍剤との併用療法、多発性硬化症の急性増悪、治療抵抗性のリウマチ性疾患

副作用発現頻度が明確となる調査を実施していない。

⑴**重大な副作用**

1)ショック（0.08%）：ショックを起こすことがある。呼吸困難、全身潮紅、血管浮腫、蕁麻疹等のアナフィラキシーを伴うことがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、血圧の維持、体液の補充管理、気道の確保等の適切な処置を行うこと。

2)心停止（頻度不明）、**循環性虚脱**（頻度不明）、**不整脈**（頻度不明）：本剤の高用量を急速静注することにより、心停止、循環性虚脱、不整脈等があらわれたとの報告があるので、本剤の高用量を使用する場合には緩徐に投与すること。

3)感染症（2.54%）：ウイルス、細菌、真菌、原虫、寄生虫等による感染症の誘発又は徴候の隠蔽、感染症の悪化等があらわれることがある。これらの感染症の発現頻度は、副腎皮質ホルモン剤を増量すると高くなるとの報告があるので、抗菌剤等による適切な処置を行うこと。また、B型肝炎ウイルスの増殖による肝炎があらわれることがある。観察を十分に行い、異常が認められた場合には適切な処置を行うこと。

4)続発性副腎皮質機能不全（頻度不明）：続発性副腎皮質機能不全があらわれることがあるので、観察を十分に行い、異常が認められた場合には直ちに再投与又は増量するなど適切な処置を行うこと。

5)骨粗鬆症（頻度不明）、**骨頭無菌性壊死**（0.36%）：骨粗鬆症があらわれ、脊椎圧迫骨折、病的骨折を起こすことがある。また、大腿骨及び上腕骨等の骨頭無菌性壊死があらわれることがある。疼痛等の症状の観察を十分に行い、異常が認められた場合にはMRI等の検査を実施し、投与を中止するなど適切な処置を行うこと。

6)胃腸穿孔（0.02%）、**消化管出血**（0.80%）、**消化性潰瘍**（0.02%）：胃腸穿孔、消化管出血、消化性潰瘍があらわれることがあるので、便潜血のチェック等の観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

7)ミオパチー（頻度不明）：連用によりミオパチーがあらわれることがある。また、非脱分極性筋弛緩剤との併用又は重症筋無力症等の神経筋接合部位障害のある患者において短期間でミオパチーがあらわれ、四肢麻痺に至ったことが報告されているので、筋力低下、CK（CPK）の上昇等の観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

8)血栓症（頻度不明）：心筋梗塞、腸間膜動脈血栓症等の血栓症があらわれることがある。また、血液凝固能亢進に伴って血小板減少が生じることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

9)頭蓋内圧亢進（頻度不明）、**痙攣**（頻度不明）：頭蓋内圧亢進、痙攣があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

10)精神変調（0.06%）、**うつ状態**（0.02%）：精神変調、うつ状態があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11)糖尿病（3.95%）：糖尿病があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

※※**12)緑内障**（頻度不明）、**後嚢白内障**（0.09%）、**中心性漿液性脈絡網膜症**（頻度不明）、**多発性後極部網膜色素上皮症**（頻度不明）：連用により眼圧上昇、緑内障、後嚢白内障（症状：眼のかすみ）、中心性漿液性脈絡網膜症・多発性後極部網膜色素上皮症（症状：視力の低下、ものがゆがんで見えたり小さく見えたり、視野の中心がゆがんで見えにくくなる。中心性漿液性脈絡網膜症では限局性の網膜剝離がみられ、進行すると広範な網膜剝離を生じる多発性後極部網膜色素上皮症となる。）を来すことがあるので、定期的に検査をすることが望ましい。なお、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

13)気管支喘息（頻度不明）：喘息発作の誘発又は悪化があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

14)心破裂（頻度不明）：急性心筋梗塞を起こした患者で、心破裂があらわれたとの報告があるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

15)膵炎（0.03%）：出血性膵炎等の膵炎があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、輸液等の適切な処置を行うこと。

16)うっ血性心不全（0.02%）：うっ血性心不全があらわれることがあるので、観察を十分に行い、異常が認められた場合には心電図等の検査を実施し、投与を中止するなど適切な処置を行うこと。

17)食道炎（頻度不明）：食道炎があらわれたとの報告があるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

18)カポジ肉腫（頻度不明）：カポジ肉腫があらわれたとの報告があるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

19)腱断裂（頻度不明）：アキレス腱等の腱断裂があらわれたとの報告があるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

20)肝機能障害（1.21%）、**黄疸**（頻度不明）：AST（GOT）、ALT（GPT）、Al-Pの上昇等を伴う肝機能障害、黄疸があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

⑵**その他の副作用**

以下のような副作用があらわれた場合には、症状に応じて適切な処置を行うこと。

	0.1～5%未満	0.1%未満	頻度不明
内分泌			月経異常、クッシング様症状
消化器		嘔吐、悪心	下痢、腹痛、胸やけ、腹部膨満感、食欲不振、食欲亢進
循環器	血圧降下、血圧上昇	徐脈	
精神神経系			多幸症、不眠、頭痛、めまい
筋・骨格		関節痛	筋力低下、筋肉痛
脂質・蛋白質代謝		満月様顔貌	窒素負平衡、体重増加
肝臓			脂肪肝
体液・電解質			浮腫、低カリウム性アルカローシス、カリウム低下、ナトリウム貯留
眼			網膜障害、眼球突出
血液	白血球増多		
皮膚	創傷治癒障害		紫斑、ざ瘡、発汗異常、脂肪織炎、皮膚菲薄化・脆弱化、多毛症、皮膚線条
過敏症		そう痒、発疹、紅斑	
その他		発熱	疲労感、仮性脳腫瘍、しゃっくり、易刺激性

発現頻度は、承認時の臨床試験及び使用成績調査の結果に基づいている。

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5. 高齢者への投与

高齢者には、慎重に投与すること。[長期投与した場合、感染症の誘発、糖尿病、骨粗鬆症、高血圧症、後嚢白内障、緑内障等の副作用があらわれやすい。]

6. 妊婦、産婦、授乳婦等への投与

⑴妊婦

妊婦又は妊娠している可能性のある婦人には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。[動物実験（マウス）で催奇形作用（口蓋裂）が報告されており、また、新生児に副腎不全を起こすことがある。]

⑵授乳婦

本剤投与中は授乳を避けさせること。[母乳中へ移行することがある。]

7. 小児等への投与

⑴観察を十分に行うこと。[小児等の発育抑制があらわれることがある。]

⑵長期投与した場合、頭蓋内圧亢進症状があらわれることがある。

⑶治療抵抗性のリウマチ性疾患における低出生体重児、新生児、乳児等に対する安全性は確立していない。[使用経験が少ない]

8. 適用上の注意

⑴投与経路

本剤は、用法・用量にしたがって、静注又は点滴静注のみに使用すること。本剤は動脈注射、筋肉内注射、脊髄腔内注射、硬膜外注射、眼科用等に対して使用しないこと。

※⑵調製時

本剤は、添付の溶解用液を用いて用時溶解すること。溶解した液を輸液と混合して使用する場合には、５％ブドウ糖注射液、生理食塩液等を使用すること。なおその際、本剤はpHの変動等により白沈を生じることがあるので、輸液等と混合する場合には注意すること。また、本剤を数種薬剤と混合して使用する場合には、特に注意する必要がある。

⑶静脈内投与時

静脈内投与により、血管痛、静脈炎があらわれることがあるので、これを予防するため、注射液の調製、注射部位、注射方法等について十分注意し、その注射速度はできるだけ遅くすること。

⑷アンプルカット時

40 mg、125 mg製剤に添付の溶解用アンプルは、アンプルのカット部分をエタノール綿等で清拭してからカットすることが望ましい。

⑸調製後の使用

溶解後はなるべく速やかに使用すること。なお、保存を必要とする場合でも10℃以下で保存し24時間以内に使用すること。

9. その他の注意

⑴免疫抑制剤による治療を受けた腎移植患者では、腫瘍（特に悪性リンパ腫、皮膚癌）の発生率が高いとする報告がある。

⑵β_2-刺激剤との併用により、低カリウム血症があらわれることがある。

⑶外国において、死菌ワクチン又は不活化ワクチンの効果を減弱させるとの報告がある。

⑷副腎皮質ホルモン剤の投与により、皮膚試験の反応が抑制されることがあるので、本剤投与中に皮膚試験を実施する場合は注意すること。

【薬物動態】

1. 血中濃度[8, 9]

健康成人（外国人）に本剤をメチルプレドニゾロンとして500 mg/ヒトを静脈内投与した結果、定常状態において、血漿中メチルプレドニゾロンのAUCは11.3±1.2 μg･hr/mL（平均値±標準偏差）、消失速度定数は0.33±0.02 hr^{-1}（半減期：2.1 hr）であった。また、本剤をメチルプレドニゾロンとして10～3,000 mg/ヒトの投与量の範囲において血漿中メチルプレドニゾロンのAUCは投与量に比例して増加した。

[参考]

2. 分布[10, 11]

ラットに^{3}H-メチルプレドニゾロンコハク酸エステルナトリウムをメチルプレドニゾロンとして30 mg/kg静脈内投与したとき、５分後にはほとんどの組織に放射能の分布がみられ、臓器内濃度は肝、腸で最も高く、次いで腎、副腎、血漿、心、膵、脳下垂体、肺、胃の順に高かった。投与後24時間には、各組織内濃度は速やかに減少した。損傷30分後の脊髄損傷ネコにメチルプレドニゾロンとして30 mg/kgを静脈内投与したとき、損傷脊髄濃度は0.5～１時間後に最高値に達し、その後は２相性の消失を示した。

ラットにおいて、胎児移行が認められた。

3. 代謝[12]

一般にステロイド骨格の６β水酸化反応はCYP3A4により触媒され、本薬の活性本体であるメチルプレドニゾロンにおいても６β水酸化体が主要代謝物であった。

4. 排泄[10]

ラットに^{3}H-メチルプレドニゾロンコハク酸エステルナトリウムをメチルプレドニゾロンとして30 mg/kg静脈内投与したとき、24時間後に尿中へ14.3％、糞中へ67.2％が排泄された。また、ラットにおいて乳汁移行が認められた。

【臨床成績】[13～21]

1. 急性循環不全（出血性ショック、感染性ショック）に対する効果

急性循環不全（出血性ショック、感染性ショック）患者を対象として、二重盲検比較試験を含む臨床試験を行った結果、本剤の有用性が認められた。

2. 腎臓移植に伴う免疫反応の抑制に対する効果

腎臓移植患者を対象として、比較試験を含む臨床試験を行った結果、本剤の有用性が認められた。

3. 急性脊髄損傷における神経機能障害の改善に対する効果

急性脊髄損傷患者を対象として、比較臨床試験を行った結果、運動機能障害のみを示す患者では対照群と比較して有意差は認められなかったが、運動機能障害及び感覚機能障害を有する患者において有意な改善が認められた。

4. 気管支喘息に対する効果

気管支喘息の急性増悪患者を対象とした海外における二重盲検比較試験の文献報告を検討した結果、本剤の有用性が認められた。

【薬効薬理】[22～41]

1. 抗ショック作用

ライソゾーム膜の安定化
膜透過性亢進の抑制
心筋抑制因子（MDF）の増加抑制

2. 抗炎症作用

3. 抗アレルギー作用、抗体産生の抑制

4. 脊髄損傷に対する改善効果

運動障害の改善
脊髄血流量低下の抑制
エネルギー代謝の改善
脂質過酸化の抑制

5. 抗喘息作用

炎症メディエーター産生抑制
血管透過性亢進抑制
炎症性サイトカイン・ケモカイン産生抑制
好酸球などの炎症細胞の気管・肺への浸潤抑制
アドレナリンβ受容体感受性低下抑制
気道における粘液分泌抑制

【有効成分に関する理化学的知見】

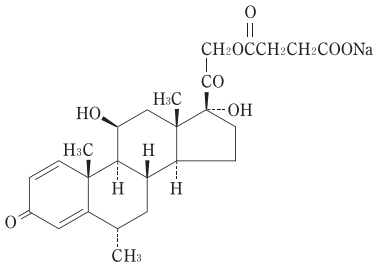
一般名：メチルプレドニゾロンコハク酸エステルナトリウム
（Methylprednisolone Sodium Succinate）

化学名：11β, 17, 21-trihydroxy-6α-methyl-1, 4-pregnadiene-3, 20-dione 21-sodium succinate

分子式：$C_{26}H_{33}NaO_8$

分子量：496.53

構造式：



性　状：白色の結晶性の粉末で、においはない。水、メタノール又はエタノール（95）に極めて溶けやすく、クロロホルムにほとんど溶けない。

【取扱い上の注意】

外箱から取り出した後は、光を避けて保存すること。

【包　　装】

ソル・メドロール静注用40mg：５バイアル
（溶解用液　日局 注射用水　１mL添付）

ソル・メドロール静注用125mg：１バイアル、５バイアル
（溶解用液　日局 注射用水　２mL添付）

ソル・メドロール静注用500mg：１バイアル、５バイアル
（溶解用液　日局 注射用水　８mL添付）

ソル・メドロール静注用1000mg：１バイアル、５バイアル
（溶解用液　日局 注射用水　16mL添付）

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【文献請求先】

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アクテムラ点滴静注用80 mg，同200 mg，同400 mg
（トシリズマブ（遺伝子組換え））

［サイトカイン放出症候群］

第1部　（モジュール1）：

申請書等行政情報及び添付文書に関する情報

1.8 添付文書（案）

最新の添付文書を参照すること。

中外製薬株式会社

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1.8　添付文書（案）

1.8.1　効能・効果，用法・用量の設定の根拠

1.8.1.1　効能・効果及びその設定理由

1.8.1.1.1　効能・効果

効能・効果を以下に示す。

○既存治療で効果不十分な下記疾患
関節リウマチ（関節の構造的損傷の防止を含む）、多関節に活動性を有する若年性特発性関節炎、全身型若年性特発性関節炎
○キャッスルマン病に伴う諸症状及び検査所見（C 反応性タンパク高値、フィブリノーゲン高値、赤血球沈降速度亢進、ヘモグロビン低値、アルブミン低値、全身倦怠感）の改善。ただし、リンパ節の摘除が適応とならない患者に限る。
○抗悪性腫瘍療法に伴う T 細胞誘発性サイトカイン放出症候群

＜下線部分を追加＞

1.8.1.1.2　効能・効果の設定理由

キメラ抗原受容体（CAR）は，T 細胞の活性化に必要な T 細胞受容体の細胞内シグナル伝達ドメインに腫瘍細胞上の標的抗原を認識するモノクローナル抗体の特異性を付加する改変を加えた人工 T 細胞受容体である。CAR-T 細胞療法とは，単離した患者の（又は同種異系ドナーの）T 細胞に CAR をコードするウイルスベクターを導入して改変された CAR-T 細胞を製造し，患者に再注入する治療法である。体内に注入された CAR-T 細胞はただちに標的腫瘍細胞を認識し，攻撃する。この CAR-T 細胞は増殖能をもち，数カ月から数年生存するため，効果は長期間持続する。

サイトカイン放出症候群（CRS）はCAR-T細胞療法下で非常に多くみられる副作用であり，発現率は50%～100%である。CAR-T 細胞療法後の CRS は，10%～65%が NCI-CTCAE 分類 Grade 3以上の事象であり，管理に失敗すれば死に至ることもある。CRS の発症時期は通常，CAR-T 細胞輸注から数日ないし数週間後であり，これは体内で CAR-T 細胞の増加がピークに達する時期と重なる。したがって，CRS は CAR-T 細胞療法の深刻な副作用である反面，有効性の作用機序と切り離せないものと考えられ，CRS 発症と CAR-T 細胞療法の有効性とは強く相関することが，多くの研究グループによって報告されている[1)]。

IL-6はCRSにおける主要なメディエーターであることが示唆されており，CRS を誘発する治療の種類が何かを問わず，CRS では血清中 IL-6濃度が高値となる[2)-4)]。また，血清中 IL-6濃度と CRS の重症度にも相関が認められ，NCI CTCAE Grade 4～5の CRS の発現例では，CRS を発現しない患者や発現しても比較的軽度であった患者（NCI CTCAE Grade 0~3）に比べ，はるかに高い IL-6濃度が認められている[5)]。したがって，抗 IL-6R 抗体であるトシリズマブにより，CAR-T 細胞療法に伴う CRS の治療が可能であると考えられた。

ノバルティス社はCAR-T療法（開発コード：CTL019）の ALL 小児患者を対象とした B2202 試験及び成人 DLBCL 患者を対象とした C2201試験において，CRS 管理のアルゴリズムを治験実施計画書に規定した。そのアルゴリズムではCTL019輸注後に発症した CRS に対して，第一選択の治療として酸素，補液，低用量の昇圧薬及び解熱薬を規定し，症状の改善が認められない場合は第二選択の治療としてトシリズマブを規定した。トシリズマブは体重が30 kg 未満の場合は12 mg/kg の静注，体重が30 kg 以上の場合は8 mg/kg の静注（最大用量800 mg まで）と規定しており，トシリズマブの投与後症状の改善が認められない場合は，ステロイドの投与を考慮した上で各試験の治験実施計画書に従い追加のトシリズマブ投与を可能とした。

B2202試験及び C2201試験ではトシリズマブの有効性の評価項目として初回の CRS における，

トシリズマブ投与から CRS 回復判断時点までの期間，CRS の持続期間，抗サイトカイン療法（トシリズマブ以外の抗サイトカイン薬剤、ステロイドを含む）開始から解熱までの期間，抗サイトカイン療法開始から昇圧剤を離脱するまでの期間，抗サイトカイン療法開始から気管挿管チューブの抜管までの期間，炎症マーカー及びサイトカインの推移を評価した。

トシリズマブの投与に至った初回の CRS において，トシリズマブ投与から CRS 回復判断時点までの期間を評価した。CRS 回復は，24時間以上平熱が持続し，昇圧薬服用の必要がないと判断した期間が24時間以上持続した時点と定義した。B2202試験の有効性解析対象例は28例であり，全例（100.0%）がトシリズマブ投与後に回復した。トシリズマブ投与から CRS 回復判断時点までの期間の中央値［95%信頼区間（CI）］は，5.0（4.0，7.0）日（最小値～最大値：2～29日）であった。日本人の1例では，トシリズマブ投与から CRS 回復判断時点までの期間は11日であった。C2201試験の有効性解析対象例は15例であり，14例（93.3%）が回復し，1例は死亡（Patient ID_1611002, 死因：疾患進行）により評価が打ち切られた。トシリズマブ投与から CRS 回復判断時点までの期間の中央値（95%CI）は，6.0（3.0，7.0）日（最小値～最大値：2～14日）であった。

トシリズマブの投与に至った初回の CRS の発現日から回復日までの期間を CRS の持続期間として評価した。B2202試験で，CRS の持続期間の中央値（95%CI）は9.5（8.0，13.0）日（最小値～最大値：5～29日）であった。日本人の1例の CRS の持続期間は18日であった。C2201試験で，CRS の持続期間の中央値（95%CI）は8.0（6.0，9.0）日（最小値～最大値：4～14日）であった。

トシリズマブの投与に至った初回 CRS の抗サイトカイン療法開始から解熱までの期間の中央値（最小値～最大値）は，B2202試験は25/28例で評価され，2.000（0.09～25.00）日であり，C2201試験は14/15例で評価され，1.000（0.08～7.00）日であった。

トシリズマブの投与に至った初回 CRS の抗サイトカイン療法開始から昇圧剤離脱までの期間の中央値（最小値～最大値）は，B2202試験は24/28例で評価され，3.000（0.04～14.00）日であり，C2201試験は10/15例で評価され4.000（1.00～10.00）日であった。

トシリズマブの投与に至った初回 CRS の抗サイトカイン療法開始から気管挿管チューブの抜管まで期間の中央値（最小値～最大値）は，B2202試験は10/28例で評価され，6.000（3.00～18.00）日であり，C2201試験は6/15例で評価され10.000（3.00～20.00）日であった。

炎症マーカーとサイトカインパラメーターである CRP，Ferritin，IFNγ，IL-10，IL-13，IL-1β，IL-2，IL-4，IL-6，sIL-6R，IL-8，IL-12P70，TNFα の変動比（トシリズマブ初回投与後から最終投与後8日以内の最小値／CRS 発現時からトシリズマブ初回投与までの最大値）の中央値は，B2202試験及び C2201試験で，CRP，Ferritin，IFNγ，IL-10，IL-13，IL-1β，IL-2，IL-4，IL-6，IL-8，IL-12P70，TNFα は減少しており，sIL-6R は増加していた。sIL-6R の血中濃度の増加は，トシリズマブが sIL-6R との免疫複合体を形成することにより，sIL-6R のクリアランスが小さくなっていることが原因と考えられる。

日本人の患者は B2202試験での1例であった。本例の CRS はトシリズマブ投与後に回復しており，日本人においても日本人以外と同様の効果が期待できると考えられた。

B2202試験及び C2201試験において，トシリズマブの初回投与日同日以降，CTL019輸注後3カ月目までをトシリズマブの安全性評価期間としたが，その期間で最も発現率の高かった有害事象は CRS であり，B2202試験で22/28例（78.6%）及び C2201試験で8/15例（53.3%）であった。また，重篤な有害事象で最も高頻度に認められた事象は CRS であり，20/28例（71.4%）及び6/15例（40.0%）であった。認められた CRS のほとんどは，トシリズマブ投与前に発現し，事象継続している中で Grade 変化が認められたために有害事象として挙げられた事象であり，初回 CRS が回復した後に新たに発現した CRS は1例であった。CRS 以外の有害事象で最も発現率の高かった有害事象は，B2202試験では，発熱8/28例（28.6%），アスパラギン酸アミノトランスフェラーゼ増加8/28例（28.6%），好中球数減少8/28例（28.6%），低カリウム血症8/28

例（28.6%）であり，C2201試験では，血小板数減少7/15例（46.7%），低血圧7/15例（46.7%）であった。CRS 以外で，トシリズマブの安全性で懸念となる新たなリスクは認められなかった。

トシリズマブの安全性評価期間中の死亡例は，B2202試験では4/28例（14.3%），C2201試験では9/15例（60.0%）で，死因は疾患進行が多かった。疾患進行以外の死因においては，いずれも初回の CRS がトシリズマブ投与により回復した後に認められた事象であり，また，頻度が高く認められた有害事象あるいは特徴的に発現した有害事象は認められなかった。したがって，CRS 患者に対するトシリズマブ投与によって，新たな懸念となるリスクは認められなかった。

公表文献調査[6)-28)]からは，CTL019を含む複数の CAR-T 細胞療法等に伴う CRS に対し，トシリズマブ投与により，109例中104例（95.4%）が回復したことが確認できた。また，トシリズマブは，CAR-T 細胞療法の有効性を得るために必要な細胞増殖に影響を与えないことが報告された[17)]（調査日：2016年7月）。一般的に重症度の高い CRS の治療に用いる高用量のコルチコステロイドは，T 細胞の活性化，機能及び増殖を阻害する性質があり，CAR-T 細胞療法の有効性を減じるおそれがある。一方，トシリズマブは，CAR-T 細胞数の増殖を抑制しない。よって，CAR-T 細胞療法に伴う CRS に対する治療では，トシリズマブ投与が有用であると考えられる。

更に，公表文献調査では，CAR-T 細胞療法以外に，二重特異性 T 細胞誘導抗体治療（ブリナツモマブ）[7), 29)]，抗 PD-1抗体治療[30)-32)]及び T 細胞受容体遺伝子導入 T 細胞（TCR-T）療法[33)-36)]に伴う CRS に対してトシリズマブを投与し，CRS が回復したことが報告されている（調査日：2017年9月及び2018年7月）。いずれも CAR-T 細胞療法のように，T 細胞の増殖，活性化，細胞傷害活性の増強等の作用を有する抗悪性腫瘍療法であり，これらの療法に伴う CRS に対しても，トシリズマブ投与は有用であると考えられた。

以上より，本剤は T 細胞の増殖，活性化，細胞障害活性の増強等の作用を有する抗悪性腫瘍療法に伴う CRS に対して臨床上の有用性があり，その効果は現行治療では満たせないアンメットメディカルニーズを満たすものと考えられることから，本申請効能・効果を「抗悪性腫瘍療法に伴う T 細胞誘発性サイトカイン放出症候群」と設定した。

なお，審査の過程において効能・効果は「腫瘍特異的 T 細胞輸注療法に伴うサイトカイン放出症候群」となった。

1.8.1.1.3　効能・効果に関連する使用上の注意

効能・効果に関連する使用上の注意を以下に示す。

＜効能・効果に関連する使用上の注意＞
関節リウマチ及び多関節に活動性を有する若年性特発性関節炎：過去の治療において、少なくとも1剤の抗リウマチ薬による適切な治療を行っても、効果不十分な場合に投与すること。
全身性若年性特発性関節炎：
1. 過去の治療において、副腎皮質ステロイド薬による適切な治療を行っても、効果不十分な場合に投与すること。
2. 重篤な合併症としてマクロファージ活性化症候群（MAS）を発症することがある。MAS を合併している患者では MAS に対する治療を優先させ本剤の投与を開始しないこと。また、本剤投与中に MAS が発現した場合は、投与を中止し、速やかに MAS に対する適切な治療を行うこと。

サイトカイン放出症候群：本剤の投与にあたっては、学会のガイドライン等の最新の情報を参考に適応患者を選択し、その他の対症療法の実施とともに使用すること。

＜下線部分を追加＞

1.8.1.1.4　効能・効果に関連する使用上の注意の設定理由

CRSの管理は，CAR-T細胞輸注後，綿密なモニタリングを行い，CRSを発症した場合には，症状に対する処置を行う。一般的に重症度の高い CRS の治療に用いる高用量のコルチコステロイドは，T細胞の活性化，機能及び増殖を阻害する性質があり，CAR-T細胞療法の有効性を減じるおそれがある。そのため，ペンシルベニア大学とフィラデルフィア小児病院ではCTL019の臨床試験における CRS 治療の臨床経験に基づき，CRS の重症度分類（NCI-CTCAE分類 Grade 1～Grade 4）毎に推奨する治療方法を示した CRS 管理アルゴリズムを規定した[4)]。ノバルティス社はこのアルゴリズムをベースに CRS 管理のアルゴリズムを策定し，B2202試験及び C2201試験においてそのアルゴリズムに基づいてトシリズマブを使用した。ペンシルベニア大学とフィラデルフィア小児病院の CRS 管理のアルゴリズムとノバルティス社が策定した CRS 管理のアルゴリズムでは，後者でトシリズマブとステロイドの投与順序やトシリズマブの用法・用量が明確に規定されているものの CRS 管理の考え方に明確な差異はない。ノバルティス社の2試験において CRS に対するトシリズマブの有効性及び安全性が認められたことから，CRS 管理のアルゴリズムは有用であると考えられる。

また，2016年に日本臨床腫瘍学会において，日本がん免疫学会と日本臨床免疫学会の協力のもと，「がん免疫療法ガイドライン」[37)]が発行され，Grade2以上の CRS の管理としてトシリズマブの使用が規定されている。

以上より，トシリズマブは CAR-T 療法の治験実施計画書，又は学会から発行されるガイドライン等の公表文献で規定された CRS 管理のアルゴリズムに基づいて使用することが妥当であり，学会のガイドライン等は CAR-T 療法の進歩に伴う改良が想定されることから，「本剤の投与にあたっては、学会のガイドライン等の最新の情報を参考に適応患者を選択し、その他の対症療法の実施とともに使用すること。」を，効能・効果に関連する使用上の注意として設定した。

1.8.1.2　用法・用量及びその設定理由

1.8.1.2.1　用法・用量

用法・用量を以下に示す。

○関節リウマチ、多関節に活動性を有する若年性特発性関節炎
通常、トシリズマブ(遺伝子組換え)として1回8 mg/kg を4週間隔で点滴静注する。
○全身型若年性特発性関節炎、キャッスルマン病
通常、トシリズマブ(遺伝子組換え)として1回8 mg/kg を2週間隔で点滴静注する。なお、症状により1週間まで投与間隔を短縮できる。
○サイトカイン放出症候群
通常、トシリズマブ（遺伝子組換え）として、体重30 kg以上は1回8 mg/kg、体重30 kg 未満は1回12 mg/kg を点滴静注する。

＜下線部分を追加＞

1.8.1.2.2　用法・用量の設定理由

ノバルティス社は ALL 小児患者を対象とした B2202試験及び成人 DLBCL 患者を対象とした C2201試験において，CRS 管理のアルゴリズムを治験実施計画書に規定しており，そのアルゴリズムではトシリズマブの用法・用量を体重が30 kg 未満の場合は12 mg/kg の静注，体重が30 kg 以上の場合は8 mg/kg の静注（最大用量800 mg まで）と規定した。これらの用法・用量は

米国におけるトシリズマブの sJIA に対する用法・用量に基づいて設定されており，国内未承認の用法・用量である12 mg/kg は治験及び市販後において米国の使用経験は豊富である。

B2202試験において，体重30 kg 以上の場合は8 mg/kg，30 kg 未満の場合は12 mg/kg でトシリズマブを投与した際の初回投与後の血清中トシリズマブ濃度は用量間で大きな差は認められず，C_{max} と $AUC_{0\text{-}Day3}$の中央値は用量間でほぼ同様な値が得られたことから，ALL 小児患者の CRS 管理においては体重に応じてトシリズマブの投与量を調節することは妥当と考えられた。

C2201試験では全例が8 mg/kg でトシリズマブが投与されたが，初回投与時の血清中トシリズマブ濃度及び薬物動態パラメータ（C_{max}，$AUC_{0\text{-}Day3}$の中央値）は B2202試験とほぼ同様な値を示し，2試験間で差は認められなかったことから，トシリズマブの静脈内投与時の薬物動態において，がん種及び小児/成人による差はないと考えられた。

日本人患者は B2202試験の1例で，12 mg/kg のトシリズマブが投与された。当該患者におけるトシリズマブ初回投与時の血清中トシリズマブ濃度及び $AUC_{0\text{-}Day2}$は当該患者が含まれる投与用量（12 mg/kg）グループの中央値とほぼ同じ値を示していた。以上より，12 mg/kg は国内未承認の用量であり，1例のみのデータではあるものの，血清中トシリズマブの薬物動態に民族差はないと考えられた。

1.8.1.1.2項に記載したとおり，CRS に対してトシリズマブを体重が30 kg 未満の場合は12 mg/kg を静注，体重が30 kg 以上の場合は8 mg/kg を静注することにより，B2202試験では28/28例（100.0%），C2201試験では14例/15例（93.3%）が回復した。また，B2202試験及び C2201試験において CRS 患者に対するトシリズマブ投与によって，新たな懸念となるリスクは認められなかった。

公表文献調査[6)-28)]におけるトシリズマブの用法・用量は，記載がある場合は4又は8 mg/kg の静脈内投与であった。この用法・用量は米国で承認されている用量（成人の RA では4 mg/kg 静注 4週間毎で開始，臨床反応に応じ8 mg/kg 静注 4週間毎へ増量；小児の sJIA では体重30 kg 以上の小児で8 mg/kg 静注 2週間毎；pJIA では体重30 kg 以上の小児で8 mg/kg 静注 4週間毎）を反映していると考えられ，いずれの用量も治験及び市販後において使用経験は豊富である。本邦では，8 mg/kg 静注は RA と pJIA では4週間毎，sJIA とキャッスルマン病では2週間毎で承認されており，使用経験は豊富にある。

したがって，B2202試験と C2201試験の結果及び国内外の承認用法・用量から，本剤のサイトカイン放出症候群に対する用法・用量を「通常、トシリズマブ（遺伝子組換え）として、体重30 kg 以上は1回8 mg/kg、体重30 kg 未満は1回12 mg/kg を点滴静注する。」と設定した。

なお，審査の過程において用法・用量は「通常、トシリズマブ（遺伝子組換え）として体重30 kg 以上は1回8 mg/kg、体重30 kg 未満は1回12 mg/kg を点滴静注する。」となった。

1.8.1.2.3　用法・用量に関連する使用上の注意

「用法・用量に関連する使用上の注意」を以下に示す。

＜用法・用量に関連する使用上の注意＞

1. 血清中トシリズマブ濃度が維持されない状態で投与を継続すると，抗トシリズマブ抗体が発現する可能性が高くなるため，用法・用量を遵守すること。
2. 全身型若年性特発性関節炎：症状改善が不十分であり，かつ CRP*を指標として IL-6作用の抑制効果が不十分と判断される場合に限り，投与間隔を短縮できる。
3. キャッスルマン病：投与毎に CRP を測定し，症状改善が不十分と判断される場合に限り，CRP を指標として投与間隔を短縮できる。　＊：C 反応性タンパク
4. 希釈方法：本剤の各バイアル中のトシリズマブ濃度は20 mg/mL である。患者の体重か

ら換算した必要量を体重25kg 以下の場合は50mL，25kg を超える場合は100～250mL の日局生理食塩液に加え，希釈する。 〈〈体重あたりの換算式〉〉 抜き取り量（mL）＝体重（kg）× 8（mg/kg）＊＊／ 20（mg/mL） ＊＊：サイトカイン放出症候群患者で体重30 kg 未満の場合は12 mg/kg とする。 5. 投与方法 ⑴本剤はインラインフィルターを用いて投与すること（「適用上の注意」の項参照）。 ⑵投与開始時は緩徐に点滴静注を行い，患者の状態を十分に観察し，異常がないこと確認後，点滴速度を速め 1 時間程度で投与する。

＜下線部分を追加＞

1.8.1.2.4　用法・用量に関連する使用上の注意の設定理由

サイトカイン放出症候群の用法・用量に「12 mg/kg」を追加したため，「4.希釈方法」の「体重あたりの換算式」に体重30 kg 未満の場合として，12 mg/kg を記載した。

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1.8.2　使用上の注意の設定の根拠

トシリズマブは，点滴静注用製剤及び皮下注製剤が承認されており，アクテムラ点滴静注用製剤として，以下の効能・効果を取得している。

- 既存治療で効果不十分な関節リウマチ（関節の構造的損傷の防止を含む）
- 既存治療で効果不十分な多関節に活動性を有する若年性特発性関節炎
- 既存治療で効果不十分な全身型若年性特発性関節炎
- キャッスルマン病に伴う諸症状及び検査所見（C 反応性タンパク高値，フィブリノーゲン高値，赤血球沈降速度亢進，ヘモグロビン低値，アルブミン低値，全身倦怠感）の改善。ただし，リンパ節の摘除が適応とならない患者に限る。

CAR-T 細胞療法の臨床試験（B2202試験（ALL 小児患者）及び C2201試験（DLBCL 成人患者））（以下，本試験）において，CRS 発症後にトシリズマブを投与した際に懸念すべき新たなリスクは認められなかった。したがって，本申請における使用上の注意については，本試験結果を反映し，以下のとおりとした。

＜下線部分を追加・変更＞

使用上の注意（案）	設定根拠
【警告】 １．感染症 本剤投与により、敗血症、肺炎等の重篤な感染症があらわれ、致命的な経過をたどることがある。本剤は IL-6の作用を抑制し治療効果を得る薬剤である。IL-6は急性期反応（発熱、CRP 増加等）を誘引するサイトカインであり、本剤投与によりこれらの反応は抑制されるため、感染症に伴う症状が抑制される。そのため感染症の発見が遅れ、重篤化することがあるので、本剤投与中は患者の状態を十分に観察し問診を行うこと。症状が軽微であり急性期反応が認められないときでも、白血球数、好中球数の変動に注意し、感染症が疑われる場合には、胸部 X 線、CT 等の検査を実施し、適切な処置を行うこと（「重要な基本的注意」、「重大な副作用」の項参照）。 ２．治療開始に際しては、重篤な感染症等の副作用があらわれることがあること及び本剤が疾病を完治させる薬剤でないことも含めて患者に十分説明し、理解したことを確認した上で、治療上の有益性が危険性を上回ると判断される場合にのみ本剤を投与すること。 ３．関節リウマチ患者及び多関節に活動性を有する若年性特発性関節炎患者では、本剤の治療を行う前に、少なくとも1剤の抗リウマチ薬の使用を十分勘案すること。また、本剤についての十分な知識といずれかの疾患の治療経験をもつ医師が使用すること。 ４．全身型若年性特発性関節炎患者では、本剤についての十分な知識と全身型若年性特発性関節炎治療の経験をもつ医師が使用すること。 ５．サイトカイン放出症候群患者では、本剤についての	１～４．変更なし。 ５．アクテムラ点滴静注用製剤の使

使用上の注意（案）	設定根拠
十分な知識と腫瘍特異的 T 細胞輸注療法に伴うサイトカイン放出症候群の治療の知識・経験をもつ医師が使用すること。	用にあたっては，アクテムラ点滴静注用製剤の安全性プロファイルが理解され，適応疾患の知識をもつ医師のもとで適正に使用される必要がある旨の注意喚起が必要と判断し，記載した。なお，平成30年12月27日付追加照会事項3に対する回答に基づき記載した。
【禁忌（次の患者には投与しないこと）】 １．重篤な感染症を合併している患者［感染症が悪化するおそれがある。］ ２.活動性結核の患者［症状を悪化させるおそれがある。］ ３．本剤の成分に対し過敏症の既往歴のある患者	変更なし。
【使用上の注意】 １．慎重投与（次の患者には慎重に投与すること） （１）感染症を合併している患者又は感染症が疑われる患者［感染症が悪化するおそれがある。］（「重要な基本的注意」の項参照） （２）結核の既感染者（特に結核の既往歴のある患者及び胸部 X 線上結核治癒所見のある患者）［結核を活動化させる可能性が否定できないので、胸部 X 線検査等を定期的に行うなど、結核症状の発現に十分注意すること。］（「重要な基本的注意」の項参照） （３）易感染性の状態にある患者［感染症を誘発するおそれがある。］ （４）間質性肺炎の既往歴のある患者［間質性肺炎が増悪又は再発することがある。］（「重大な副作用」の項参照） （５）腸管憩室のある患者（「重大な副作用」の項参照） （６）白血球減少、好中球減少、血小板減少のある患者［白血球減少、好中球減少、血小板減少が更に悪化するおそれがある。］（「重大な副作用」の項参照）	変更なし。
２．重要な基本的注意 （１）アナフィラキシーショック、アナフィラキシーがあらわれることがあるので、適切な薬物治療（アドレナリン、副腎皮質ステロイド薬、抗ヒスタミン薬等）や緊急処置を直ちに実施できるようにしておくこと。異常が認められた場合には直ちに投与を中止すること。 （２）本剤投与中又は投与当日に Infusion Reaction（発熱、悪寒、嘔気、嘔吐、頭痛、発疹等）が発現する可能性があるため、患者の状態を十分に観察し、異常が認められた場合には直ちに投与を中止し、適切な処置（抗ヒスタミン薬、解熱鎮痛薬の投与等）を行うこと。 （３）感染症を合併している患者に本剤を投与することにより、感染症が重篤化するおそれがあるため、下記の点に留意すること。	（１）～（３）３）変更なし。

使用上の注意（案）	設定根拠
1）投与開始に際しては、肺炎等の感染症の有無を確認すること。なお、キャッスルマン病、全身型若年性特発性関節炎、多関節に活動性を有する若年性特発性関節炎、関節リウマチ、サイトカイン放出症候群の臨床症状（発熱、悪寒、倦怠感、リンパ節腫脹等）は感染症の症状と類似しているため、鑑別を十分に行うこと。	1）平成31年1月30日付追加照会事項1に対する回答に基づき記載した。
2）易感染性の状態では、日和見感染が顕在化するおそれがあることから、投与を避けることが望ましい。なお、リンパ球数減少が遷延化した場合（目安として500/μL）は、投与を開始しないこと。	
3）感染症を合併している場合は感染症の治療を優先すること。	
4）サイトカイン放出症候群患者においては、治療上の有益性と危険性を考慮し、治療方針を十分に検討すること。	4）CRS 患者においては，患者の状態により治療上の有益性と危険性を考慮し本剤の投与や感染症治療など総合的に治療方針を検討する必要がある。臨床試験においても感染症治療と並行して本剤を投与された症例が確認されており，本剤投与に起因したと考えられる感染症の重篤化による症例転帰の悪化は認められていないことから，感染症発現下においても本剤投与が考慮できるよう記載を変更した。
（4）抗リウマチ生物製剤を投与されたB型肝炎ウイルスキャリアの患者又は既往感染者（HBs 抗原陰性、かつHBc 抗体又はHBs 抗体陽性）において、B 型肝炎ウイルスの再活性化が報告されている。本剤投与に先立って、B 型肝炎ウイルス感染の有無を確認すること。B 型肝炎ウイルスキャリアの患者及び既往感染者に本剤を投与する場合は、最新のB 型肝炎治療ガイドラインを参考に肝機能検査値や肝炎ウイルスマーカーのモニタリングを行うなど、B 型肝炎ウイルスの再活性化の徴候や症状の発現に注意すること。	（4）～（13） 変更なし。
（5）本剤投与により、急性期反応（発熱、CRP 増加等）、感染症状が抑制され、感染症発見が遅れる可能性があるため、急性期反応が認められないときでも、白血球数、好中球数を定期的に測定し、これらの変動及び喘鳴、咳嗽、咽頭痛等の症状から感染症が疑われる場合には、胸部 X 線、CT 等の検査を実施し適切な処置を行うこと。また、呼吸器感染のみならず皮膚感染や尿路感染等の自他覚症状についても注意し、異常が見られる場合には、速やかに担当医師に相談するよう、患者を指導すること。	
（6）本剤投与に先立って結核に関する十分な問診（結核の既往歴、結核患者との濃厚接触歴等）及び胸部X線検査に加え、インターフェロンーγ遊離試験又はツベルクリン反応検査を行い、適宜胸部 CT 検査等を行うことにより、結核感染の有無を確認すること。結核の既往歴を有する場合及び結核感染が疑われる場合には、結核の診療経験がある医師に相談すること。以下のいずれかの患者には、原則として本剤の投与開始前に適切に抗結核薬を投与すること。	
1）胸部画像検査で陳旧性結核に合致するか推定される陰影を有する患者	

使用上の注意（案）	設定根拠
2）結核の治療歴（肺外結核を含む）を有する患者 3）インターフェロンーγ遊離試験やツベルクリン反応検査等の検査により、既感染が強く疑われる患者 4）結核患者との濃厚接触歴を有する患者 本剤投与中は、胸部X線検査等の適切な検査を定期的に行うなど結核症の発現には十分に注意し、患者に対し、結核を疑う症状が発現した場合（持続する咳、発熱等）には速やかに担当医師に連絡するよう説明すること。なお、結核の活動性が確認された場合は本剤を投与せず、結核の治療を優先すること。 （7）本剤投与中は、生ワクチン接種により感染するおそれがあるので、生ワクチン接種は行わないこと。 （8）臨床試験において胸膜炎（感染症が特定できなかったものを含む）が報告されている。治療期間中に胸膜炎（所見：胸水貯留、胸部痛、呼吸困難等）が認められた場合には、その病因を十分に鑑別し、感染症でない場合も考慮して適切な処置を行うこと。 （9）総コレステロール値、トリグリセリド値、LDLコレステロール値の増加等の脂質検査値異常があらわれることがあるので、投与開始3カ月後を目安に、以後は必要に応じて脂質検査を実施し、臨床上必要と認められた場合には、高脂血症治療薬の投与等の適切な処置を考慮すること。 （10）肝障害を起こす可能性のある薬剤と併用する場合や活動性肝疾患又は肝障害の患者に投与する場合には、トランスアミナーゼ値上昇に注意するなど観察を十分に行い、異常が認められた場合には投与を中止するなどの適切な処置を行うこと（「その他の注意」の項参照）。 （11）全身型若年性特発性関節炎及びキャッスルマン病の場合 本剤を休薬・中止する際には、IL-6の作用が過剰に発現し病態が悪化する可能性が否定できないので、必要に応じて副腎皮質ステロイド薬の追加・増量等の適切な処置を考慮すること。 （12）臨床試験において心障害が認められていることから、患者の状態を十分に観察し、必要に応じて心電図検査、血液検査、胸部エコー等を実施すること。心疾患を合併している患者に投与する際は、定期的に心電図検査を行いその変化に注意すること。 （13）本剤と他の抗リウマチ生物製剤の併用について安全性及び有効性は確立していないので併用を避けること。また、他の抗リウマチ生物製剤から本剤に切り替える際には、感染症の徴候について患者の状態を十分に観察すること。	
３．副作用 キャッスルマン病、関節リウマチ、多関節に活動性を有	変更なし。 なお，本試験においては有害事象と

使用上の注意（案）	設定根拠
する若年性特発性関節炎及び全身型若年性特発性関節炎の国内臨床試験の安全性解析対象症例計828例（各々35例、625例、19例、149例）において、副作用は802例（96.9%）に認められた。主な副作用は、上気道感染574例（69.3%）、コレステロール増加310例（37.4%）、発疹239例（28.9%）、LDL 増加163例（19.7%）、胃腸炎148例（17.9%）等であった。（再審査終了時） キャッスルマン病、関節リウマチ、多関節に活動性を有する若年性特発性関節炎及び全身型若年性特発性関節炎の製造販売後調査の安全性解析対象症例計9,726例（各々384例、8,747例、178例、417例）において、副作用は4,237例（43.6%）に認められた。主な副作用は、上気道感染546例（5.6%）、肝機能異常499例（5.1%）、白血球減少402例（4.1%）、肺炎281例（2.9%）、発疹230例（2.4%）等であった。（再審査終了時） 「重大な副作用」及び「その他の副作用」の発現頻度は、国内臨床試験及び製造販売後調査の結果を合わせて算出した。	本剤の関連性を評価していないことから，副作用の発現頻度の集計には含めず，主な有害事象について臨床成績の項に記載する。また，本試験では詳細に CRS を評価する目的で，CRS の報告方法をそれ以外の有害事象の報告方法と変えて集計されていたものの，トシリズマブ投与後に発現した CRS は1例のみであったことから，主な有害事象として記載しない。
（1）重大な副作用 1）アナフィラキシーショック（0.1%）、アナフィラキシー（0.1%）：血圧低下、呼吸困難、意識消失、めまい、嘔気、嘔吐、瘙痒感、潮紅等があらわれることがあるので、本剤投与中は、患者の状態を十分に観察し、異常が認められた場合には直ちに投与を中止し、アドレナリン、副腎皮質ステロイド薬、抗ヒスタミン薬を投与するなど適切な処置を行うとともに症状が回復するまで患者の状態を十分に観察すること。また、投与終了後も症状のないことを確認すること。 2）感染症：肺炎（3.3%）、帯状疱疹（2.0%）、感染性胃腸炎（0.7%）、蜂巣炎（1.4%）、感染性関節炎（0.5%）、敗血症（0.6%）、非結核性抗酸菌症（0.4%）、結核（0.1%）、ニューモシスチス肺炎（0.3%）等の日和見感染を含む重篤な感染症があらわれ、致命的な経過をたどることがある。本剤投与後は、患者の状態を十分に観察し、異常が認められた場合には投与を中止するなどの適切な処置を行うこと。 3）間質性肺炎（0.5%）：関節リウマチ患者では、間質性肺炎があらわれることがあるので、発熱、咳嗽、呼吸困難等の呼吸器症状に十分に注意し、異常が認められた場合には、速やかに胸部 X 線、CT 及び血液ガス検査等を実施し、本剤の投与を中止するとともにニューモシスチス肺炎との鑑別診断（β-D-グルカンの測定等）を考慮に入れ適切な処置を行うこと。なお、間質性肺炎の既往歴のある患者には、定期的に問診を行うなど、注意すること。 4）腸管穿孔（0.2%）：腸管穿孔が報告されている。	変更なし。 なお，本試験においては有害事象と本剤の関連性を評価していないことから，副作用の発現頻度の集計には含めていない。

使用上の注意（案）	設定根拠
本剤投与により、憩室炎等の急性腹症の症状（腹痛、発熱等）が抑制され、発見が遅れて穿孔に至る可能性があるため、異常が認められた場合には、腹部X線、CT等の検査を実施するなど十分に観察し、適切な処置を行うこと。 ５）無顆粒球症（0.1%未満）、白血球減少（4.5%）、好中球減少（1.6%）、血小板減少（2.1%）：無顆粒球症、白血球減少、好中球減少、血小板減少があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなどの適切な処置を行うこと。 ６）心不全（0.2%）：心不全の報告があるので、患者の状態を十分に観察し、異常が認められた場合には投与を中止するなどの適切な処置を行うこと。	
（２）その他の副作用 次のような副作用が認められた場合には、休薬・中止など適切な処置を行うこと。 別表参照	変更なし。 なお，本試験においては有害事象と本剤の関連性を評価していないことから，副作用の発現頻度の集計には含めていない。
４．高齢者への投与 一般に高齢者では生理機能が低下しているので、患者の状態を十分に観察しながら慎重に投与すること。	変更なし。
５．妊婦、産婦、授乳婦等への投与 （１）妊婦又は妊娠している可能性のある婦人には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。[本剤の妊娠中の投与に関する安全性は確立されていない。また、カニクイザルにおいて本剤は胎盤関門を通過することが報告されている。] （２）授乳婦に投与する場合には授乳を中止させること。[授乳中の投与に関する安全性は確立していない。]	変更なし。
６．小児等への投与 低出生体重児、新生児又は乳児に対する安全性は確立していない（「薬物動態」の項参照）。	変更なし。
７．適用上の注意 （１）調製時 １） 希釈時及び希釈後に泡立つような激しい振動を与えないこと。[本剤はポリソルベートを含有しているので、泡立ちやすい。] ２） 用時調製し、調製後は速やかに使用すること。また、残液は廃棄すること。 （２） 投与時 １） 本剤は点滴静注用としてのみ用い、皮下・筋肉内には投与しないこと。 ２） 本剤は無菌・パイロジェンフリーのインラインフィルター（ポアサイズ1.2ミクロン以下）を用い独立したラインにて投与すること。 ３） 他の注射剤、輸液等と混合しないこと。	変更なし。
８．その他の注意	変更なし。

使用上の注意（案）	設定根拠
（１）本剤投与により抗トシリズマブ抗体が発現したとの報告がある（国内臨床試験・疾患別、関節リウマチ：601例中18例（3.0%）、多関節に活動性を有する若年性特発性関節炎：19例中1例（5.3%）、全身型若年性特発性関節炎：128例中11例（8.6%）［以上、効能追加時］、キャッスルマン病：35例中1例（2.9%）［承認時］）。 （２）本邦において、本剤と抗リウマチ薬（DMARD）との併用療法における有効性及び安全性は確立していない。なお、海外の関節リウマチを対象とした臨床試験では、トランスアミナーゼ値上昇の発現頻度が本剤単剤療法時に比べてDMARD併用療法時で高かった。基準値の3倍を超えるALT（GPT）あるいはAST（GOT）上昇の発現頻度は、DMARD 併用療法：本剤8mg/kg+DMARD 群103/1582例（6.5%）、プラセボ+DMARD 群18/1170例（1.5%）、単剤療法：本剤8mg/kg群6/288例（2.1%）、MTX単剤群14/284例（4.9%）で、これらの異常は一過性で肝炎や肝不全に伴うものではなかった。 （３）国内の臨床試験では2.9年（投与期間0.1～8.1年の中央値）まで、海外の関節リウマチを対象とした臨床試験では4.6年（投与期間0.0～5.8年の中央値）までの期間で実施されており、これらの期間を超えた本剤の長期投与時の安全性は確立していない。 （４）ヒト肝細胞を用いたin vitro試験において、IL-6が肝薬物代謝酵素（CYPs）発現を抑制することが報告されていることから、ヒト肝細胞にIL-6をトシリズマブ共存下で添加したところ、CYPsの発現に変化は認められなかった。また、炎症反応を有する患者では、IL-6の過剰産生によりCYPsの発現が抑制されているとの報告がある。関節リウマチ患者を対象とした臨床試験において、本剤投与後にIL-6阻害に伴ってCYP3A4、CYP2C19及びCYP2D6発現量が増加することが示唆された。このことから、過剰のIL-6によって抑制されていたCYPsの発現が本剤投与により回復し、炎症反応の改善に伴って併用薬の効果が減弱する可能性は否定できない。 （５）動物実験（マウス）において、gp130を介したシグナル伝達が心筋細胞の保護作用を有することが報告されている。gp130を介してシグナル伝達に関与するサイトカインは複数知られており、IL-6もその一つである。本薬はIL-6の作用を阻害することから、心臓への影響は否定できない。 （６）本薬はヒトとカニクイザルのIL-6レセプターに対しては中和活性を示すが、マウス及びラットのIL-6レセプターに対しては中和活性を示さない。このため、がん原性試験は実施されていない。 （７）関節リウマチを対象とした本剤の海外臨床試験において、本剤8mg/kg投与時の重篤な感染症の発現頻度が	

使用上の注意（案）	設定根拠
体重100kgを超える患者群で高い傾向が認められたため、海外における1回投与量の上限は800mgとされている。 （8）関節リウマチを対象とした海外臨床試験において、本剤との因果関係は不明であるが脱髄関連疾患が認められたとの報告がある。	

その他の副作用　別表

項目名	1%以上	0.1～1%未満	0.1%未満
抵抗機構	ヘルペスウイルス感染	インフルエンザ、口腔カンジダ症、耳下腺炎、創傷感染	
呼吸器	上気道感染〔鼻咽頭炎、上気道炎等〕（10.6%）、気管支炎、咽喉頭疼痛	咳嗽、副鼻腔炎、鼻炎、鼻漏、胸膜炎、喀血、喘息、咽頭不快感、咽頭紅斑、鼻閉、鼻出血	気管支拡張症
代謝	コレステロール増加（4.9%）、トリグリセリド増加、高脂血症、高コレステロール血症、LDL増加	LDH 上昇、HDL 増加、高トリグリセリド血症、血中尿酸増加、CK（CPK）上昇、総蛋白減少、糖尿病増悪、血中カリウム減少、血糖増加、血中リン増加、血清フェリチン減少	血中リン減少、血中カルシウム減少
肝臓	肝機能異常、ALT（GPT）上昇、AST（GOT）上昇	γ-GTP 上昇、ビリルビン増加、Al-P 上昇、脂肪肝、胆石症	
循環器	高血圧	血圧上昇、血圧低下、動悸、T 波逆転、T 波振幅減少、上室性期外収縮、心室性期外収縮	ST部分上昇、ST部分下降、T 波振幅増加
血液・凝固		リンパ球数減少、貧血、白血球数増加、フィブリノゲン減少、好酸球数増加、フィブリン分解産物〔FDP、D ダイマー〕増加、ヘマトクリット減少、ヘモグロビン減少、リンパ節炎、リンパ節腫脹、好中球数増加、赤血球数減少	TAT 増加
消化器	口内炎、下痢、胃腸炎、腹痛	悪心、便秘、嘔吐、腹部不快感、口唇炎、腹部膨満、食欲不振、胃・腸ポリープ、逆流性食道炎、痔核、消化不良、舌炎、胃潰瘍、急性膵炎	口渇

項目名	1%以上	0.1～1%未満	0.1%未満
		歯周病、齲歯、歯痛	
精神神経	頭痛	浮動性めまい、感覚減退、不眠症、末梢性ニューロパシー	
耳		中耳炎、眩暈、突発難聴、外耳炎、耳鳴	耳不快感
眼		結膜炎、麦粒腫、眼乾燥、結膜出血、霰粒腫、白内障、眼瞼炎	硝子体浮遊物、網膜出血
皮膚	発疹〔湿疹、痒疹、丘疹等〕、瘙痒症、白癬、皮膚感染	爪感染、蕁麻疹、紅斑、皮膚潰瘍、皮下出血、嵌入爪、ざ瘡、皮膚乾燥、水疱、角化症、脱毛症、皮膚嚢腫	
筋・骨格		関節痛、背部痛、筋痛〔筋痛、肩こり〕、四肢痛、骨粗鬆症、骨密度減少、頚部痛、若年性関節炎増悪	
泌尿器		膀胱炎、尿路感染、BUN 増加、尿中赤血球陽性、腎盂腎炎、尿糖、尿蛋白、腎結石、NAG 増加、頻尿	尿中白血球陽性
生殖器		腟感染、性器出血	子宮頚管ポリープ
その他	膿瘍、発熱	浮腫、倦怠感、免疫グロブリン G 減少、胸痛、胸部不快感、季節性アレルギー、CRP 増加、悪寒、潮紅、アレルギー性鼻炎、気分不良、ほてり、注射部位反応〔紅斑、腫脹、血腫、疼痛、静脈炎、発疹等〕、血栓性静脈炎、DNA 抗体陽性[注3)]、体重増加、抗核抗体陽性[注3)]	リウマチ因子陽性、発汗障害

注３）関節リウマチ第Ⅲ相2試験での DNA 抗体の推移は、217例において陰性化10例（4.6%）、陽性化0例である。抗核抗体の推移は216例において陰性化24例（11.1%）、陽性化18例（8.3%）である。

** 20　年　月改訂(第　版)
* 20　年　月改訂

規制区分：生物由来製品
劇薬
処方箋医薬品注1）
貯　　法：遮光、2～8℃保存
使用期限：包装に表示の使用期限内に使用すること

ヒト化抗ヒトIL-6レセプターモノクローナル抗体

アクテムラ®点滴静注用80mg
アクテムラ®点滴静注用200mg
アクテムラ®点滴静注用400mg

ACTEMRA®

トシリズマブ（遺伝子組換え）注

日本標準商品分類番号		
876399		

	80mg	200mg	400mg
承認番号	22000AMX01593	21900AMX01337	22000AMX01594
薬価収載	2008年6月	2007年12月	2008年6月
販売開始	2008年6月	2005年6月	2008年6月
効能追加	2008年4月		
再審査結果	2016年9月		
国際誕生	2005年4月		

CHUGAI
ロシュ グループ

【警告】

1.感染症

本剤投与により、敗血症、肺炎等の重篤な感染症があらわれ、致命的な経過をたどることがある。本剤はIL-6の作用を抑制し治療効果を得る薬剤である。IL-6は急性期反応（発熱、CRP増加等）を誘引するサイトカインであり、本剤投与によりこれらの反応は抑制されるため、感染症に伴う症状が抑制される。そのため感染症の発見が遅れ、重篤化することがあるので、本剤投与中は患者の状態を十分に観察し問診を行うこと。症状が軽微であり急性期反応が認められないときでも、白血球数、好中球数の変動に注意し、感染症が疑われる場合には、胸部X線、CT等の検査を実施し、適切な処置を行うこと（「重要な基本的注意」、「重大な副作用」の項参照）。

2.治療開始に際しては、重篤な感染症等の副作用があらわれることがあること及び本剤が疾病を完治させる薬剤でないことも含めて患者に十分説明し、理解したことを確認した上で、治療上の有益性が危険性を上回ると判断される場合にのみ本剤を投与すること。

3.関節リウマチ患者及び多関節に活動性を有する若年性特発性関節炎患者では、本剤の治療を行う前に、少なくとも1剤の抗リウマチ薬の使用を十分勘案すること。また、本剤についての十分な知識といずれかの疾患の治療経験をもつ医師が使用すること。

4.全身型若年性特発性関節炎患者では、本剤についての十分な知識と全身型若年性特発性関節炎治療の経験をもつ医師が使用すること。

5.サイトカイン放出症候群患者では、本剤についての十分な知識と腫瘍特異的T細胞輸注療法に伴うサイトカイン放出症候群の治療の知識・経験をもつ医師が使用すること。

【禁忌（次の患者には投与しないこと）】

1. 重篤な感染症を合併している患者［感染症が悪化するおそれがある。］
2. 活動性結核の患者［症状を悪化させるおそれがある。］
3. 本剤の成分に対し過敏症の既往歴のある患者

【組成・性状】

販売名		アクテムラ点滴静注用	80mg	200mg	400mg
成分・含有量（1バイアル中）	内容量		4mL	10mL	20mL
	有効成分	トシリズマブ（遺伝子組換え）注2）	80mg	200mg	400mg
	添加物	精製白糖	200mg	500mg	1000mg
		ポリソルベート80	2mg	5mg	10mg
		リン酸水素ナトリウム水和物	適量	適量	適量
		リン酸二水素ナトリウム水和物	適量	適量	適量

剤形	注射剤（バイアル）
性状	無色～微黄色の液
pH	6.0～7.0
浸透圧比	0.5～1.0（生理食塩液に対する比）

注2）本剤は、チャイニーズハムスター卵巣細胞を用いて製造される。~~また、細胞培養工程の培地成分として、ウシの乳由来のガラクトースを使用している。~~

【効能・効果】

○ 既存治療で効果不十分な下記疾患
関節リウマチ（関節の構造的損傷の防止を含む）、多関節に活動性を有する若年性特発性関節炎、全身型若年性特発性関節炎

○ キャッスルマン病に伴う諸症状及び検査所見（C反応性タンパク高値、フィブリノーゲン高値、赤血球沈降速度亢進、ヘモグロビン低値、アルブミン低値、全身倦怠感）の改善。ただし、リンパ節の摘除が適応とならない患者に限る。

○ 腫瘍特異的T細胞輸注療法に伴うサイトカイン放出症候群

＜効能・効果に関連する使用上の注意＞

関節リウマチ及び多関節に活動性を有する若年性特発性関節炎：過去の治療において、少なくとも1剤の抗リウマチ薬による適切な治療を行っても、効果不十分な場合に投与すること。

全身型若年性特発性関節炎：

1. 過去の治療において、副腎皮質ステロイド薬による適切な治療を行っても、効果不十分な場合に投与すること。
2. 重篤な合併症としてマクロファージ活性化症候群（MAS）を発症することがある。MASを合併している患者ではMASに対する治療を優先させ本剤の投与を開始しないこと。また、本剤投与中にMASが発現した場合は、投与を中止し、速やかにMASに対する適切な治療を行うこと。

サイトカイン放出症候群：
本剤の投与にあたっては、学会のガイドライン等の最新の情報を参考に適応患者を選択し、その他の対症療法の実施とともに使用すること。

【用法・用量】

○ 関節リウマチ、多関節に活動性を有する若年性特発性関節炎
通常、トシリズマブ（遺伝子組換え）として1回8mg/kgを4週間隔で点滴静注する。

○ 全身型若年性特発性関節炎、キャッスルマン病
通常、トシリズマブ（遺伝子組換え）として1回8mg/kg

注1）注意－医師等の処方箋により使用すること

を 2 週間隔で点滴静注する。なお、症状により 1 週間まで投与間隔を短縮できる。

○ サイトカイン放出症候群

通常、トシリズマブ（遺伝子組換え）として体重 30 kg 以上は 1 回 8 mg/kg、体重 30 kg 未満は 1 回 12 mg/kg を点滴静注する。

＜用法・用量に関連する使用上の注意＞

1. 血清中トシリズマブ濃度が維持されない状態で投与を継続すると、抗トシリズマブ抗体が発現する可能性が高くなるため、用法・用量を遵守すること。
2. **全身型若年性特発性関節炎**：症状改善が不十分であり、かつ CRP*を指標として IL-6 作用の抑制効果が不十分と判断される場合に限り、投与間隔を短縮できる。
3. **キャッスルマン病**：投与毎に CRP を測定し、症状改善が不十分と判断される場合に限り、CRP を指標として投与間隔を短縮できる。

＊：C 反応性タンパク

4. 希釈方法：本剤の各バイアル中のトシリズマブ濃度は 20mg/mL である。患者の体重から換算した必要量を体重 25kg 以下の場合は 50mL、25kg を超える場合は 100～250mL の日局生理食塩液に加え、希釈する。

<<体重あたりの換算式>>

$$\text{抜き取り量（mL）} = \frac{\text{体重（kg）} \times 8\ (\text{mg/kg})^{**}}{20\ (\text{mg/mL})}$$

＊＊：サイトカイン放出症候群患者で体重 30 kg 未満の場合は 12 mg/kg とする。

5. 投与方法
   (1) 本剤はインラインフィルターを用いて投与すること（「適用上の注意」の項参照）。
   (2) 投与開始時は緩徐に点滴静注を行い、患者の状態を十分に観察し、異常がないことを確認後、点滴速度を速め 1 時間程度で投与する。

【使用上の注意】

1. **慎重投与(次の患者には慎重に投与すること)**
   (1) 感染症を合併している患者又は感染症が疑われる患者［感染症が悪化するおそれがある。］（「重要な基本的注意」の項参照）
   (2) 結核の既感染者（特に結核の既往歴のある患者及び胸部 X 線上結核治癒所見のある患者）［結核を活動化させる可能性が否定できないので、胸部 X 線検査等を定期的に行うなど、結核症状の発現に十分注意すること。］（「重要な基本的注意」の項参照）
   (3) 易感染性の状態にある患者［感染症を誘発するおそれがある。］
   (4) 間質性肺炎の既往歴のある患者［間質性肺炎が増悪又は再発することがある。］（「重大な副作用」の項参照）
   (5) 腸管憩室のある患者（「重大な副作用」の項参照）
   (6) 白血球減少、好中球減少、血小板減少のある患者［白血球減少、好中球減少、血小板減少が更に悪化するおそれがある。］（「重大な副作用」の項参照）
2. **重要な基本的注意**
   (1) アナフィラキシーショック、アナフィラキシーがあらわれることがあるので、適切な薬物治療（アドレナリン、副腎皮質ステロイド薬、抗ヒスタミン薬等）や緊急処置を直ちに実施できるようにしておくこと。異常が認められた場合には直ちに投与を中止すること。
   (2) 本剤投与中又は投与当日に Infusion Reaction（発熱、悪寒、嘔気、嘔吐、頭痛、発疹等）が発現する可能性があるため、患者の状態を十分に観察し、異常が認められた場合には直ちに投与を中止し、適切な処置（抗ヒスタミン薬、解熱鎮痛薬の投与等）を行うこと。
   (3) 感染症を合併している患者に本剤を投与することにより、感染症が重篤化するおそれがあるため、下記の点に留意すること。
      1) 投与開始に際しては、肺炎等の感染症の有無を確認すること。なお、キャッスルマン病、全身型若年性特発性関節炎、多関節に活動性を有する若年性特発性関節炎、関節リウマチ、サイトカイン放出症候群の臨床症状（発熱、悪寒、倦怠感、リンパ節腫脹等）は感染症の症状と類似しているため、鑑別を十分に行うこと。
      2) 易感染性の状態では、日和見感染が顕在化するおそれがあることから、投与を避けることが望ましい。なお、リンパ球数減少が遷延化した場合（目安として 500/μL）は、投与を開始しないこと。
      3) 感染症を合併している場合は感染症の治療を優先すること。
      4) サイトカイン放出症候群患者においては、治療上の有益性と危険性を考慮し、治療方針を十分に検討すること。
   (4) 抗リウマチ生物製剤を投与された B 型肝炎ウイルスキャリアの患者又は既往感染者（HBs 抗原陰性、かつ HBc 抗体又は HBs 抗体陽性）において、B 型肝炎ウイルスの再活性化が報告されている。本剤投与に先立って、B 型肝炎ウイルス感染の有無を確認すること。B 型肝炎ウイルスキャリアの患者及び既往感染者に本剤を投与する場合は、最新の B 型肝炎治療ガイドラインを参考に肝機能検査値や肝炎ウイルスマーカーのモニタリングを行うなど、B 型肝炎ウイルスの再活性化の徴候や症状の発現に注意すること。
   (5) 本剤投与により、急性期反応（発熱、CRP 増加等）、感染症状が抑制され、感染症発見が遅れる可能性があるため、急性期反応が認められないときでも、白血球数、好中球数を定期的に測定し、これらの変動及び喘鳴、咳嗽、咽頭痛等の症状から感染症が疑われる場合には、胸部 X 線、CT 等の検査を実施し適切な処置を行うこと。また、呼吸器感染のみならず皮膚感染や尿路感染等の自他覚症状についても注意し、異常が見られる場合には、速やかに担当医師に相談するよう、患者を指導すること。
   (6) 本剤投与に先立って結核に関する十分な問診（結核の既往歴、結核患者との濃厚接触歴等）及び胸部 X 線検査に加え、インターフェロンーγ遊離試験又はツベルクリン反応検査を行い、適宜胸部 CT 検査等を行うことにより、結核感染の有無を確認すること。結核の既往歴を有する場合及び結核感染が疑われる場合には、結核の診療経験がある医師に相談すること。以下のいずれかの患者には、原則として本剤の投与開始前に適切に抗結核薬を投与すること。
      1) 胸部画像検査で陳旧性結核に合致するか推定される陰影を有する患者
      2) 結核の治療歴（肺外結核を含む）を有する患者

3) インターフェロンーγ遊離試験やツベルクリン反応検査等の検査により、既感染が強く疑われる患者
4) 結核患者との濃厚接触歴を有する患者
本剤投与中は、胸部 X 線検査等の適切な検査を定期的に行うなど結核症の発現には十分に注意し、患者に対し、結核を疑う症状が発現した場合（持続する咳、発熱等）には速やかに担当医師に連絡するよう説明すること。なお、結核の活動性が確認された場合は本剤を投与せず、結核の治療を優先すること。

(7) 本剤投与中は、生ワクチン接種により感染するおそれがあるので、生ワクチン接種は行わないこと。

(8) 臨床試験において胸膜炎（感染症が特定できなかったものを含む）が報告されている。治療期間中に胸膜炎（所見：胸水貯留、胸部痛、呼吸困難等）が認められた場合には、その病因を十分に鑑別し、感染症でない場合も考慮して適切な処置を行うこと。

(9) 総コレステロール値、トリグリセリド値、LDL コレステロール値の増加等の脂質検査値異常があらわれることがあるので、投与開始 3 カ月後を目安に、以後は必要に応じて脂質検査を実施し、臨床上必要と認められた場合には、高脂血症治療薬の投与等の適切な処置を考慮すること。

(10) 肝障害を起こす可能性のある薬剤と併用する場合や活動性肝疾患又は肝障害の患者に投与する場合には、トランスアミナーゼ値上昇に注意するなど観察を十分に行い、異常が認められた場合には投与を中止するなどの適切な処置を行うこと（「その他の注意」の項参照）。

(11) 全身型若年性特発性関節炎及びキャッスルマン病の場合
本剤を休薬・中止する際には、IL-6 の作用が過剰に発現し病態が悪化する可能性が否定できないので、必要に応じて副腎皮質ステロイド薬の追加・増量等の適切な処置を考慮すること。

(12) 臨床試験において心障害が認められていることから、患者の状態を十分に観察し、必要に応じて心電図検査、血液検査、胸部エコー等を実施すること。心疾患を合併している患者に投与する際は、定期的に心電図検査を行いその変化に注意すること。

(13) 本剤と他の抗リウマチ生物製剤の併用について安全性及び有効性は確立していないので併用を避けること。また、他の抗リウマチ生物製剤から本剤に切り替える際には、感染症の徴候について患者の状態を十分に観察すること。

3. 副作用

キャッスルマン病、関節リウマチ、多関節に活動性を有する若年性特発性関節炎及び全身型若年性特発性関節炎の国内臨床試験の安全性解析対象症例計 828 例（各々 35 例、625 例、19 例、149 例）において、副作用は 802 例（96.9%）に認められた。主な副作用は、上気道感染 574 例（69.3%）、コレステロール増加 310 例（37.4%）、発疹 239 例（28.9%）、LDL 増加 163 例（19.7%）、胃腸炎 148 例（17.9%）等であった。（再審査終了時）

キャッスルマン病、関節リウマチ、多関節に活動性を有する若年性特発性関節炎及び全身型若年性特発性関節炎の製造販売後調査の安全性解析対象症例計 9,726 例（各々384 例、8,747 例、178 例、417 例）において、副作用は 4,237 例（43.6%）に認められた。主な副作用は、上気道感染 546 例（5.6%）、肝機能異常 499 例（5.1%）、白血球減少 402 例（4.1%）、肺炎 281 例（2.9%）、発疹 230 例（2.4%）等であった。（再審査終了時）

「重大な副作用」及び「その他の副作用」の発現頻度は、国内臨床試験及び製造販売後調査の結果を合わせて算出した。

(1) 重大な副作用

1) **アナフィラキシーショック**（0.1%）、**アナフィラキシー**（0.1%）：血圧低下、呼吸困難、意識消失、めまい、嘔気、嘔吐、瘙痒感、潮紅等があらわれることがあるので、本剤投与中は、患者の状態を十分に観察し、異常が認められた場合には直ちに投与を中止し、アドレナリン、副腎皮質ステロイド薬、抗ヒスタミン薬を投与するなど適切な処置を行うとともに症状が回復するまで患者の状態を十分に観察すること。また、投与終了後も症状のないことを確認すること。

2) **感染症**：肺炎（3.3%）、帯状疱疹（2.0%）、感染性胃腸炎（0.7%）、蜂巣炎（1.4%）、感染性関節炎（0.5%）、敗血症（0.6%）、非結核性抗酸菌症（0.4%）、結核（0.1%）、ニューモシスチス肺炎（0.3%）等の日和見感染を含む重篤な感染症があらわれ、致命的な経過をたどることがある。本剤投与後は、患者の状態を十分に観察し、異常が認められた場合には投与を中止するなどの適切な処置を行うこと。

3) **間質性肺炎**（0.5%）：関節リウマチ患者では、間質性肺炎があらわれることがあるので、発熱、咳嗽、呼吸困難等の呼吸器症状に十分に注意し、異常が認められた場合には、速やかに胸部 X 線、CT 及び血液ガス検査等を実施し、本剤の投与を中止するとともにニューモシスチス肺炎との鑑別診断（β-D-グルカンの測定等）を考慮に入れ適切な処置を行うこと。なお、間質性肺炎の既往歴のある患者には、定期的に問診を行うなど、注意すること。

4) **腸管穿孔**（0.2%）：腸管穿孔が報告されている。本剤投与により、憩室炎等の急性腹症の症状（腹痛、発熱等）が抑制され、発見が遅れて穿孔に至る可能性があるため、異常が認められた場合には、腹部 X 線、CT 等の検査を実施するなど十分に観察し、適切な処置を行うこと。

5) **無顆粒球症**（0.1%未満）、**白血球減少**（4.5%）、**好中球減少**（1.6%）、**血小板減少**（2.1%）：無顆粒球症、白血球減少、好中球減少、血小板減少があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなどの適切な処置を行うこと。

6) **心不全**（0.2%）：心不全の報告があるので、患者の状態を十分に観察し、異常が認められた場合には投与を中止するなどの適切な処置を行うこと。

(2) その他の副作用

次のような副作用が認められた場合には、休薬・中止など適切な処置を行うこと。

項目名	1%以上	0.1～1%未満	0.1%未満
抵抗機構	ヘルペスウイルス感染	インフルエンザ、口腔カンジダ症、耳下腺炎、創傷感染	
呼吸器	上気道感染〔鼻咽頭炎、上気道炎等〕(10.6%)、気管支炎、咽喉	咳嗽、副鼻腔炎、鼻炎、鼻漏、胸膜炎、喀血、喘息、咽頭不快感、咽頭紅斑、鼻	気管支拡張症

項目名	1%以上	0.1～1%未満	0.1%未満
	頭疼痛	閉、鼻出血	
代謝	コレステロール増加(4.9%)、トリグリセリド増加、高脂血症、高コレステロール血症、LDL増加	LDH上昇、HDL増加、高トリグリセリド血症、血中尿酸増加、CK（CPK）上昇、総蛋白減少、糖尿病増悪、血中カリウム減少、血糖増加、血中リン増加、血清フェリチン減少	血中リン減少、血中カルシウム減少
肝臓	肝機能異常、ALT（GPT）上昇、AST（GOT）上昇	γ-GTP上昇、ビリルビン増加、Al-P上昇、脂肪肝、胆石症	
循環器	高血圧	血圧上昇、血圧低下、動悸、T波逆転、T波振幅減少、上室性期外収縮、心室性期外収縮	ST部分上昇、ST部分下降、T波振幅増加
血液・凝固		リンパ球数減少、貧血、白血球数増加、フィブリノゲン減少、好酸球数増加、フィブリン分解産物〔FDP、Dダイマー〕増加、ヘマトクリット減少、ヘモグロビン減少、リンパ節炎、リンパ節腫脹、好中球数増加、赤血球数減少	TAT増加
消化器	口内炎、下痢、胃腸炎、腹痛	悪心、便秘、嘔吐、腹部不快感、口唇炎、腹部膨満、食欲不振、胃・腸ポリープ、逆流性食道炎、痔核、消化不良、舌炎、胃潰瘍、急性膵炎	口渇
		歯周病、齲歯、歯痛	
精神神経	頭痛	浮動性めまい、感覚減退、不眠症、末梢性ニューロパシー	
耳		中耳炎、眩暈、突発難聴、外耳炎、耳鳴	耳不快感
眼		結膜炎、麦粒腫、眼乾燥、結膜出血、霰粒腫、白内障、眼瞼炎	硝子体浮遊物、網膜出血
皮膚	発疹〔湿疹、痒疹、丘疹等〕、瘙痒症、白癬、皮膚感染	爪感染、蕁麻疹、紅斑、皮膚潰瘍、皮下出血、嵌入爪、ざ瘡、皮膚乾燥、水疱、角化症、脱毛症、皮膚嚢腫	
筋・骨格		関節痛、背部痛、筋痛〔筋痛、肩こり〕、四肢痛、骨粗鬆症、骨密度減少、頚部痛、若年性関節炎増悪	
泌尿器		膀胱炎、尿路感染、BUN増加、尿中赤血球陽性、腎盂腎炎、尿糖、尿蛋白、腎結石、NAG増加、頻尿	尿中白血球陽性
生殖器		腟感染、性器出血	子宮頚管ポリープ
その他	膿瘍、発熱	浮腫、倦怠感、免疫グロブリンG減少、胸痛、胸部不快感、季節性アレルギー、CRP増加、悪寒、潮紅、アレルギー性鼻炎、気分不良、ほてり、注射部位反応〔紅斑、腫脹、血腫、疼痛、静脈炎、発疹等〕、血栓性静脈炎、DNA抗体陽性注3）、体重増加、抗核抗体陽性注3）	リウマチ因子陽性、発汗障害

注 3) 関節リウマチ第Ⅲ相 2 試験での DNA 抗体の推移は、217 例において陰性化 10 例（4.6%）、陽性化 0 例である。抗核抗体の推移は 216 例において陰性化 24 例（11.1%）、陽性化 18 例（8.3%）である。

4. **高齢者への投与**

一般に高齢者では生理機能が低下しているので、患者の状態を十分に観察しながら慎重に投与すること。

5. **妊婦、産婦、授乳婦等への投与**

(1) 妊婦又は妊娠している可能性のある婦人には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。［本剤の妊娠中の投与に関する安全性は確立されていない。また、カニクイザルにおいて本剤は胎盤関門を通過することが報告されている。］

(2) 授乳婦に投与する場合には授乳を中止させること。［授乳中の投与に関する安全性は確立していない。］

6. **小児等への投与**

低出生体重児、新生児又は乳児に対する安全性は確立していない（「薬物動態」の項参照）。

7. **適用上の注意**

(1) **調製時**

1) 希釈時及び希釈後に泡立つような激しい振動を与えないこと。［本剤はポリソルベートを含有しているので、泡立ちやすい。］

2) 用時調製し、調製後は速やかに使用すること。また、残液は廃棄すること。

(2) **投与時**

1) 本剤は点滴静注用としてのみ用い、皮下・筋肉内には投与しないこと。

2) 本剤は無菌・パイロジェンフリーのインラインフィルター（ポアサイズ 1.2 ミクロン以下）を用い独立したラインにて投与すること。

3) 他の注射剤、輸液等と混合しないこと。

8. **その他の注意**

(1) 本剤投与により抗トシリズマブ抗体が発現したとの報告がある（国内臨床試験・疾患別、関節リウマチ：601 例中 18 例（3.0%）、多関節に活動性を有する若年性特発性関節炎：19 例中 1 例（5.3%）、全身型若年性特発性関節炎：128 例中 11 例（8.6%）［以上、効能追

加時]、キャッスルマン病：35 例中 1 例（2.9%）[承認時])。

(2) 本邦において、本剤と抗リウマチ薬（DMARD）との併用療法における有効性及び安全性は確立していない。なお、海外の関節リウマチを対象とした臨床試験では、トランスアミナーゼ値上昇の発現頻度が本剤単剤療法時に比べて DMARD 併用療法時で高かった。基準値の 3 倍を超える ALT（GPT）あるいは AST（GOT）上昇の発現頻度は、DMARD 併用療法：本剤 8mg/kg+DMARD 群 103/1582 例（6.5%）、プラセボ+DMARD 群 18/1170 例（1.5%）、単剤療法：本剤 8mg/kg 群 6/288 例（2.1%）、MTX 単剤群 14/284 例（4.9%）で、これらの異常は一過性で肝炎や肝不全に伴うものではなかった。

(3) 国内の臨床試験では 2.9 年（投与期間 0.1～8.1 年の中央値）まで、海外の関節リウマチを対象とした臨床試験では 4.6 年（投与期間 0.0～5.8 年の中央値）までの期間で実施されており、これらの期間を超えた本剤の長期投与時の安全性は確立していない。

(4) ヒト肝細胞を用いた *in vitro* 試験において、IL-6 が肝薬物代謝酵素（CYPs）発現を抑制することが報告されていることから[1)-3)]、ヒト肝細胞に IL-6 をトシリズマブ共存下で添加したところ、CYPs の発現に変化は認められなかった[4)]。また、炎症反応を有する患者では、IL-6 の過剰産生により CYPs の発現が抑制されているとの報告がある[5), 6)]。関節リウマチ患者を対象とした臨床試験において、本剤投与後に IL-6 阻害に伴って CYP3A4、CYP2C19 及び CYP2D6 発現量が増加することが示唆された。このことから、過剰の IL-6 によって抑制されていた CYPs の発現が本剤投与により回復し、炎症反応の改善に伴って併用薬の効果が減弱する可能性は否定できない[7)]。

(5) 動物実験（マウス）において、gp130 を介したシグナル伝達が心筋細胞の保護作用を有することが報告されている[8)]。gp130 を介してシグナル伝達に関与するサイトカインは複数知られており、IL-6 もその一つである。本薬は IL-6 の作用を阻害することから、心臓への影響は否定できない。

(6) 本薬はヒトとカニクイザルの IL-6 レセプターに対しては中和活性を示すが、マウス及びラットの IL-6 レセプターに対しては中和活性を示さない。このため、がん原性試験は実施されていない。

(7) 関節リウマチを対象とした本剤の海外臨床試験において、本剤 8mg/kg 投与時の重篤な感染症の発現頻度が体重 100kg を超える患者群で高い傾向が認められたため、海外における 1 回投与量の上限は 800mg とされている。

(8) 関節リウマチを対象とした海外臨床試験において、本剤との因果関係は不明であるが脱髄関連疾患が認められたとの報告がある。

【薬物動態】

1. 血中濃度

(1) 第 I 相試験（単回投与）[9)]

健康成人男性 5 例を対象に、0.15、0.50、1.0、2.0mg/kg を単回投与した（1 時間点滴静注）。Cmax は投与量に比例して上昇したものの、投与量の増加に伴って CLtotal は減少し、$T_{1/2}$ 及び MRT が有意に延長したことから、トシリズマブの体内動態に非線形性が認められた（表 1）。

表 1　単回投与時の薬物動態パラメータ

投与量（mg/kg）	Cmax（μg/mL）	AUCfinite（hr･μg/mL）	$T_{1/2}$（hr）	CLtotal（mL/hr/kg）	MRT（hr）	Vdss（mL/kg）
0.15	2.4±0.6	11±6	17±16	3.8±2.3	25±22	63.4±16.6
0.50	8.5±1.2	285±73	33± 4	1.3±0.2	47± 5	58.4± 7.1
1.0	19.5±2.7	1009±222	49± 5	0.8±0.1	69± 8	57.3±10.9
2.0	37.6±8.8	2532±569	74± 9	0.6±0.2	107±16	65.9± 8.3

（例数：5、平均値±SD）

注）本剤の承認用量は 1 回 8mg/kg である（「用法・用量」の項参照）。

(2) 関節リウマチ患者での薬物動態

1) 単回投与試験[10)]

関節リウマチ患者 31 例を対象に、8mg/kg を単回投与した（1 時間点滴静注）。血清中トシリズマブ濃度を図 1 に示した。このときの薬物動態パラメータは AUCfinite= 19852±5749hr･μg/mL（平均値±SD、以下同様）、$T_{1/2}$= 133±25.7hr、CLtotal=0.4±0.1mL/hr/kg 及び Vdss= 78.5±16.8mL/kg であった。

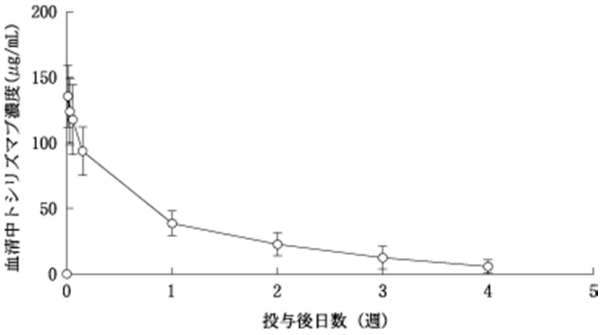


図 1　関節リウマチ患者における単回投与時の血清中トシリズマブ濃度推移(平均値±SD)

2) 反復投与試験

① 用量相関性の検討[11)]

関節リウマチ患者 15 例（1 群 5 例）を対象に、2、4 あるいは 8mg/kg を 2 週間隔にて投与した（2 時間点滴静注）。

CLtotal は投与量の増加にともなって減少し、$T_{1/2}$ は有意に延長したことから非線形性の体内動態が認められた（表 2）。

表 2　関節リウマチ患者における反復投与時の薬物動態パラメータ

投与回数	投与量（mg/kg）	C_{1hr}（μg/mL）	AUCfinite（hr･μg/mL）	$T_{1/2}$（hr）	CLtotal（mL/hr/kg）	MRT（hr）	Vdss（mL/kg）
1	2	43.6±10.1	3440± 823	74±18	0.5±0.2	107±25	55.0±13.0
	4	49.0±12.6	4663±2185	97±50	0.9±0.5	138±68	102±24.0
	8	82.5±32.4	10661±4070	160±34	0.6±0.2	227± 46	137±31.6
3	2	27.9±12.3	3014±1070	87±18	0.5±0.1	140±26	70.7±13.5
	4	49.5±10.1	6035±3200	140±71	0.7±0.5	204±105	98.5±14.6
	8	129.9±48.1	19939±8900	242±71	0.3±0.1	343±105	90.9±29.9

（例数：4-5、平均値±SD）

注）本剤の承認用量は 1 回 8mg/kg である（「用法・用量」の項参照）。

② 第 III 相試験[12)]

関節リウマチ患者 157 例を対象に、8mg/kg を 4 週間隔で 13 回投与した（1 時間点滴静注）。血清中トシリズマブ濃度は初回投与以降上昇し、血清中トシリズマブ投与直前値は 3 回目投与 4 週間後（初回投与 12 週後、平均値±SD 以下同様）で 9.8±7.5μg/mL、6 回目投与 4 週間後（初回投与 24 週間後）で 12.3±8.6μg/mL であり、初回投与 20 週後以降ほぼ一定の値で推移した（図 2）。

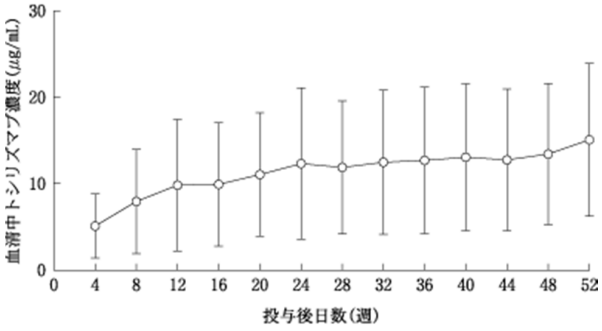


図 2　関節リウマチ患者における反復投与時の
血清中トシリズマブ濃度（投与直前値）推移（平均値±SD）

(3) 多関節に活動性を有する若年性特発性関節炎患者での薬物動態 [13)]

多関節に活動性を有する若年性特発性関節炎患者 19 例（3-19 歳、中央値 12 歳）を対象に、8mg/kg を 4 週間隔で 3 回投与した（1 時間点滴静注）。初回投与後の血清中トシリズマブ薬物動態パラメータの比較を表 3 に示した。7 歳未満の群で血清中トシリズマブの消失速度の大きい症例が認められた。

表 3　多関節に活動性を有する若年性特発性関節炎患者
における反復投与時の薬物動態パラメータ

年齢	C_{1hr}（μg/mL）	AUCfinite（hr･μg/mL）	$T_{1/2}$（hr）	CLtotal（mL/hr/kg）	MRT（hr）	Vdss（mL/kg）
3-7 未満	107.8±15.0	12970±2511	N.A.	N.A.	N.A.	N.A.
7-15 未満	158.6±34.4	20878±5328	99±12	0.3±0.0	150± 9	48.0± 7.0
15 以上	158.1±36.2	25954±6157	143±43	0.3±0.1	200±49	60.5±12.2
全例	145.0±37.5	25275±6722	123±41	0.3±0.1	178±46	58.3±13.9

（平均値±SD、N.A.：算出せず）

（3-7 歳：C_{1hr} 及び AUCfinite：n=5、7-15 歳：C_{1hr} 及び AUCfinite：n=7、その他のパラメータ：n=4、15 歳以上：n=7）

(4) 全身型若年性特発性関節炎患者での薬物動態 [14)]

全身型若年性特発性関節炎患者（2-19 歳、中央値 8 歳）を対象に、8mg/kg を 2 週間隔で 3 回反復投与し（1 時間点滴静注)、その後有効性の認められた被験者を対象に 6 回（合計 9 回、初回投与後 18 週間）投与を行った。

初回投与後及び 3 回目投与後の血清中トシリズマブ薬物動態パラメータを表 4 に示した。7 歳未満の群で血清中トシリズマブの消失速度の大きい症例が認められた。

血清中トシリズマブ濃度推移は初回投与 8 週から 14 週の範囲で定常状態となったと考えられ、血清中トシリズマブ濃度(投与直前値)は 57.4μg/mL（初回投与 18 週後、例数：13）であった。

低体重、低身長及び低年齢のいずれかの因子を有する患者において、血清中トシリズマブ濃度の消失速度が大きくなることがあった。

表 4　全身型若年性特発性関節炎患者における
反復投与時の薬物動態パラメータ

年齢	投与回数	C_{1hr}（μg/mL）	AUCfinite（hr･μg/mL）	$T_{1/2}$（hr）	CLtotal（mL/hr/kg）	MRT（hr）	Vdss（mL/kg）
2-7 未満	1	142.8±31.6	17677±5193	N.A.	N.A.	N.A.	N.A.
	3	171.7±51.2	23706±9704	100±38	0.3±0.1	155±60	45.4±7.6
7-15 未満	1	176.7±48.5	24701±7611	N.A.	N.A.	N.A.	N.A.
	3	239.8±70.2	35333±11668	127±26	0.2±0.2	188±49	43.0±17.5
15 以上	1	166.0±31.8	23653±3571	N.A.	N.A.	N.A.	N.A.
	3	214.0±40.0	33336±8115	139±30	0.2±0.0	249±21	43.6±11.2

（平均値±SD、N.A.：算出せず）

（2-7 歳：n=19-23、7-15 歳：n=25-28、15 歳以上：n=4-5）

(5) キャッスルマン病患者における薬物動態反復投与試験 [15)]

キャッスルマン病患者 28 例を対象に、8mg/kg を 2 週間隔で 8 回反復投与した（1 時間点滴静注）。

血清中トシリズマブ濃度は 8 回目投与直前値で 36.6±17.5μg/mL であり、初回投与以降上昇していた。

初回投与後 6 回目投与まで $T_{1/2}$ 及び MRT は延長したが、投与 6 回目以降はほぼ一定の値を示した（表 5）。

表 5　キャッスルマン病患者における反復投与時の
薬物動態パラメータ

投与量（mg/kg）	投与回数	C_{1hr}（μg/mL）	AUCfinite（hr･μg/mL）	$T_{1/2}$（hr）	CLtotal（mL/hr/kg）	MRT（hr）	Vdss（mL/kg）
8	1	112.9±24.7	13092±3254	99.7±17.1	0.6±0.2	145±26.8	80.1± 15.0
	8	192.3±38.7	28423±7410	139±37.4	0.2±0.1	205±54.2	46.8± 8.8

（例数：26-28、平均値±SD）

(6) サイトカイン放出症候群患者における薬物動態 [16)]

キメラ抗原受容体遺伝子導入 T 細胞輸注療法に伴うサイトカイン放出症候群 43 例（日本人 1 例）を対象に、体重 30 kg 以上の場合は 8 mg/kg、30 kg 未満の場合は 12 mg/kg を投与した（1 時間点滴静注）。

初回投与時の血清中トシリズマブ濃度の C_{max} は 43.2 ~ 210μg/mL（日本人：122μg/mL）であった。

2. 排泄 [9)]

健康成人男性 5 例を対象に、0.15、0.50、1.0、2.0mg/kg を 1 時間点滴静注したとき、いずれの投与量においてもトシリズマブは尿中に排泄されず、トシリズマブの主消失クリアランスは腎外クリアランスであることが示された。

注）本剤の承認用量は 1 回 8mg/kg である（「用法･用量」の項参照）。

【臨床成績】

1.関節リウマチ

(1) 第 III 相二重盲検比較試験 [17)]

メトトレキサートに効果不十分な関節リウマチ患者を対象とし、メトトレキサート 8mg/週+トシリズマブプラセボ（プラセボ群）及びメトトレキサートプラセボ+トシリズマブ 8mg/kg/4 週（本剤投与群）を 24 週間投与した二重盲検比較試験を実施した。成績は以下のとおりであった。

1) **症状の緩和**

最終観察時の ACR 基準#1 20%改善頻度は、プラセボ群 25.0%に対し、本剤投与群で 80.3%と有意に高かった（P<0.001）。

#1：アメリカリウマチ学会（ACR）の臨床的改善の評価基準

表 1　ACR 基準 20%改善頻度

	プラセボ注)	トシリズマブ	P 値
例数	64	61	
ACR20	25.0%	80.3%	<0.001

注）メトトレキサート 8mg/週投与

2) **日常生活動作（ADL）の改善**

投与前から最終観察時までの日常生活動作（ADL）の改善を MHAQ スコア（活動制限と介護の必要性等を評価する指標）で評価した結果、プラセボ群 0.01 に対し、本剤投与群で 0.32 と有意に改善した（P<0.001）。なお、MCID（minimum clinically important differences）として定義される 0.22 を超えて改善を示した症例は、プラセボ群 34.4%に対し、本剤投与群で 67.2%であり、本剤投与群で有意に多かった（P<0.001）。

(2) **第 III 相無作為割付群間比較試験** [18]

DMARD あるいは免疫抑制剤に効果不十分な関節リウマチ患者を対象とし、トシリズマブ 8mg/kg/4 週投与又は既存治療（DMARD あるいは免疫抑制剤の治療）を 52 週間継続する無作為割付群間比較試験を実施した。成績は以下のとおりであった。

関節の構造的損傷の防止

投与前から 52 週までの関節破壊進展を手及び足の X 線スコア（Modified Sharp Score）で評価した結果を下表に示す。Total スコアにおいて、既存治療で 6.12 悪化したのに対して、本剤投与群は 2.34 であり、有意に関節破壊の進行が抑制された（P＝0.001）。

表 2　投与 52 週後の Modified Sharp 法による各スコアの変化量

	既存治療	トシリズマブ	P 値
例数	143	157	
骨びらん	3.21（1.0）	0.85（0.0）	<0.001
関節裂隙狭小化	2.91（1.0）	1.49（0.0）	0.024
Total	6.12（2.5）	2.34（0.5）	0.001

（　）内は中央値

2.多関節に活動性を有する若年性特発性関節炎 [19]

多関節に活動性を有する若年性特発性関節炎患者 19 例を対象に、トシリズマブ 8mg/kg を 4 週間隔で 3 回投与した。最終観察時の JIA 基準#2 30%、50%、70%改善頻度はそれぞれ、94.7%、94.7%、57.9%であり、原疾患の著明な改善が認められた。

#2：Giannini 等 [20]により提唱された若年性特発性関節炎（JIA）に対する薬効評価であり標準的な評価基準

3.全身型若年性特発性関節炎 [21]

第 III 相試験

全身型若年性特発性関節炎患者 56 例を対象としてトシリズマブ 8mg/kg を 2 週間隔で 3 回反復投与するオープン期間にて、JIA 基準#2 30%以上の改善を示し、かつ CRP が 0.5mg/dL 未満に改善した解析対象患者 43 例を対象に、二重盲検比較試験にてトシリズマブ群 20 例あるいはプラセボ群 23 例として 2 週間隔で 6 回投与し、JIA 基準 30%以上の改善、かつ CRP が 1.5mg/dL 未満の改善の維持率及び維持期間を比較した。その結果、トシリズマブ群の効果維持率は 80.0%であり、プラセボ群（17.4%）に比べて有意に高かった（P<0.001）。また、効果維持期間もトシリズマブ群の方がプラセボ群に比べて有意に長かった（P<0.001）。

#2：Giannini 等 [19]により提唱された若年性特発性関節炎（JIA）に対する薬効評価であり標準的な評価基準

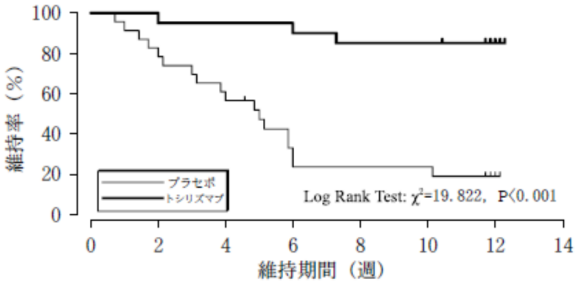


図　効果維持率の推移（Kaplan-Meier 曲線）

4.キャッスルマン病

(1)**第 II 相試験** [22]

1) **第一段階**

キャッスルマン病患者 7 例を対象として同一患者内での漸増法にて 2、4、8mg/kg と増量し（各用量ともに 2 週間隔にて 3 回反復投与）、各用量での有効性を検討した。その結果、CRP 等の炎症マーカーは、2、4mg/kg では各投与 1 週後で低下したものの 2 週後には再び上昇した症例もみられた。8mg/kg ではほとんどの症例は投与期間を通じて低下傾向が持続した。

注）本剤の承認用量は 1 回 8mg/kg である（「用法・用量」の項参照）。

2) **第二段階**

キャッスルマン病患者 28 例を対象として 8mg/kg を 2 週間隔で 8 回反復投与した。その結果、炎症マーカー（CRP、フィブリノーゲン、ESR）、全身倦怠感（Visual Analog Scale による評価）、貧血状態（Hb）、低アルブミン血症等が、初回投与後より投与期間を通じて有意に改善した（表 3）。

表 3　有効性評価項目の推移（第二段階）

項　目	投与前	投与 6 週後	投与 16 週後
CRP（mg/dL）	8.7±5.0	1.2±1.7**	0.9±2.0**
フィブリノーゲン（mg/dL）	639±188	356±149**	317±138**
ESR（mm/hr）	114±34	63±36**	48±40**
全身倦怠感（0-100mm）	29.9±22.8	17.4±17.2*	17.7±16.5**
Hb（g/dL）	9.2±2.3	11.6±1.9**	12.0±2.1**
アルブミン（g/dL）	2.7±0.5	3.6±0.5**	3.7±0.5**

＊：p<0.05、＊＊：p<0.01、対応のある t 検定（例数：24-28、平均値±SD）

(2)**継続投与試験** [23]

第 II 相試験において検討されたキャッスルマン病患者のうち 33 例を対象として、原則 8mg/kg を 2 週間

隔で長期継続投与（最長 1568 日、平均 1191 日）した結果、炎症マーカーをはじめとして治療効果が維持された。
なお、治療効果の維持が不十分であった 7 例では、投与間隔の短縮（最短 1 週間隔まで）により炎症マーカーの改善が認められた。

5. サイトカイン放出症候群[24)]

(1) 再発又は難治性の B 細胞性急性リンパ芽球性白血病の小児患者を対象とした第 II 相試験（国際共同治験）

3 歳（スクリーニング時）～21 歳（初診時）の再発又は難治性の B 細胞性急性リンパ芽球性白血病患者に対して、チサゲンレクルユーセルを投与する非盲検非対照試験を実施した。チサゲンレクルユーセルの輸注を受けた 75 例のうち、重症度が高いサイトカイン放出症候群（CRS）を発症した 28 例に、体重 30 kg 未満の患者にはトシリズマブ 12 mg/kg、体重 30 kg 以上の患者にはトシリズマブ 8 mg/kg（最大 800 mg まで）を単剤又は副腎皮質ステロイド等との併用で投与し、症状の改善が認められない場合は、最大 3 回まで反復投与した。その結果、トシリズマブが投与された 28 例全例（100.0%）が回復した。トシリズマブ投与から CRS 回復判断時点までの期間の中央値［95%信頼区間（CI）］は、5.0（4.0、7.0）日（最小値～最大値：2～29 日）であった。CRS の回復は、24 時間以上平熱が持続し、昇圧薬服用の必要がないと判断した期間が 24 時間以上持続した時点と定義した。
28 例（日本人 1 例）におけるトシリズマブ投与日以降に認められた主な有害事象は、CRS[#3)] 22 例（78.6%）、発熱、アスパラギン酸アミノトランスフェラーゼ増加、好中球数減少、低カリウム血症各 8 例（28.6%）、アラニンアミノトランスフェラーゼ増加、急性腎障害、低酸素症、高血圧各 7 例（25.0%）、貧血、腹痛、嘔吐、血中ビリルビン増加、白血球数減少、高血糖、低カルシウム血症、頭痛、低血圧各 6 例（21.4%）等であった。

(2) 再発又は難治性のびまん性大細胞型 B 細胞リンパ腫成人患者を対象とした第 II 相試験（国際共同治験）

18 歳以上の再発又は難治性のびまん性大細胞型 B 細胞リンパ腫成人患者に対して、チサゲンレクルユーセルを投与する非盲検非対照試験を実施した。チサゲンレクルユーセルの輸注を受けた 111 例のうち、重症度が高い CRS を発症した 16 例にトシリズマブ 8 mg/kg（最大 800 mg まで）[#4)] を単剤又は副腎皮質ステロイド等との併用で投与し，症状の改善が認められない場合は、最大 2 回まで反復投与した。その結果、トシリズマブが投与された 16 例のうち、15 例（93.8%）が回復，1 例が疾患進行による死亡のための評価打ち切りであった。トシリズマブ投与から CRS 回復判断時点までの期間の中央値（95%CI）は、6.0（3.0、7.0）日（最小値～最大値：2～14 日）であった。
16 例におけるトシリズマブ投与日以降に認められた主な有害事象は、CRS[#3)]、低血圧各 9 例（56.3%）、血小板数減少 8 例（50.0%）、急性腎障害、貧血各 6 例（37.5%）、下痢、白血球数減少各 5 例（31.3%）、血中クレアチニン増加、高血糖、低リン酸血症、全身性浮腫、末梢性浮腫、血中フィブリノゲン減少、好中球数減少各 4 例（25.0%）等であった。

[#3)] 有害事象の CRS は (1) 再発又は難治性の B 細胞性急性リンパ芽球性白血病の第 II 相試験の 1 例を除き，トシリズマブ初回投与日前に発現した CRS が継続している中で重症度の変化により有害事象として報告された事象，及びトシリズマブ初回投与日のトシリズマブ投与前に発現した事象であった。

[#4)] トシリズマブの用量について、体重 30 kg 以上は 1 回 8 mg/kg、体重 30 kg 未満は 1 回 12 mg/kg を投与することと規定されていたが、試験に組み入れられた患者はいずれも体重 30 kg 以上の患者であり、1 回 8 mg/kg が投与された。

6. 海外臨床試験（点滴静注用製剤）における悪性腫瘍発現頻度[25)]

海外の関節リウマチ患者を対象とした二重盲検比較試験における悪性腫瘍の発現率は、本剤投与群では 1.60/100 人・年（95%信頼区間：1.04-2.37、投与期間の中央値：0.5 年、被験者数：2,644 例、延べ投与：1,560 人・年）、比較対照薬投与群（メトトレキサートあるいは DMARD）では 1.48/100 人・年（95%信頼区間：0.74-2.65、投与期間の中央値：0.5 年、被験者数：1,454 例、延べ投与：743 人・年）であった。二重盲検比較試験を含む海外長期継続投与試験における悪性腫瘍の発現率は、1.62/100 人・年（投与期間の中央値：4.6 年、被験者数：4,009 人、延べ投与：14,994 人・年）であった。

【薬効薬理】

1. 本薬は *in vitro* において、可溶性及び膜結合性 IL-6 レセプターに結合してそれらを介した IL-6 の生物活性の発現を抑制した[26)]。
2. 本薬は、カニクイザルに投与されたヒト IL-6 の活性発現を抑制した[27)]。
3. 本薬は、カニクイザルコラーゲン誘発関節炎において、関節炎発症前からの投与により関節腫脹の発現を抑制するとともに、関節炎発症後の投与により関節の腫脹を改善した[28)、29)]。
4. 抗マウス IL-6 レセプター抗体は、IL-6 トランスジェニックマウスでの貧血状態、蛋白尿、高 γ グロブリン血症等の所見の発現を抑制し、生存日数を延長させた[30)]。

【有効成分に関する理化学的知見】

一般名：　トシリズマブ（遺伝子組換え）
（Tocilizumab（Genetical Recombination））（JAN）
構造式：　アミノ酸 214 個の軽鎖 2 分子とアミノ酸 447、448（主成分）又は 449 個の重鎖 2 分子からなる糖蛋白質
分子式：　軽鎖（$C_{1033}H_{1606}N_{278}O_{337}S_6$）
重鎖（$C_{2181}H_{3398}N_{582}O_{672}S_{15}$：主成分）
分子量：　約 148,000

【包　　装】

アクテムラ点滴静注用 80mg：4mL×1 バイアル
アクテムラ点滴静注用 200mg：10mL×1 バイアル
アクテムラ点滴静注用 400mg：20mL×1 バイアル

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14) 社内資料: 全身型若年性特発性関節炎患者に対する臨床薬理
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23) 社内資料: キャッスルマン病患者に対する第Ⅱ相継続投与試験 (MRA006JP 試験).
24) 社内資料: サイトカイン放出症候群患者に対する第Ⅱ相試験
25) 社内資料: 海外臨床試験(点滴静注用製剤)における悪性腫瘍発現頻度
26) Mihara M, et al.: Int Immunopharmacol:5, 1731 (2005).
27) Shinkura H, et al.: Anticancer Research:18, 1217 (1998) .
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30) Katsume A, et al.: Cytokine:20, 304 (2002)

【文献請求先】
主要文献に記載の社内資料につきましても下記にご請求ください。

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アクテムラ点滴静注用80 mg，同200 mg，同400 mg（トシリズマブ（遺伝子組換え））

［サイトカイン放出症候群］

第1部　（モジュール1）：

申請書等行政情報及び添付文書に関する情報

1.10 毒薬・劇薬等の指定審査資料のまとめ

中外製薬株式会社

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1.10 毒薬・劇薬等の指定審査資料のまとめ

1.10.1 現行

化学名・別名	マウス抗 IL-6レセプターモノクローナル抗体の相補性決定領域及びヒト IgG1のフレームワーク領域を含む可変領域と定常領域（重鎖；[redacted]，軽鎖；[redacted]）から成るヒト化マウス抗 IL-6レセプターモノクローナル抗体をコードする cDNA を導入したチャイニーズハムスター卵巣細胞から産生される，214個のアミノ酸残基（$C_{1033}H_{1606}N_{278}O_{337}S_6$；分子量：23,503.86）の軽鎖2分子と447，448又は449個のアミノ酸残基（主成分は，N 末端アミノ酸残基のグルタミンがピログルタミン酸に変換し，C 末端リジンがプロセシングした448個のアミノ酸残基から成るポリペプチド鎖，$C_{2181}H_{3398}N_{582}O_{672}S_{15}$；分子量：49,004.79）の重鎖2分子から成る糖タンパク質（分子量：約148,000）（別名トシリズマブ（遺伝子組換え））及びその製剤
構造式	アミノ酸配列は別紙のとおり
効能・効果	○既存治療で効果不十分な下記疾患 関節リウマチ（関節の構造的損傷の防止を含む），多関節に活動性を有する若年性特発性関節炎，全身型若年性特発性関節炎 ○キャッスルマン病に伴う諸症状及び検査所見（C 反応性タンパク高値，フィブリノーゲン高値，赤血球沈降速度亢進，ヘモグロビン低値，アルブミン低値，全身倦怠感）の改善。ただし，リンパ節の摘除が適応とならない患者に限る。
用法・用量	○関節リウマチ，多関節に活動性を有する若年性特発性関節炎 通常，トシリズマブ（遺伝子組換え）として1回8 mg/kg を4週間隔で点滴静注する。 ○全身型若年性特発性関節炎，キャッスルマン病 通常，トシリズマブ（遺伝子組換え）として1回8 mg/kg を2週間隔で点滴静注する。なお，症状により1週間まで投与間隔を短縮できる。
劇薬等の指定	生物由来製剤，劇薬，指定医薬品，処方せん医薬品
市販名及び有効成分・分量	原体：アクテムラ原液 製剤： アクテムラ点滴静注用80 mg ［1バイアル（4 mL）中に,トシリズマブ（遺伝子組換え）として80 mg 含有］ アクテムラ点滴静注用200 mg ［1バイアル（10 mL）中に,トシリズマブ（遺伝子組換え）として200 mg 含有］ アクテムラ点滴静注用400 mg ［1バイアル（20 mL）中に,トシリズマブ（遺伝子組換え）として400 mg 含有］
毒性	【急性】

		静脈内投与
概略の致死量（mg/kg）	ラット ♂・♀	> 150
	カニクイザル ♂・♀	> 100

【亜急性】

動物種	投与期間	投与経路	投与量（mg/kg/日）	無毒性量（mg/kg/日）	主な所見
ラット	1カ月	静脈内	0，2，10，50	10	50 mg/kg 群の雌で体重加抑制，摂餌量，摂量の低下。
カニクイザル	1カ月	静脈内	0，2，10，50	10	50 mg/kg/日で軽度の好中球減少。

【慢性】

動物種	投与期間	投与経路	投与量（mg/kg/日）	無毒性量（mg/kg/日）	主な所見
カニクイザル	6カ月	静脈内	0，1，10，100	100	投薬の影響と考えられる毒性変化なし。

副　作　用

副作用・臨床検査値異常発現率

関節リウマチ	585/601例 ＝97.3%
多関節に活動性を有する若年性特発性関節炎	18/19例 ＝94.7%
全身型若年性特発性関節炎	115/128例 ＝89.8%
キャッスルマン病	33/35例 ＝94.3%

副作用・臨床検査値異常の種類　件数

＜関節リウマチ＞

鼻咽頭炎	960
血中コレステロール増加	331
頭痛	180
LDL 増加	167
血中トリグリセリド増加	136

＜全身型若年性特発性関節炎＞

鼻咽頭炎	278
上気道感染	129
胃腸炎	95
上気道の炎症	64
咽頭炎	58 等

＜多関節に活動性を有する若年性特発性関節炎＞

鼻咽頭炎	28
咽頭炎	11
上気道感染	10
湿疹	6
上気道の炎症	5 等

＜キャッスルマン病＞

鼻咽頭炎	31
発疹	17
腹痛	11
そう痒症	10

	好中球減少	9
	頭痛	8
	倦怠感	8
	咽喉頭疼痛	7
	下痢	7
	TAT 上昇	7
	トリグリセリド上昇	7　等
会　　社	中外製薬株式会社　原体：製造，製剤：製造	

別　紙

```
1                                   10                                  20
pGlu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln Thr Leu Ser Leu
21                                  30                                  40
Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp His Ala Trp Ser Trp Val Arg Gln
41                                  50                                  60
Pro Pro Gly Arg Gly Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ile Thr Thr Tyr
61                                  70                                  80
Asn Pro Ser Leu Lys Ser Arg Val Thr Met Leu Arg Asp Thr Ser Lys Asn Gln Phe Ser
81                                  90                                  100
Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ser Leu
101                                 110                                 120
Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Gln Gly Ser Leu Val Thr Val Ser Ser Ala
121                                 130                                 140
Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
141                                 150                                 160
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
161                                 170                                 180
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
181                                 190                                 200
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
201                                 210                                 220
Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
221                                 230                                 240
Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
241                                 250                                 260
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
261                                 270                                 280
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
281                                 290                                 300
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
301                                 310                                 320
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
321                                 330                                 340
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
341                                 350                                 360
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
361                                 370                                 380
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
381                                 390                                 400
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
401                                 410                                 420
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
421                                 430                                 440
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
441                                 450
Lys Ser Leu Ser Leu Ser Pro Gly
```

図1　トシリズマブ主成分の H 鎖のアミノ酸配列（pGlu1 - Gly448）
アンダーライン部分はマウスの CDR 領域を示す。

*1: H222-L214 disulfide bond　　*2: H228-H228 disulfide bond（推定）
*3: H231-H231 disulfide bond（推定）　　*4: Glycosylation site
pGlu: Pyroglutamic acid

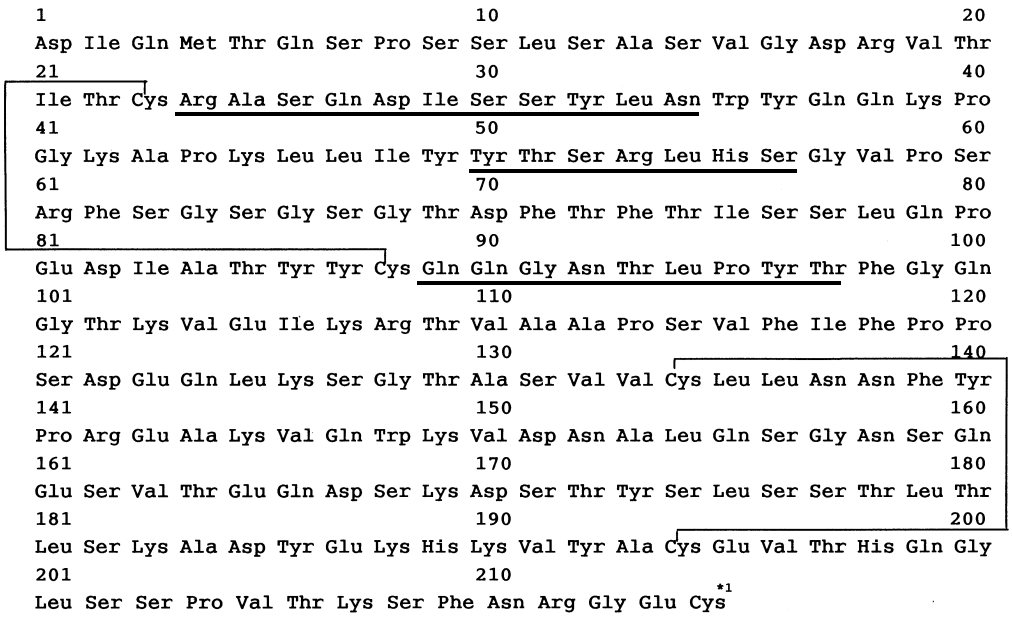
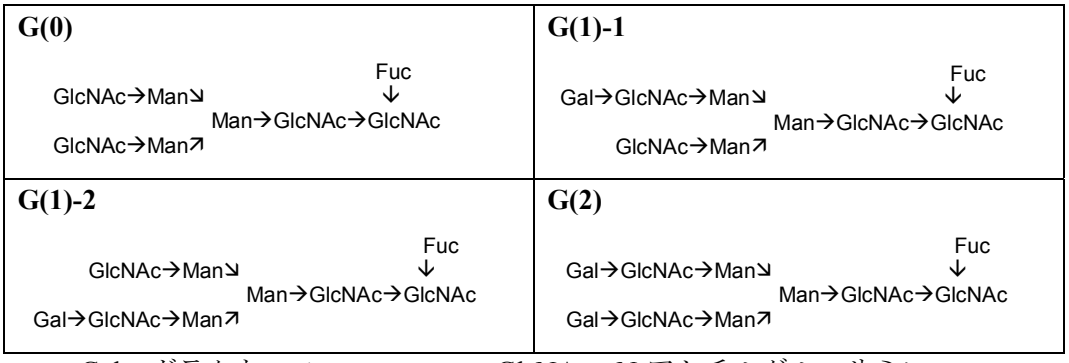


図2　トシリズマブ L 鎖のアミノ酸配列（Asp1 - Cys214）
アンダーライン部分はマウスの CDR 領域を示す。
*1: H222-L214 disulfide bond

表1　トシリズマブの H 鎖及び L 鎖の末端残基

H 鎖	L 鎖		
N 末端残基	C 末端残基	N 末端残基	C 末端残基
pGlu1（主成分），Gln1	Gly448（主成分），[redacted]447，Lys449	Asp1	Cys214



Gal：ガラクトース　　GlcNAc：N-アセチルグルコサミン
Man：マンノース　　Fuc：フコース

図3　トシリズマブの N 結合型糖鎖の構造

1.10.2 追加

化学名・別名	
構造式	
効能・効果	○既存治療で効果不十分な下記疾患 関節リウマチ（関節の構造的損傷の防止を含む），多関節に活動性を有する若年性特発性関節炎，全身型若年性特発性関節炎 ○キャッスルマン病に伴う諸症状及び検査所見（C 反応性タンパク高値，フィブリノーゲン高値，赤血球沈降速度亢進，ヘモグロビン低値，アルブミン低値，全身倦怠感）の改善。ただし，リンパ節の摘除が適応とならない患者に限る。 ○腫瘍特異的 T 細胞輸注療法に伴うサイトカイン放出症候群 （下線部追加）
用法・用量	○関節リウマチ，多関節に活動性を有する若年性特発性関節炎 通常，トシリズマブ（遺伝子組換え）として1回8 mg/kg を4週間隔で点滴静注する。 ○全身型若年性特発性関節炎，キャッスルマン病 通常，トシリズマブ（遺伝子組換え）として1回8 mg/kg を2週間隔で点滴静注する。なお，症状により1週間まで投与間隔を短縮できる。 ○サイトカイン放出症候群 通常，トシリズマブ（遺伝子組換え）として体重30 kg 以上は1回8 mg/kg，体重30 kg 未満は1回12 mg/kg を点滴静注する。 （下線部追加）
劇薬等の指定	
市販名及び有効成分・分量	
毒性	
副作用	副作用・臨床検査値異常発現率 関節リウマチ　585/601例 ＝97.3% 多関節に活動性を有する若年性特発性関節炎　18/19例 ＝94.7% 全身型若年性特発性関節炎　115/128例 ＝89.8% キャッスルマン病　33/35例 ＝94.3% 副作用・臨床検査値異常の種類　件数 ＜関節リウマチ＞ 鼻咽頭炎 960 血中コレステロール増加 331 頭痛 180 LDL 増加 167 血中トリグリセリド増加 136 ＜全身型若年性特発性関節炎＞ 鼻咽頭炎 278 上気道感染 129 胃腸炎 95 上気道の炎症 64 咽頭炎 58 等 ＜多関節に活動性を有する若年性特発性関節炎＞ 鼻咽頭炎 28 咽頭炎 11 上気道感染 10

	湿疹　6 上気道の炎症　5 等 ＜キャッスルマン病＞ 鼻咽頭炎　31 発疹　17 腹痛　11 そう痒症　10 好中球減少　9 頭痛　8 倦怠感　8 咽喉頭疼痛　7 下痢　7 TAT 上昇　7 トリグリセリド上昇　7　等 有害事象発現率[注)] サイトカイン放出症候群　28/28例 ＝100.0%（B2202試験） 15/15例 ＝100.0%（C2201試験） 有害事象の種類[注)]　例数 ＜サイトカイン放出症候群＞ （B2202試験） サイトカイン放出症候群　22 発熱　8 アスパラギン酸アミノトランスフェラーゼ増加　8 好中球数減少　8 低カリウム血症　8 （C2201試験） サイトカイン放出症候群　9 低血圧　9 血小板数減少　8 急性腎障害　6 貧血　6　等 注）B2202試験及び C2201試験においては，トシリズマブ投与に対する因果関係評価は実施していない。 （下線部追加）
会　　社	

アクテムラ点滴静注用80 mg，同200 mg，同400 mg（トシリズマブ（遺伝子組換え））

［サイトカイン放出症候群］

第1部　（モジュール1）：

申請書等行政情報及び添付文書に関する情報

1.12 添付資料一覧

中外製薬株式会社

第4部（モジュール4）　非臨床試験報告書　添付資料一覧

4.3 参考文献

CTD No.-資料番号	著者	表 題	掲載誌・その他	引用 CTD No.
4.3-1	Sato K, Tsuchiya M, Saldanha J, Koishihara Y, Ohsugi Y, Kishimoto T, et al.	Reshaping a human antibody to inhibit the interleukin 6-dependent tumor cell growth.	Cancer Res 1993;53:851-6.	2.4-1
4.3-2	Mihara M, Kasutani K, Okazaki M, Nakamura A, Kawai S, Sugimoto M, et al.	Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family.	Int Immunopharmacol 2005;5:1731-40.	2.4-2
4.3-3	Akira S, Hirano T, Taga T, Kishimoto T.	Biology of multifunctional cytokines: IL 6 and related molecules (IL 1 and TNF).	FASEB J 1990;4:2860-7.	2.4-3
4.3-4	Tanaka T, Narazaki M, Kishimoto T.	IL-6 in inflammation, immunity, and disease.	Cold Spring Harb Perspect Biol 2014;6:a016295.	2.4-4
4.3-5	van der Stegen SJ, Davies DM, Wilkie S, Foster J, Sosabowski JK, Burnet J, et al.	Preclinical in vivo modeling of cytokine release syndrome induced by ErbB-retargeted human T cells: identifying a window of therapeutic opportunity?	J Immunol 2013;191:4589-98.	2.4-5
4.3-6	Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E.	Monoclonal antibody-induced cytokine-release syndrome.	Expert Rev Clin Immunol 2009;5(5):499-521.	2.4-6
4.3-7	Bugelski PJ, Martin PL.	Concordance of preclinical and clinical pharmacology and toxicology of therapeutic monoclonal antibodies and fusion proteins: cell surface targets.	Br J Pharmacol 2012;166:823-46.	2.4-7

第5部（モジュール5）　臨床試験報告書　添付資料一覧

5.2 全臨床試験一覧表

CTD No.-資料番号	表 題	実施期間	実施場所（国内／海外）	掲載誌・その他	評価／参考の別
5.2	全臨床試験一覧表	―	―	社内資料	―

第5部（モジュール5）　臨床試験報告書　添付資料一覧

5.3 臨床試験報告書

CTD No.-資料番号	著者	表 題	実施期間	実施場所（国内／海外）	掲載誌・その他	評価／参考の別	申請電子データ有無
5.3.1　生物薬剤学試験報告書							
5.3.1.1　バイオアベイラビリティ(BA)試験報告書							
該当資料なし	－	－	－	－	－	－	－
5.3.1.2　比較BA試験及び生物学的同等性(BE)試験報告書							
該当資料なし	－	－	－	－	－	－	－
5.3.1.3　In Vitro-In Vivoの関連を検討した試験報告書							
該当資料なし	－	－	－	－	－	－	－
5.3.1.4 生物学的及び理化学的分析法検討報告書							
5.3.1.4-1	Hengst den C.D., Ph.D.	CTL019 PRA Study No. NPH074EL-140743-B Quantitative determination of free Tocilizumab in human serum samples by ECLA Method description and validation (DMPK-R1480009-pk)	－	海外	社内資料	評価	－
5.3.1.4-2	Hengst den C.D., Ph.D.	CTL019 PRA Study No. NPH074EL-140743-B Quantitative determination of free Tocilizumab in human serum samples by ECLA Method description and validation Amendment No. 1 (DMPK R1480009-pk-01)	－	海外	社内資料	評価	－
5.3.2　ヒト生体試料を用いた薬物動態関連の試験報告書							
該当資料なし	－	－	－	－	－	－	－

第5部（モジュール5）　臨床試験報告書　添付資料一覧

5.3 臨床試験報告書

CTD No.-資料番号	著者	表 題	実施期間	実施場所（国内／海外）	掲載誌・その他	評価／参考の別	申請電子データ有無
5.3.3　臨床薬物動態（PK）試験報告書							
該当資料なし	－	－	－	－	－	－	－
5.3.4　臨床薬力学（PD）試験報告書							
該当資料なし	－	－	－	－	－	－	－
5.3.5　有効性及び安全性試験報告書							
5.3.5.1　申請する適応症に関する比較対照試験報告書							
該当資料なし	－	－	－	－	－	－	－
5.3.5.2　非対照試験報告書							
5.3.5.2-1	－	A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia (ALL)	2015 年4 月[redacted]日～実施中	国内及び海外	ノバルティス社キムリア点滴静注申請資料	評価	－
5.3.5.2-2	－	A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia	2014 年8 月14 日～実施中	海外	ノバルティス社キムリア点滴静注申請資料	参考	－

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5.3 臨床試験報告書

CTD No.-資料番号	著者	表 題	実施期間	実施場所（国内／海外）	掲載誌・その他	評価／参考の別	申請電子データ有無
5.3.5.2-3	－	A Phase I/IIa Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR zeta and 4-1BB Signaling Domains in Patients with Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma	2012 年3 月[redacted] 日～実施中	海外	ノバルティス社キムリア点滴静注申請資料	参考	－
5.3.5.2-4	－	A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	2015 年7 月29 日～実施中	国内及び海外	ノバルティス社キムリア点滴静注申請資料	評価	－
5.3.5.3　複数の試験成績を併せて解析した報告書							
5.3.5.3-1	－	トシリズマブ用解析結果	－	国内及び海外	社内資料	評価	－
5.3.5.3-2	－	トシリズマブ用解析結果2　日本人部分集団解析	－	国内及び海外	社内資料	評価	－
5.3.5.3-3	－	トシリズマブ用解析結果3　C2201試験追加解析（データカットオフ日：2017年12月8日）	－	国内及び海外	社内資料	評価	－
5.3.5.4　その他の試験報告書							
5.3.5.4-1	－	Pilot study of redirected autologous T cells engineered to contain anti-CD19 attached to TCR-ζ and 4-1BB signaling domains in patients with chemotherapy resistant or refractory CD19+ leukemia and lymphoma	2010 年3 月[redacted] 日～2015 年7 月[redacted]日	海外	ノバルティス社キムリア点滴静注申請資料	参考	－

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5.3.6　市販後の使用経験に関する報告書							
該当資料なし	－	－	－	－	－	－	－
5.3.7　患者データー覧表及び症例記録							
5.3.7.1　症例一覧表							
5.3.7.1-1	－	症例一覧表（B2202試験）	－	国内及び海外	社内資料	評価	－
5.3.7.1-2	－	症例一覧表（C2201試験）	－	国内及び海外	社内資料	評価	－
5.3.7.2　有害事象症例一覧表							
5.3.7.2-1	－	有害事象症例一覧表(B2202試験)	－	国内及び海外	社内資料	評価	－
5.3.7.2-2	－	有害事象症例一覧表(C2201試験)	－	国内及び海外	社内資料	評価	－
5.3.7.2-3	－	有害事象症例一覧表(B2205J試験)	－	海外	社内資料	参考	－
5.3.7.2-4	－	有害事象症例一覧表(B2101J試験)	－	海外	社内資料	参考	－
5.3.7.2-5	－	有害事象症例一覧表(B2102J試験)	－	海外	社内資料	参考	－
5.3.7.3　重篤な有害事象症例一覧表							
5.3.7.3-1	－	重篤な有害事象症例一覧表(B2202試験)	－	国内及び海外	社内資料	評価	－
5.3.7.3-2	－	重篤な有害事象症例一覧表(C2201試験)	－	国内及び海外	社内資料	評価	－
5.3.7.3-3	－	重篤な有害事象症例一覧表(B2205J試験)	－	海外	社内資料	参考	－
5.3.7.3-4	－	重篤な有害事象症例一覧表(B2101J試験)	－	海外	社内資料	参考	－
5.3.7.3-5	－	重篤な有害事象症例一覧表(B2102J試験)	－	海外	社内資料	参考	－
5.3.7.4　臨床検査値異常変動症例一覧表							
5.3.7.4-1	－	臨床検査値異常変動症例一覧表（B2202試験）	－	国内及び海外	社内資料	評価	－

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5.3.7.4-2	－	臨床検査値異常変動症例一覧表（C2201試験）	－	国内及び海外	社内資料	評価	－
5.3.7.5　臨床検査値変動図							
5.3.7.5-1	－	臨床検査値変動図（B2202試験）	－	国内及び海外	社内資料	評価	－
5.3.7.5-2	－	臨床検査値変動図（C2201試験）	－	国内及び海外	社内資料	評価	－

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5.4 参考文献

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5.4-2	Doessegger L, Banholzer ML.	Clinical development methodology for infusion-related reactions with monoclonal antibodies.	Clin Transl Immunology. 2015 Jul 17;4(7).	2.5-2
5.4-3	Brudno JN, Kochenderfer JN.	Toxicities of chimeric antigen receptor T cells: recognition and management.	Blood. 2016 Jun 30;127(26):3321-30.	2.5-3
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5.4-6	Chen F, Teachey DT, Pequignot E, Frey N, Porter D, Maude SL, et al.	Measuring IL-6 and sIL-6R in serum from patients treated with tocilizumab and/or siltuximab following CAR T cell therapy.	J Immunol Methods. 2016 Jul;434:1-8.	2.5-6
5.4-7	Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al.	Chimeric antigen receptor-modified T cells foracute lymphoid leukemia.	N Engl J Med. 2013 Apr 18;368(16):1509-18.	2.5-7
5.4-8	Grupp SA, Maude SL, Shaw PA, Aplenc R, Barrett DM, Callahan C, et al.	Durable remissions in children with relapsed/refractory ALL treated with T cells engineered with a CD19-targeted chimeric antigen receptor (CTL019).	Blood. 2015;126(23):681.	2.5-8

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5.4-14	Reagan JL, Fast LD, Safran H, Nevola M, Winer ES, Castillo JJ, et al.	Cellular immunotherapy for refractory hematological malignancies.	J Transl Med. 2013 Jun 19;11:150.	2.5-14
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5.4-17	Food and Drug Administration (FDA)	FDA Briefing Document Oncologic Drugs Advisory Committee Meeting BLA 125646 Tisagenlecleucel 12-Jul-2017.	https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566166.pdf (accessed 2018-04-06)	2.5-17
5.4-18	Novartis	FDA Advisory Committee Briefing Docum ONCOLOGIC DRUGS ADVISORY COMMITTEE　Tisagenlecleucel (CTL019) 12-Jul-2017.	https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566168.pdf. (accessed 2018-04-06)	2.5-18
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5.4-31	Curran KJ, Riviere I, Silverman LB, Kobos R, Shukla N, Steinherz PG, et al.	Multi-center clinical trial of CAR T cells in pediatric/young adult patients with relapsed B-cell ALL.	Blood. 2015;126(23):2533.	2.5-31

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