レボレード錠 12.5mg，同 25mg
に関する資料

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「起源又は発見の経緯及び開発の経緯」等の資料

目　　次

目　　次 2
略号一覧 3
1　起原又は発見の経緯 4
2　再生不良性貧血について 4
2.1　臨床的／病態生理学的特性及び治療法 4
3　開発の経緯 5
4　特徴及び有用性 7
5　まとめ 9
6　参考文献 10

略号一覧

略号	省略していない表現 (英)	省略していない表現 (日)
AA	aplastic anemia	再生不良性貧血
ATG	anti-thymocyte globulin	抗ヒト胸腺細胞免疫グロブリン
CsA	ciclosporin	シクロスポリン
ITP	idiopathic thrombocytopenic purpura	特発性血小板減少性紫斑病
NIH	National Institute of Health	米国国立衛生研究所
PNH	paroxysmal nocturnal hemoglobinuria	発作性夜間ヘモグロビン尿症
QOL	Quality of life	生活の質
SAA	severe aplastic anemia	重症再生不良性貧血
TPO	thrombopoietin	トロンボポエチン
TPO-R	thrombopoietin-receptor	トロンボポエチン受容体

1 起原又は発見の経緯

エルトロンボパグ　オラミンは，エルトロンボパグの二モノエタノールアミン塩（以下，エルトロンボパグ）であり，経口投与可能なトロンボポエチン受容体（thrombopoietin-receptor，TPO-R）の低分子アゴニストである。エルトロンボパグは，TPO-との特異的な相互作用を介して，トロンボポエチン（thrombopoietin，TPO）のシグナル伝達経路の一部を活性化することにより骨髄前駆細胞から巨核球に至る過程における細胞の増殖および分化を促進させると考えられ（Erickson-Miller et al. 2010, Sun et al. 2012），健康成人男性及び慢性特発性血小板減少性紫斑病（chronic idiopathic thrombocytopenic purpura，慢性 ITP）患者を対象とした臨床試験において用量依存的に血小板数を増加させることが明らかとなっている。外国では，慢性 ITP の治療薬として 2008 年 11 月 20 日に米国で承認されて以来，慢性 ITP，C 型慢性肝炎患者のインターフェロン治療における血小板減少症に対する治療薬として，世界 95 ヵ国で承認されている。本邦では，グラクソ・スミスクライン社が 2009 年 9 月に国内及び海外臨床試験成績に基づき慢性 ITP の適応症に対する承認申請を行い，2010 年 10 月に製造販売承認を取得している（販売名：レボレード錠 12.5 mg，同 25 mg）。

また，TPO-R は血小板・巨核球系細胞だけでなく造血幹細胞や他の系統の前駆細胞にも発現していることから（Alexander et al. 1996），米国国立衛生研究所（National Institute of Health，NIH）のグループは，TPO の造血刺激作用による造血回復を期待して，免疫抑制療法に不応の重症再生不良性貧血（severe aplastic anemia，SAA）にエルトロンボパグを投与する試験（NIH 09-H-0154（ELT112523）試験，以下 154 試験）を実施し，約 40%に 1 系統以上の造血回復が得られること，造血回復が持続した一部の患者では投与中止後も骨髄細胞密度の正常化が維持することを明らかにした。本研究成果に基づき，GlaxoSmithKline 社（GSK 社）及び Novartis 社（エルトロンボパグの製造販売承認の承継会社）は製造販売承認申請を行い，米国では 2014 年 8 月，欧州では 2015 年 9 月に「免疫抑制療法抵抗性の重症再生不良性貧血」の適応で承認され，現在までに世界 30 ヵ国以上で承認されている。

なお，本邦では 2015 年 11 月にエルトロンボパグの製造販売承認はグラクソ・スミスクライン社よりノバルティスファーマ社に承継された。

2 再生不良性貧血について

2.1 臨床的／病態生理学的特性及び治療法

AA は，末梢血における汎血球減少と骨髄における細胞密度の低下を特徴とする症候群である。難治性疾患克服研究事業の臨床調査研究分野の対象疾患のうち医療費公的助成対象として特定疾患治療研究対象疾患に指定されており，本邦における総患者数は特定疾患医療受給者証所持者数及び特定疾患登録者証所持者数より 14009 人（2013 年）と推定されている。AA 患者（特に，重症例）は，かつては汎血球減少の遷延による感染症や出血により半年で 50%が死亡するとされて

いたが，抗菌剤，G-CSF，輸血等の支持療法が発達し，抗ヒト胸腺細胞免疫グロブリン（anti-thymocyte globulin，ATG）を含む免疫抑制療法や造血幹細胞移植が発症後早期に行われるようになり最近では予後が飛躍的に改善している。

AA の治療は，年齢，重症度，ドナーの有無，免疫抑制療法に対する反応性等によって決定される。AA に対する根治療法は骨髄移植であり，HLA 適合同胞ドナーを有する，やや重症～最重症の 40 歳未満の患者が移植適応となる。一方， 40 歳以上や HLA 適合同胞ドナーが得られない場合は ATG / シクロスポリン（ciclosporin，CsA）が第一選択となる。20～40 歳未満であっても移植に伴う治療関連死亡のリスクが高いため ATG / CsA が選択されるケースもある。本邦では 2008 年以降，ウサギ ATG を用いた免疫抑制療法が移植非適応の未治療例に対する標準治療として位置づけられている。しかしながら，ATG 治療には，1）投与後に血小板数が著減し，血小板輸血が必要となる，2）ウサギ ATG が以前使用可能であったウマ ATG の治療成績より優れているとの報告はなく，ウサギ ATG / CsA の 6 ヵ月時点の奏効率が 50%を上回る報告はほとんどない，3）60 歳以上の高齢者では ATG 治療の奏効率及び 5 年生存率は若年者に比べ低い等の問題があるため，ATG 治療に伴う血小板低下のコントロールの他，ATG / CsA の治療効果を向上し得る薬剤の開発が求められている。

また，ATG / CsA を行ったとしても重症例の約 3 割に治療抵抗性又は再発を認める。非重症例が自然寛解することはまれであり，無治療経過観察後に輸血依存性となった時点（診断から治療までの経過期間が長い）で ATG / CsA を行ったとしても奏効率は低い。現時点では免疫抑制療法が無効又は使用できない患者に対して確立された治療法はなく，輸血を中心とする支持療法が行われているのが現状である。多くの場合，定期的な輸血によって通常の社会生活は可能であるが，輸血には血小板輸血に対する不応性，輸血後感染症のリスク，輸血後鉄過剰症による心毒性，肝毒性，内分泌異常等の問題があるため，輸血療法に代わり得る治療法の確立が実地医療の場で求められている。

3 開発の経緯

エルトロンボパグの品質，毒性の試験成績については，ITP の承認申請時において提出済みである。AA に対する開発の経緯図を Figure 3-1 に示す。

Figure 3-1 開発の経緯図

国内	CETB115E1201 試験（E1201 試験）	[redacted]
	CETB115E1202 試験（E1202 試験）	
外国	NIH 09-H-0154 試験（154 試験）	
	NIH 13-H-0133 試験（133 試験）	
	NIH 12-H-0150 試験（150 試験）	
	薬物相互作用試験 RAD201583 試験（583 試験）	

データカットオフ：E1201 試験（各被験者の投与 52 週時点，▲は最終登録被験者の投与 52 週時点），E1202 試験（各被験者の投与 26 週及び 52 週時点，▲は最終登録被験者の投与 26 週及び 52 週時点），154 試験（20[redacted]年[redacted]月[redacted]日），133 試験（20[redacted]年[redacted]月[redacted]日），150 試験（20[redacted]年[redacted]月[redacted]日）

外国の開発状況

SAA 患者を対象としたエルトロンボパグの医師主導試験が NIH のグループにより実施された。治療抵抗性の SAA 患者を対象とした第 II 相試験（154 試験）は 2009 年 6 月，未治療の SAA 患者を対象とした第 I/II 相試験［NIH 12-H-0150 試験（150 試験）］は 2012 年 6 月，治療抵抗性の SAA 患者を対象とした第 II 相試験［NIH 13-H-0133 試験（133 試験）］は 2013 年 6 月より開始され，いずれもエルトロンボパグの開発会社であった GSK 社によって支援された。

154 試験の結果，エルトロンボパグは投与 12 週～16 週時点で約 40%に 1 系統以上の造血改善をもたらすことが明らかになったことから，GSK 社は治療抵抗性の SAA に対する効能･効果追加申請について FDA と協議し，米国では 154 試験の成績を主たる成績として 2014 年 2 月に効能･効果追加申請を行い，同年 8 月に「免疫抑制療法抵抗性の重症再生不良性貧血」の適応で承認を取得した。一方，欧州では，154 試験の成績に基づき，2014 年 11 月に米国と同様の効能･効果追加申請を行い，2015 年 9 月に承認を取得した。現在，エルトロンボパグは治療抵抗性の SAA 患者の治療薬として 30 ヵ国以上で承認されている。なお，2015 年 3 月にエルトロンボパグは GSK 社より Novartis 社に移管された。

また，外国人健康被験者を対象とした CsA との薬物相互作用試験［RAD201583 試験（583 試験）］では，エルトロンボパグ単独投与時及び CsA 併用時におけるエルトロンボパグの薬物動態を評価した。

未治療 SAA 患者を対象に ATG / CsA の治療効果に対するエルトロンボパグの上乗せ効果を検討する 150 試験で良好な中間成績が得られており，Novartis 社では未治療 SAA に対する効能･効果追加申請を現在計画中である。

国内の開発状況

国内では，154 試験の良好な中間成績が NIH の Olnes らのグループから発表されたことを受け（Olnes et al. 2012），グラクソ・スミスクライン社は免疫抑制療法抵抗性又は再発，もしくは ATG 療法を受けられない中等症以上の AA 患者を対象とした第 II/III 相試験［CETB115E1201 試験（E1201 試験）］を計画した。[redacted]にあたっては，医薬品医療機器総合機構と[redacted]等についての対面助言［[redacted]相談：実施日 20[redacted]年[redacted]月[redacted]日（受付番号[redacted]号）］を行い，[redacted]との見解が得られ，2014 年 7 月より試験を開始した。また，同対面助言並びに 20[redacted]年[redacted]月[redacted]日に実施した[redacted]相談（受付番号[redacted]号）では，[redacted]等についての相談を行い，[redacted]を得て，2015 年 5 月より試験を開始した。

以上を踏まえ，国内で実施された 2 試験（E1201 試験，E1202 試験）及び外国で実施された CsA との相互作用試験（583 試験）の成績を評価資料，外国で実施された医師主導試験 3 試験（154 試験，133 試験，150 試験）の成績を参考資料として臨床データパッケージを構成し，「再生不良性貧血」を予定効能又は効果として製造販売承認事項一部変更承認申請を行うこととした。

なお，エルトロンボパグは「再生不良性貧血」の適応に対する希少疾病用医薬品指定を 2016 年 11 月に受けた。

4 特徴及び有用性

エルトロンボパグは難治性再生不良性貧血の日本人患者の汎血球減少を改善する

E1201 試験では，エルトロンボパグを投与することにより，他に治療選択肢がない難治性 AA 患者の 47.6%（21 名中 10 名，投与 26 週時点）に 1 系統以上の血球改善効果を示した。また，投与継続により血球改善効果のさらなる向上が認められ，投与 52 週時点では反応例の 10 名中 4 名に 3 系統の血球改善が認められた。この結果は，免疫抑制療法に不応の SAA 患者を対象とした外国 154 試験の結果と同様であった。

エルトロンボパグはウサギ ATG / CsA との併用において，未治療再生不良性貧血の日本人患者の奏効率を向上させる

E1202 試験では，ウサギ ATG / CsA とエルトロンボパグの併用により 10 名中 7 名の被験者に奏効が得られた（投与 26 週時点）。この結果は，ウサギ ATG / CsA の公表論文に基づく奏効率（概ね 50 %）と比べて高い結果であった。微少発作性夜間ヘモグロビン尿症（paroxysmal nocturnal hemoglobinuria，PNH） 型血球が検出される例では，免疫抑制療法が奏効しやすいことが知られているが（再生不良性貧血診療の参照ガイド平成 26 年度改訂版），部分集団解析の結果では微

少 PNH 型血球の有無にかかわらず治療効果が示された。治療開始 3 ヵ月（14 週）時点の奏効率は 20%と低かったが，治療 26 週までに奏効を認めた被験者については，治療 14 週までに好中球数，網赤血球数が増加し，造血の回復傾向が示された。

エルトロンボパグは再生不良性貧血患者の輸血依存状態を解消する

E1201 試験では，エルトロンボパグを投与することにより輸血依存性の患者の 7 割以上で輸血量の減少が可能であった。また，血小板輸血依存であった 6 名中 4 名が非依存（輸血非依存状態が 28 日間以上持続）となり，赤血球輸血依存であった 19 名中 9 名が非依存（輸血非依存状態が 56 日間以上持続）となった。この結果は，免疫抑制療法に不応の SAA 患者を対象とした外国 154 試験の結果と同様であった。

E1202 試験では，ウサギ ATG / CsA とエルトロンボパグの併用により輸血依存性の患者の 7 割以上で輸血量の減少が可能であった。また，血小板輸血依存であった 8 名中 5 名が非依存（輸血非依存状態が 28 日間以上持続）となり，赤血球輸血依存であった 6 名中 4 名が非依存（輸血非依存状態が 56 日間以上持続）となった。

エルトロンボパグによる造血改善効果は長期間にわたり持続する

E1201 試験では，エルトロンボパグによる血液学的反応に持続性が認められ，反応例における効果持続期間の中央値は 9.12 ヵ月であった。また，投与 52 週までに明らかな再発は認められていない。データカットオフ時点で 8 名が Extension パートにて観察を継続中であり，効果持続期間はさらに延長する可能性が高い。この結果は，外国 154 試験において，免疫抑制療法に不応の SAA 患者を対象とした試験の結果と概ね類似していた。さらに，外国 154 試験では 3 系統の造血回復を認めた被験者（5 名）において，エルトロンボパグの漸減中止後も効果の持続が認められている（フォローアップ期間の中央値は 20.6 ヵ月）。

E1202 試験では，治療 26 週までに奏効を認めた被験者における効果持続期間の中央値は 2.33 ヵ月であり，治療 26 週までに再発は認められていない。奏効例はすべて Extension パートに移行した。治療 26 週までに奏効を認めた 7 名中 6 名は治療 52 週時点でも治療効果が持続しており，52 週解析のデータカットオフ時点での効果持続期間の中央値は 8.31 ヵ月であった。

エルトロンボパグは再生不良性貧血患者の骨髄細胞密度を正常化させる

外国 154 試験では，ベースライン時点で，反応例の多く（88%）は骨髄低形成であった。Extension パート期間中に 6 名がエルトロンボパグ投与開始の約 2 年後［中央値で 548.5（274～812）日］に正形成髄となり，他の 6 名でも骨髄細胞密度のベースラインからの改善が認められた。5 名では骨髄細胞密度に変化は認められなかった。エルトロンボパグの漸減中止後，正形成髄への改善を認めた 2 名が徐々に低形成になったが，いずれも 3 系統の造血改善は持続していた。

エルトロンボパグは経口剤であり，外来診療において利便性の高い薬剤である

造血刺激による AA の治療は，骨髄微小環境の造血前駆細胞や造血幹細胞を刺激する必要があるため治療には長期を要する。このため，経口投与可能なエルトロンボパグは AA の治療に対して利便性の高い薬剤である。

5 まとめ

移植非適応の難治性（治療抵抗性，再発，ATG 療法を受けられない患者を含む）の AA 患者に対する治療は輸血療法が中心となるが，輸血には一定のリスクを伴うため代替治療の確立が実地医療の場で求められている。一方，移植非適応の未治療の AA 患者に対する標準治療は ATG / CsA であるが，ATG 治療による血小板低下のコントロールに加え，現在使用可能なウサギ ATG / CsA の治療効果を向上し得る薬剤の開発が求められている。

国内 2 試験の結果から，エルトロンボパグは日本人 AA 患者の汎血球減少を改善するとともに，ウサギ ATG / CsA との併用において既存治療の治療効果を上回る結果が示された。また，輸血依存状態を解消する明らかなエビデンスが示されており，他の治療選択肢のない難治性 AA 患者の QOL を著しく改善し得る薬剤であると言える。また，日本人 AA 患者に対して，エルトロンボパグは良好な安全性プロファイルを示した。

したがって，エルトロンボパグは従来の免疫抑制療法のような AA の免疫病態に即した治療とは異なり，未分化な造血幹細胞に作用し造血を促進させるという新しい作用機序をもつ薬剤として有用であると考える。

以上より，下記の内容にて製造販売承認事項一部変更承認申請を行うこととした。なお，現行の本剤の承認内容からの追加部分を下線で示す。

【申請品目】

レボレード錠 12.5 mg，レボレード錠 25 mg

【一般名】

エルトロンボパグ オラミン

【効能又は効果（案）】

<u>1. 慢性特発性血小板減少性紫斑病</u>

<u>2. 再生不良性貧血</u>

【用法及び用量（案）】

<u>1. 慢性特発性血小板減少性紫斑病の場合</u>

通常、成人には、エルトロンボパグとして初回投与量 12.5mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、血小板数、症状に応じて適宜増減する。また、1 日最大投与量は 50mg とする。

<u>2. 再生不良性貧血の場合</u>

抗胸腺細胞免疫グロブリンで未治療の場合

抗胸腺細胞免疫グロブリンとの併用において、通常、成人には、エルトロンボパグとして75mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜減量する。

既存治療で効果不十分な場合

通常、成人には、エルトロンボパグとして初回投与量 25mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜増減する。また、1 日最大投与量は 100mg とする。

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1.6 外国における使用状況等に関する資料

目　次

目　次 2
表 一 覧 2
1 外国における使用状況等 3
2 外国の添付文書等の概要 3
2.1 米国の添付文書の概略 3
2.1.1 販売名，剤型，含量 3
2.1.2 効能・効果 3
2.1.3 用法・用量 4
2.1.4 禁忌 8
2.1.5 警告及び使用上の注意 8
2.2 EU 共通の添付文書の概略 10
2.2.1 販売名，剤型，含量 10
2.2.2 効能・効果 10
2.2.3 用法・用量 10
2.2.4 禁忌 15
2.2.5 警告及び使用上の注意 15

表 一 覧

Table 1-1 再生不良性貧血に対する主要国での承認状況 3
Table 2-1 慢性免疫性（特発性）血小板減少患者におけるエルトロンボパグの用量調整 5
Table 2-2 C 型慢性肝炎による血小板減少症を有する成人におけるエルトロンボパグの用量調整 6
Table 2-3 重症再生不良性貧血患者におけるエルトロンボパグの用量調整 7
Table 2-4 ITP 患者におけるエルトロンボパグの用量調整 11
Table 2-5 抗ウイルス療法中の HCV 患者におけるエルトロンボパグの用量調整 12
Table 2-6 重症再生不良性貧血患者におけるエルトロンボパグの用量調整 13

1 外国における使用状況等

米国では 2014 年 2 月に治療抵抗性の重症再生不良性貧血に対する効能･効果追加申請を行い，同年 8 月に承認を取得した。欧州では，2014 年 11 月に米国と同様の効能･効果追加申請を行い，2015 年 9 月に承認を取得した。2016 年 9 月 30 日時点で，慢性 ITP，C 型肝炎ウイルス感染に伴う血小板減少症，重症再生不良性貧血に対する治療薬として，世界 70 ヵ国以上で承認されている。また，2017 年 6 月現在，エルトロンボパグは治療抵抗性の重症再生不良性貧血に対する治療薬として 30 ヵ国以上で承認されている。主要国での承認状況を，Table 1-1 に示す。

Table 1-1 再生不良性貧血に対する主要国での承認状況

国名	販売名	承認年月	剤型・含量	効能・効果
米国	PROMACTA	2014 年 8 月	錠剤・12.5 mg，25 mg，50 mg，75 mg，100 mg 経口用懸濁剤・25 mg	免疫抑制療法に対する反応が不十分な重症再生不良性貧血の患者の治療
EU	REVOLADE	2015 年 9 月	錠剤・12.5 mg，25 mg，50 mg，75 mg 経口用懸濁剤・25 mg	免疫抑制療法による前治療が無効であった，または多数の前治療を行った患者で，造血幹細胞移植の適応がない成人の後天性重症再生不良性貧血

2 外国の添付文書等の概要

米国の添付文書（2017 年 7 月改訂）の概略を 2.1 項に，EU 共通の添付文書（2017 年 1 月改訂）の概略を 2.2 項に示す。

2.1 米国の添付文書の概略

改訂年月：2017 年 7 月

2.1.1 販売名，剤型，含量

販売名：PROMACTA

剤型・含量：錠剤・12.5 mg，25 mg，50 mg，75 mg，100 mg，経口用懸濁剤・25 mg

2.1.2 効能・効果

慢性 ITP 患者における血小板減少症の治療

エルトロンボパグは，コルチコステロイド，免疫グロブリンまたは脾臓摘出術に対する反応が不十分な慢性免疫性（特発性）血小板減少性紫斑病（ITP）を有する成人及び 1 歳以上の小児の患者において，血小板減少症の治療に用いる。

投与の制限；エルトロンボパグは，血小板減少の程度及び臨床状態からみて出血のリスクが高い ITP 患者に限って用いること。

C 型慢性肝炎患者における血小板減少症の治療

エルトロンボパグは，C 型慢性肝炎患者においてインターフェロン療法の開始及び継続を可能にするため，血小板減少症の治療に用いる。

投与の制限；

- エルトロンボパグは，血小板減少症の程度からみてインターフェロン療法の開始または継続が困な C 型慢性肝炎患者に限って用いること。
- C 型慢性肝炎の治療としてインターフェロンを併用しないで，直接作用型抗ウイルス薬とエルトロンボパグを併用した場合の安全性及び有効性は確立されていない。

重症再生不良性貧血

エルトロンボパグは，免疫抑制療法に対する反応が不十分な重症再生不良性貧血の患者の治療に用いる。

2.1.3 用法・用量

慢性免疫性（特発性）血小板減少症

出血のリスクを抑えるため，血小板数が 50 x 10^9/L 以上になり，その状態が維持される最小限の用量でエルトロンボパグを投与すること。用量は血小板数の反応に応じて調整すること。血小板数を正常化する目的でエルトロンボパグを用いてはならない。臨床試験では，血小板数は一般にエルトロンボパグの投与開始後 1～2 週間以内に上昇し，エルトロンボパグの投与中止後 1～2 週間以内に低下していた。

<u>初期用法・用量：</u>***成人及び 6 歳以上の小児の ITP 患者：***東アジア（中国，日本，台湾または韓国）系の患者または軽度から重度の肝機能障害（Child-Pugh 分類 A，B，C）を有する患者を除き，エルトロンボパグ 50 mg の 1 日 1 回投与で治療を開始する。

東アジア（中国，日本，台湾または韓国）系の ITP 患者では，初期用量を減量してエルトロンボパグ 25 mg の 1 日 1 回投与で治療を開始する。

軽度，中等度または重度の肝機能障害（Child-Pugh 分類 A，B，C）を有する ITP 患者では，初期用量を減量してエルトロンボパグ 25 mg の 1 日 1 回投与で治療を開始する。

肝機能障害（Child-Pugh 分類 A，B，C）を有する東アジア系の ITP 患者では，初期用量を減量してエルトロンボパグ 12.5 mg の 1 日 1 回投与で治療を開始することを考慮する。

1～5 歳の小児 ITP 患者：エルトロンボパグ 25 mg の 1 日 1 回投与で治療を開始する。

<u>患者の観察及び用量の調整：</u>治療開始後は出血リスク抑制の必要性に応じて，血小板数が 50 x 10^9/L 以上になり，その状態が維持されるよう用量を調整すること。1 日投与量は 75 mg を超えないこと。エルトロンボパグによる治療中は血液学的検査及び肝機能検査を定期的に実施し，Table 2-1 に示すように血小板数に基づいてエルトロンボパグの用量を変更すること。エルトロン

ボパグによる治療中は，血小板数が安定するまでは血小板数及び白血球分画を含む全血球計算を毎週実施すること。その後は血小板数及び白血球分画を含む全血球計算を毎月実施すること。
経口懸濁用粉末と錠剤を切り替えるときには，週 1 回の血小板数測定を 2 週間行い，その後は標準的な毎月の全血球検査を行うこと。

Table 2-1 慢性免疫性（特発性）血小板減少患者におけるエルトロンボパグの用量調整

血小板数の検査結果	用量調整または対応措置
エルトロンボパグを少なくとも 2 週間投与後に 50 x 10^9/L 未満	1 日投与量を 25 mg ずつ最大 75 mg/日まで増量。 1 日 1 回 12.5 mg を投与している患者では，1 日 1 回 25 mg に増量した後，25 mg ずつ増量する。
いずれの時点であれ 200 x 10^9/L～400 x 10^9/L	1 日投与量を 25 mg ずつ減量。この効果を評価するのに 2 週間待ち，必要に応じてさらに用量を調整。 1 日 1 回 25 mg を投与している患者では，1 日 1 回 12.5 mg に減量。
400 x 10^9/L 超	エルトロンボパグの投与を中断。血小板数の測定頻度を週 2 回に増加。 血小板数が 150 x 10^9/L 未満になった場合，1 日投与量を 25 mg 減量して投与を再開。 1 日 1 回 25 mg を投与している患者では，1 日投与量 12.5 mg で再開。
エルトロンボパグを最低用量で 2 週間投与後に 400 x 10^9/L 超	エルトロンボパグの投与を中止。

肝機能障害（Child-Pugh 分類 A，B，C）を有する ITP 患者では，エルトロンボパグの投与開始後，または増量後，3 週間待ってから増量すること。
併用している他の ITP 治療薬の用法・用量は医学的な必要性に応じて適宜変更し，エルトロンボパグによる治療中に血小板数が過度に上昇しないようにすること。エルトロンボパグの投与間隔が 24 時間以内にならないようにすること。
投与中止：最大 1 日投与量の 75 mg で 4 週間投与後も臨床的に重大な出血を抑えるのに十分なレベルまで血小板数が増加しない場合には，エルトロンボパグの投与を中止すること。血小板数が Table 2-1 に示すような過剰な反応を示した場合，または重大な肝機能検査値異常が認められた場合も，エルトロンボパグの投与を中止する必要がある。エルトロンボパグの投与中止後，少なくとも 4 週間は血小板数及び白血球分画を含む全血球計算を毎週実施すること。

C 型慢性肝炎に関連する血小板減少症

ペグインターフェロン及びリバビリンを用いた抗ウイルス療法を開始し継続するために必要な血小板数が達成され維持される最小限の用量でエルトロンボパグを投与すること。用量は血小板数の反応に応じて調整する。血小板数を正常化する目的でエルトロンボパグを用いてはならない。
臨床試験では，血小板数は一般にエルトロンボパグの投与開始後 1 週間以内に上昇し始めた。
初期用法・用量：エルトロンボパグ 25 mg の 1 日 1 回投与で治療を開始する。

患者の観察及び用量の調整：抗ウイルス療法の開始に必要な目標血小板数に達するまで必要に応じて 2 週間ごとに 25 mg ずつエルトロンボパグを増量する。抗ウイルス療法の開始前は血小板数を毎週測定すること。

抗ウイルス療法中は，ペグインターフェロンの減量を避けるようエルトロンボパグの用量を調整すること。抗ウイルス療法中は，血小板数が安定するまでは血小板数及び白血球分画を含む全血球計算を毎週実施すること。その後は血小板数を毎月測定すること。1 日投与量は 100 mg を超えないこと。エルトロンボパグによる治療中は血液学的検査及び肝機能検査を定期的に実施すること。

ペグインターフェロンまたはリバビリンの具体的な用量は，各薬剤の添付文書を参照すること。

Table 2-2 C 型慢性肝炎による血小板減少症を有する成人におけるエルトロンボパグの用量調整

血小板数の検査結果	用量調整または対応措置
エルトロンボパグを少なくとも 2 週間投与後に 50 x 10^9/L 未満	1 日投与量を 25 mg ずつ最大 100 mg/日まで増量。
いずれの時点であれ 200 x 10^9/L～400 x 10^9/L	1 日投与量を 25 mg ずつ減量。 この効果を評価するのに 2 週間待ち，必要に応じてさらに用量を調整。
400 x 10^9/L 超	エルトロンボパグの投与を中断。血小板数の測定頻度を週 2 回に増加。 血小板数が 150 x 10^9/L 未満になった場合，1 日投与量を 25 mg 減量して投与を再開。 1 日 1 回 25 mg を投与している患者では，1 日投与量 12.5 mg で再開。
エルトロンボパグを最低用量で 2 週間投与後に 400 x 10^9/L 超	エルトロンボパグの投与を中止。

投与中止：ペグインターフェロン及びリバビリンの添付文書では，治療無効の場合の抗ウイルス療法中止について推奨している。治療無効の場合の抗ウイルス療法中止に関する推奨は，ペグインターフェロン及びリバビリンの添付文書を参照すること。

抗ウイルス療法を中止した場合は，エルトロンボパグの投与を中止すること。血小板数が Table 2-2 に示すような過剰な反応を示した場合，または重大な肝機能検査値異常が認められた場合も，エルトロンボパグの投与を中止する必要がある。

重症再生不良性貧血

血液学的効果を達成し維持するための最小限の用量でエルトロンボパグを投与すること。用量は血小板数に応じて調整すること。血液学的効果を得るには通常 150 mg までの増量が必要であり，エルトロンボパグの投与開始から 16 週間を要することがある。

初期用法・用量：エルトロンボパグ 50 mg の 1 日 1 回投与で治療を開始する。

東アジア系の患者または軽度，中等度または重度の肝機能障害（Child-Pugh 分類 A，B，C）を有する患者では，初期用量を減量してエルトロンボパグ 25 mg の 1 日 1 回投与で治療を開始する。

患者の観察及び用量の調整：血小板数が目標の 50 x 10^9/L 以上になるよう必要に応じて 2 週間ごとにエルトロンボパグを 50 mg ずつ増量する。1 日投与量は 150 mg を超えないこと。エルトロンボパグによる治療中は血液学的検査及び肝機能検査を定期的に実施し，Table 2-3 に示すように血小板数に基づいてエルトロンボパグの用量を変更すること。

Table 2-3 重症再生不良性貧血患者におけるエルトロンボパグの用量調整

血小板数の検査結果	用量調整または対応措置
エルトロンボパグを少なくとも 2 週間投与後に 50 x 10^9/L 未満	1 日投与量を 50 mg ずつ最大 150 mg/日まで増量。 1 日 1 回 25 mg を投与している患者では，1 日 1 回 50 mg に増量した後，50 mg ずつ増量する。
いずれの時点であれ 200 x 10^9/L～400 x 10^9/L	1 日投与量を 50 mg ずつ減量。この効果を評価するのに 2 週間待ち，必要に応じてさらに用量を調整。
400 x 10^9/L 超	エルトロンボパグの投与を 1 週間中断。 血小板数が 150 x 10^9/L 未満になった場合，1 日投与量を 50 mg 減量して投与を再開。
エルトロンボパグを最低用量で 2 週間投与後に 400 x 10^9/L 超	エルトロンボパグの投与を中止。

輸血非依存を含め，8 週間以上にわたって 3 系統で効果が得られた患者では，エルトロンボパグの用量を 50%減量することができる。減量後 8 週間血球数が安定している場合は，エルトロンボパグを中止し血球数を観察すること。血小板数 30 x 10^9/L 未満，ヘモグロビン 9 g/dL 未満，または好中球数 0.5 x 10^9/L 未満に減少した場合は，エルトロンボパグを有効用量で再開することができる。

投与中止：エルトロンボパグを 16 週間投与しても血液学的効果が認められない場合は，エルトロンボパグを中止すること。新たな細胞遺伝学的異常が検出された場合は，エルトロンボパグの投与中止を考慮すること。血小板数が Table 2-3 に示すような過剰な反応を示した場合，または重大な肝機能検査値異常が認められた場合も，エルトロンボパグの投与を中止する必要がある。

投与方法

経口懸濁剤の調製：経口懸濁剤を投与する前に，必ず患者または介護者にエルトロンボパグ経口懸濁剤の適切な用法・用量及び調製について習熟させること。

経口懸濁剤は調製後直ちに投与すること。**調製後 30 分以内に投与しなかった懸濁剤は廃棄すること。**

懸濁剤の調製には水のみを用いること。注意：調製に湯を用いないこと。

懸濁剤の調製及び投与法の詳細については「**使用説明書**」を参照すること。

錠剤及び経口懸濁剤の投与：エルトロンボパグは空腹時（食事の 1 時間前または食事の 2 時間後）に服用すること。エルトロンボパグの服用は，他の薬剤（制酸剤等），カルシウムに富んだ食品（乳製品，カルシウム強化ジュース等）または多価陽イオン（鉄，カルシウム，アルミニウム，マグネシウム，セレン，亜鉛等）を含有するサプリメントの摂取前 2 時間以上または摂取後 4 時間以上間隔をあけること。
錠剤を粉砕して食物または液体と混合しないこと。
懸濁剤の調製には水のみを用いること。

2.1.4 禁忌

なし

2.1.5 警告及び使用上の注意

C 型慢性肝炎患者における肝代償不全

エルトロンボパグは，C 型慢性肝炎患者においてインターフェロン及びリバビリンと併用したとき，肝代償不全のリスクを増大させる可能性がある。C 型慢性肝炎及び血小板減少症を有する患者の比較臨床試験 2 試験において，腹水及び脳症の発現頻度はプラセボ及び抗ウイルス療法群（4%）よりエルトロンボパグ及び抗ウイルス療法群（7%）の方が高かった。エルトロンボパグ及び抗ウイルス療法群で，ベースラインにおいて低アルブミン値（3.5 g/L 以下）または末期肝疾患モデル（MELD）スコア 10 以上であった患者は，肝代償不全のリスクがより高かった。抗ウイルス療法を中止した場合はエルトロンボパグを中止すること。

肝毒性

エルトロンボパグの投与により重症及び生命を脅かす可能性のある肝毒性のリスクを増大させる可能性がある。エルトロンボパグ投与開始前，及び用量調整期は 2 週間ごと，用量確定後は 1 ヵ月ごとに，血清 ALT，AST 及びビリルビン値を測定すること。エルトロンボパグは UDP-グルクロン酸転移酵素（UGT）1A1 及び有機アニオン輸送ポリペプチド（OATP）1B1 を阻害するため，高間接ビリルビン血症に至ることがある。ビリルビン値が上昇している場合はビリルビン分画検査も実施すること。血清肝機能検査値異常が認められた場合には，3～5 日以内に再検査を実施すること。異常が確認された場合は，値が正常化または安定化するまで，血清肝機能検査を毎週実施すること。ALT 値が上昇し［肝機能正常の患者では正常値上限の 3 倍以上，投与前にトランスアミナーゼが上昇していた患者ではベースライン値の 3 倍以上（もしくは正常値上限の 5 倍超で低い方）］，かつ以下のいずれかに該当する場合はエルトロンボパグの投与を中止すること。

- 進行性である
- 4 週間以上持続
- 直接ビリルビンの上昇を伴う
- 肝障害の臨床症状または肝代償不全の徴候を伴う

エルトロンボパグ再投与の有益性が肝毒性発現のリスクを上回ると判断される場合にのみエルトロンボパグの投与を注意深く再開し，用量調整期には血清肝機能検査を週 1 回実施すること。エルトロンボパグの再投与により肝毒性が再度発現する可能性がある。肝機能検査値異常が持続，悪化または再発したならば，エルトロンボパグの投与は完全に中止すること。

重症の肝障害が臨床試験でまれに認められている。エルトロンボパグの投与開始の約 3 ヵ月後に肝機能検査値の上昇が認められ，全ての症例でエルトロンボパグの投与を中断することにより回復した。

血栓性／血栓塞栓性合併症

血栓性／血栓塞栓性合併症はエルトロンボパグ投与による血小板数増加に起因する可能性がある。報告された血栓性／血栓塞栓性合併症には静脈性及び動脈性事象の両者が含まれ，血小板数が低値または正常値でも認められた。

血栓塞栓症の既知の危険因子（第 V 因子ライデン，ATIII 欠損症，抗リン脂質抗体症候群，慢性肝疾患等）を有する患者にエルトロンボパグを投与するときは，血栓塞栓症のリスクが増大する可能性を考慮すること。血栓性／血栓塞栓性合併症のリスクを抑えるため，血小板数を正常化する目的でエルトロンボパグを使用しないこと。目標血小板を達成し維持するための用量調整ガイドラインに従うこと。

C 型慢性肝炎及び血小板減少症を有する患者の臨床比較試験 2 試験で，エルトロンボパグ投与群の 3%（31/955）及びプラセボ群の 1%（5/484）に血栓性事象が発現した。大部分が門脈系の事象であった（エルトロンボパグ群 1%，プラセボ群 1%未満）。

ITP に関連しない血小板減少症及び慢性肝疾患を有し，待機的に侵襲的治療を実施する患者の比較試験（N = 292）において，エルトロンボパグ 75 mg を 1 日 1 回投与した患者で血栓性事象のリスクが高まった。エルトロンボパグ投与群で 7 件（6 例），プラセボ群で 3 件（2 例）の血栓性合併症が発現した。エルトロンボパグ投与群で発現した血栓性合併症はすべて門脈血栓症（PVT）であった。PVT の症状には，腹痛，悪心，嘔吐，下痢が含まれた。エルトロンボパグ投与群の 6 例中 5 例は，エルトロンボパグの最終投与後 30 日以内で，血小板数 200 x 10^9/L 超のときに血栓性合併症を発現した。血小板減少症を有する慢性肝疾患患者に侵襲的治療の準備としてエルトロンボパグ 75 mg を 1 日 1 回，2 週間投与すると，門脈血栓症のリスクが増大した。

白内障

成人慢性 ITP 患者における比較臨床試験 3 試験では，エルトロンボパグの 1 日 50 mg 投与群の 15 例（7%），プラセボ群の 8 例（7%）で白内障が発現または悪化した。長期継続投与試験では，エルトロンボパグによる治療開始前に眼の検査を実施した患者の 11%で白内障の発現または悪化が認められた。C 型慢性肝炎及び血小板減少症を有する患者の臨床比較試験 2 試験では，エルトロンボパグ投与群の 8%，プラセボ群の 5%で白内障が発現または悪化した。

げっ歯類を用いたエルトロンボパグの毒性試験で白内障が認められた。エルトロンボパグ投与開始前に眼の検査を実施し，エルトロンボパグによる治療中も定期的に検査を実施し，白内障の徴候・症状がないか観察すること。

2.2 EU 共通の添付文書の概略

改訂年月日：2017 年 1 月

2.2.1 販売名，剤型，含量

販売名：REVOLADE

剤型・含量：錠剤・12.5 mg，25 mg，50 mg，75 mg，経口用懸濁剤・25 mg

2.2.2 効能・効果

他の治療法（副腎皮質ステロイド，免疫グロブリン等）では効果がない，1 歳以上の慢性免疫性（特発性）血小板減少性紫斑病（ITP）

適切なインターフェロン療法の開始または維持を妨げる主な要因が血小板減少症である，成人の慢性 C 型肝炎ウイルス（HCV）感染症における血小板減少症

免疫抑制療法による前治療が無効であった，または多数の前治療を行った患者で，造血幹細胞移植の適応がない成人の後天性重症再生不良性貧血（SAA）

2.2.3 用法・用量

エルトロンボパグによる治療は血液疾患または C 型慢性肝炎及び合併症の治療の経験がある医師の管理下で行う。

用量

エルトロンボパグの用量は各患者の血小板数に基づいて調整しなければならない。エルトロンボパグによる治療の目的は血小板数を正常化することではない。

経口懸濁用粉末では錠剤よりエルトロンボパグの曝露量が高くなる可能性がある。経口懸濁用粉末と錠剤を切り替えるときには，週 1 回の血小板数測定を 2 週間行う。

慢性免疫性（特発性）血小板減少症

血小板数が 50,000/μl 以上になり，その状態が維持される最少用量を投与すること。血小板数に応じて用量を調整する。血小板数を正常化するために使用してはならない。臨床試験では血小板数は概ねエルトロンボパグの投与開始後 1～2 週間で増加し，中止後 1～2 週間で減少した。

成人及び 6～17 歳の小児

推奨開始用量は 1 日 1 回 50 mg（エルトロンボパグとして）である。東アジア系の患者（中国人，日本人，台湾人，韓国人，タイ人等）では開始用量を 1 日 1 回 25 mg に減量する。

1～5 歳の小児

推奨開始用量は 1 日 1 回 25 mg（エルトロンボパグとして）である。

患者の観察及び用量の調整

治療開始後は出血リスク抑制の必要性に応じて，血小板数が 50,000/µl 以上になり，その状態が維持されるよう用量を調整すること。1 日投与量は 75 mg を超えない。

エルトロンボパグ投与中は定期的に血液学的検査及び肝機能検査を実施し，Table 2-4 の目安に従って血小板数に基づいてエルトロンボパグの用量を調整する。エルトロンボパグ投与中は血小板数及び末梢血塗抹検査を含む全血球計算（FBC）を血小板数が安定（50,000/µl 以上が 4 週間以上持続）するまで週 1 回実施する。その後は血小板数及び末梢血塗抹検査を含む FBC を月 1 回実施する。

Table 2-4 ITP 患者におけるエルトロンボパグの用量調整

血小板数	用量調整または対応
投与開始後 2 週間以上経過して 50,000/µl 未満の場合	1 日量を 25 mg ずつ，最高 75 mg/日まで増量する*。
50,000/µl 以上～150,000/µl 以下	出血を予防または減少させる血小板数を維持するためエルトロンボパグ及び併用 ITP 治療薬の最低用量を投与する。
150,000/µl 超～250,000/µl 以下	1 日量を 25 mg ずつ減量する。2 週間待って減量及びその後の用量調整の効果を評価する♦。
250,000/µl 超	エルトロンボパグの投与を中止する。血小板数測定の頻度を週 2 回に増やす。 血小板数が 100,000/µl 以下になったら，1 日量を 25 mg 減らして投与を再開する。

*；25 mg を隔日投与している患者では，1 日 1 回 25 mg に増量する。

♦；1 日 1 回 25 mg を投与している患者では，1 日 1 回 12.5 mg にするか，25 mg を隔日投与にするか検討する。

エルトロンボパグは他の ITP 治療薬と併用することができる。エルトロンボパグ投与中に血小板数が過度に増加しないように併用 ITP 治療薬の用量を適切に調整する。

2 週間以上待って血小板数に対する用量調整の効果を評価し，次の用量調整を検討する。

減量する場合も増量する場合も，エルトロンボパグの増減量は 1 日 1 回 25 mg とする。

投与中止

1 日 1 回 75 mg で投与開始後 4 週間経過しても臨床的に重要な出血を予防するのに十分な血小板数に達しない場合，エルトロンボパグの投与を中止する。

担当医は患者を定期的に診察し，患者ごとに治療の継続の必要性を判断する。脾臓摘出を受けていない患者では，脾臓摘出と比較して判断する。投与中止後，血小板減少症が再発する可能性がある。

C 型慢性肝炎（HCV）に関連した血小板減少症

エルトロンボパグと抗ウイルス薬を併用する場合は，各併用薬の詳細な添付文書の関連する安全性情報または禁忌の詳細を参照する。

臨床試験では血小板数は概ねエルトロンボパグの投与開始後 1 週間で増加し始める。エルトロンボパグ投与の目的は，臨床的推奨に従って抗ウイルス療法を開始するのに必要な最低限の血小板数を達成することである。抗ウイルス療法中のエルトロンボパグ投与の目的は，出血性合併症のリスクを抑えるのに必要な血小板数（通常は 50,000～75,000/µl）を維持することである。75,000/µl 超の血小板数は避ける。目標達成に必要な最少用量を投与する。用量調整は血小板数の反応に基づく。

投与開始

開始用量は 1 日 1 回 25 mg（エルトロンボパグとして）とする。東アジア系の HCV 患者または肝機能障害が軽度である患者では用量調整は必要ない。

患者の観察及び用量の調整

抗ウイルス療法の開始に必要な目標血小板数に達するまで 2 週間ごとに 25 mg 増量する。抗ウイルス療法開始前は 1 週間に 1 回血小板数を測定する。抗ウイルス療法開始時に血小板数が減少することがあるので，エルトロンボパグを直ちに減量することは避ける。（Table 2-5）。

抗ウイルス療法中は出血リスクをもたらすような血小板数減少によりペグインターフェロンを減量することがないよう，必要に応じて用量を調整すること（Table 2-5）。抗ウイルス療法開始後は血小板数が安定（通常は 50,000～75,000/µl）するまで，1 週間に 1 回血小板数を測定する。その後は血小板数及び末梢血塗抹検査を含む FBC を月 1 回実施する。血小板数が必要な目標値を超えた場合は，1 日投与量を 25 mg 減量することを考慮する。2 週間待って減量及びその後の用量調整の効果を評価することが推奨される。

1 日投与量は 100 mg を超えない。

Table 2-5 抗ウイルス療法中の HCV 患者におけるエルトロンボパグの用量調整

血小板数	用量調整または対応
投与開始後 2 週間以上経過して 50,000/µl 未満の場合	1 日量を 25 mg ずつ，最高 100 mg/日まで増量する。
50,000/µl 以上～100,000/µl 以下	ペグインターフェロンの減量を避けるために必要なエルトロンボパグの最低用量を投与する。
100,000/µl 超～150,000/µl 以下	1 日量を 25 mg ずつ減量する。2 週間待って減量及びその後の用量調整の効果を評価する♦。
150,000/µl 超	エルトロンボパグの投与を中止する。血小板数測定の頻度を週 2 回に増やす。 血小板数が 100,000/µl 以下になったら，1 日量を 25 mg 減らして投与を再開する*。

*；1 日 1 回 25 mg を投与している患者では，25 mg 隔日投与で再開することを検討する。

♦；抗ウイルス療法を開始すると血小板数が減少することがあるため，エルトロンボパグを直ちに減量することは避ける。

投与中止

エルトロンボパグ 100 mg を 2 週間投与して，抗ウイルス療法の開始に必要な血小板数に達しない場合は，エルトロンボパグを中止すること。

抗ウイルス療法を中止したときは，他に正当な理由がない限りエルトロンボパグを中止する。血小板数が過度に増加した場合，または重要な肝機能検査値の異常があった場合もエルトロンボパグの中止が必要である。

重症再生不良性貧血

投与開始

エルトロンボパグの開始用量は 1 日 1 回 50 mg である。東アジア系の患者では 1 日 1 回 25 mg に減量して開始する。第 7 染色体に細胞遺伝学的異常がある患者にはエルトロンボパグを投与しないこと。

患者の観察及び用量の調整

血液学的効果を得るには一般的に 150 mg までの用量調整が必要であり，エルトロンボパグ開始後 16 週間を要することがある。目標血小板数（50,000/µl 以上）に達するまで必要に応じて 2 週間ごとに 50 mg 増量する。1 日 1 回 25 mg を投与している患者では，1 日 1 回 50 mg に増量した後，50 mg ずつ増量する。1 日投与量は 150 mg を超えないこと。エルトロンボパグ投与中は定期的に血液学的検査及び肝機能検査を実施し，Table 2-6 の目安に従って血小板数に基づいてエルトロンボパグの用量を調整する。

Table 2-6 重症再生不良性貧血患者におけるエルトロンボパグの用量調整

血小板数	用量調整または対応
投与開始後 2 週間以上経過して 50,000/µl 未満の場合	1 日量を 50 mg ずつ，最高 150 mg/日まで増量する。 1 日 1 回 25 mg を投与している患者では，1 日 1 回 50 mg に増量した後，50 mg ずつ増量する。
50,000/µl 以上～150,000/µl 以下	血小板数を維持するためエルトロンボパグの最低用量を投与する。
150,000/µl 超～250,000/µl 以下	1 日量を 50 mg ずつ減量する。2 週間待って減量及びその後の用量調整の効果を評価する。
250,000/µl 超	エルトロンボパグの投与を 1 週間以上中止する。 血小板数が 100,000/µl 以下になったら，1 日量を 50 mg 減らして投与を再開する。

3 系統（白血球，赤血球，血小板）奏効患者における減量

輸血非依存を含め，8 週間以上にわたって 3 系統で効果が得られた患者では，エルトロンボパグの用量を 50%減量することができる。

減量後 8 週間血球数が安定している場合は，エルトロンボパグを中止し血球数を観察する。血小板数 30,000/µl 未満，ヘモグロビン 9 g/dL 未満，または好中球数 0.5×10^9/L 未満に減少した場合は，エルトロンボパグを有効用量で再開する。

投与中止

エルトロンボパグを 16 週間投与しても血液学的効果が認められない場合は，エルトロンボパグを中止する。新たな細胞遺伝学的異常が検出された場合は，エルトロンボパグの継続が適切であるか評価すること。血小板数が過度に増加した場合（Table 2-6 に目安を示す），または重要な肝機能検査値の異常があった場合もエルトロンボパグの中止が必要である。

特別な患者集団

腎機能障害

腎機能障害患者ではエルトロンボパグの用量を調整する必要はない。腎機能障害患者には慎重に投与し，血清クレアチニン検査及び尿検査等を実施して十分に観察する。

肝機能障害

期待される有益性が特定されている門脈血栓症の危険性を上回らない限り，肝機能障害（Child-Pugh スコア 5 以上）のある ITP 患者にはエルトロンボパグを投与しない。

肝機能障害のある ITP 患者にエルトロンボパグの投与が必要な場合，開始用量は 1 日 1 回 25 mg としなければならない。肝機能障害患者ではエルトロンボパグの投与開始後，用量を増量するまで 3 週間の間隔をおく。

軽度の肝機能障害（Child-Pugh スコア 6 以下）及び C 型慢性肝炎を有する血小板減少症患者ではエルトロンボパグの用量を調整する必要はない。C 型慢性肝炎患者及び肝機能障害を有する重症再生不良性貧血患者では，エルトロンボパグの開始用量は 1 日 1 回 25 mg としなければならない。肝機能障害患者ではエルトロンボパグの投与開始後，用量を増量するまで 2 週間の間隔をおく。

侵襲的治療の準備として，または HCV 患者の抗ウイルス療法を行うため，進行性の慢性肝疾患を有する血小板減少症患者にエルトロンボパグを投与すると，肝代償不全及び血栓塞栓性事象等の有害事象の危険性が増大することが知られている。

高齢者

65 歳以上の ITP 患者にエルトロンボパグを投与したときのデータは限られており，85 歳を超える ITP 患者では臨床使用経験がない。エルトロンボパグの臨床試験において，65 歳以上の被験者と 65 歳未満の被験者でエルトロンボパグの安全性に臨床的に有意な差はなかった。その他の臨床使用経験でも高齢者と非高齢者の間で反応に差は認められなかったが，高齢者の中に感受性が高い患者がいることは否定できない。

75 歳を超える HCV 患者及び SAA 患者にエルトロンボパグを投与したときのデータは限られており，これらの患者には慎重に投与する。

東アジア系の患者

肝機能障害の患者を含め，東アジア系の患者（中国人，日本人，台湾人，韓国人，タイ人等）の場合，開始用量を 1 日 1 回 25 mg とする。

血小板数の検査を継続し，その後は標準的な基準に従って用量を調整する。

小児

安全性及び有効性のデータが十分にないため 1 歳未満の慢性 ITP の小児への投与は推奨しない。慢性 HCV に関連する血小板減少症，又は重症再生不良性貧血の小児（18 歳未満）におけるエルトロンボパグの有効性及び安全性は確立していない。データが得られていない。

投与方法

錠剤を経口投与する。

制酸剤，乳製品（またはその他のカルシウムを含む食品），または多価陽イオン（鉄，カルシウム，マグネシウム，アルミニウム，セレン，及び亜鉛等）を含むミネラル栄養補助食品等の製品を摂取する前 2 時間以上または摂取後 4 時間以上の間隔をおいて服用する。

2.2.4 禁忌

エルトロンボパグの成分又は添加剤に対する過敏症のある患者

2.2.5 警告及び使用上の注意

低アルブミン値（35 g/L 以下）または末期肝疾患モデル（MELD）スコア 10 以上で定義される進行性慢性肝疾患を有する，血小板減少性 HCV 患者では，エルトロンボパグとインターフェロン治療を併用したとき，致死的となり得る肝代償不全及び血栓塞栓性事象等の副作用の危険性が増大する。さらにこれらの患者（特にベースラインのアルブミンが 35 g/L 以下の患者）ではプラセボと比較したウイルス学的著効（SVR）達成率でみた治療の有益性は，群全体と比べてわずかである。これらの患者におけるエルトロンボパグの投与開始は進行性 HCV の管理に熟練した医師のみが行い，血小板減少症の危険性または抗ウイルス治療を控えることの危険性が介入を必要とする場合に限る。臨床的にエルトロンボパグの適応と考えられる場合は，患者の厳密な監視が必要である。

<u>直接作用型抗ウイルス薬との併用</u>

C 型慢性肝炎の治療に承認されている直接作用型抗ウイルス薬との併用の安全性及び有効性は確立していない。

<u>肝毒性の危険性</u>

エルトロンボパグの投与により肝機能異常及び死亡の可能性のある重篤な肝障害が発現することがある。慢性 ITP におけるエルトロンボパグの臨床比較試験において血清中アラニンアミノトランスフェラーゼ（ALT），アスパラギン酸アミノトランスフェラーゼ（AST）及びビリルビンの上昇が認められた。

これらの所見の大部分は軽度（グレード 1～2）で可逆性であり，肝機能障害を示唆するような重大な臨床症状は認められなかった。成人慢性 ITP におけるプラセボ対照試験 3 試験で，プラセ

ボ群の 1 例及びエルトロンボパグ群の 1 例にグレード 4 の肝機能検査値異常が認められた。小児慢性 ITP 患者（年齢 1～17 歳）におけるプラセボ対照試験 2 試験で，正常上限（ULN）の 3 倍以上の ALT 上昇が，エルトロンボパグ投与群及びプラセボ群のそれぞれ 4.7%及び 0%に報告された。

HCV 患者における比較試験 2 試験で，ULN の 3 倍以上の ALT または AST 上昇が，エルトロンボパグ投与群の 34%，及びプラセボ群の 38%で報告された。エルトロンボパグとペグインターフェロン／リバビリン治療を併用した患者の大部分に高間接ビリルビン血症が発現する。全体では ULN の 1.5 倍以上の総ビリルビン値がエルトロンボパグ投与群の 76%，及びプラセボ群の 50%で報告された。

エルトロンボパグの投与開始前，用量調整期間中は2週間に1回，維持用量到達後は月に1回，血清中 ALT，AST，及びビリルビンを測定する。エルトロンボパグは UGT1A1 及び OATP1B1 を阻害するため，高間接ビリルビン血症に至ることがある。ビリルビンが上昇した場合，分画測定を行う。肝機能検査値異常は 3～5 日以内に再検査を実施して評価する。異常値が確認された場合，異常値が消失または安定化するか，投与開始前値に戻るまで肝機能検査を実施する。ALT 値が上昇（肝機能正常の患者では正常上限の 3 倍以上，投与前にトランスアミナーゼが上昇していた患者ではベースライン値の 3 倍以上もしくは ULN の 5 倍超で低い方）し，かつ以下のいずれかに該当する場合は，エルトロンボパグの投与を中止する。

- 進行性である，あるいは
- 4 週間以上持続する，あるいは
- 直接ビリルビンの上昇を伴う，あるいは
- 肝機能障害の臨床症状または肝代償不全の徴候を伴う

肝疾患を有する患者には慎重に投与する。ITP 及び SAA の患者では低用量で開始する。肝機能障害を有する患者に投与する場合は，厳密に監視する必要がある。

<u>肝代償不全（インターフェロンとの併用）</u>

C 型慢性肝炎患者における肝代償不全：ベースラインで低アルブミン値（35 g/L 以下）または MELD スコア 10 以上の患者では観察が必要である。

肝硬変を有する慢性 HCV 患者はアルファインターフェロン療法を行ったときに肝代償不全の危険性がある。血小板減少症のある HCV 患者を対象とした比較試験 2 試験で，肝代償不全（腹水，肝性脳症，静脈瘤出血，特発性細菌性腹膜炎）の発現頻度はプラセボ群（6%）よりエルトロンボパグ投与群（11%）の方が高かった。ベースラインにおいて低アルブミン値（35 g/L 以下）または MELD スコア 10 以上であった患者では，より軽症の肝疾患患者と比較して，肝代償不全の危険性が 3 倍上昇し，死に至る有害事象の危険性が上昇した。さらにこれらの患者（特にベースラインのアルブミンが 35 g/L 以下の患者）ではプラセボと比較した SVR 達成率でみた，治療

の有益性は群全体と比べてわずかである。期待される有益性と危険性を比較し慎重に検討した場合に限って，エルトロンボパグを投与する。肝代償不全の徴候及び症状を厳密に監視する。各インターフェロンの添付文書で中止基準を参照する。肝代償不全のために抗ウイルス療法を中止した場合はエルトロンボパグを中止する。

血栓性／血栓塞栓性合併症

血小板減少症を伴い，インターフェロン療法を受けている HCV 患者を対象とした比較試験（n=1,439）で，エルトロンボパグ投与群 955 例中 38 例（4%）及びプラセボ群 484 例中 6 例（1%）に血栓塞栓性事象（TEE）が発現した。報告された血栓性／血栓塞栓性合併症には静脈性及び動脈性事象の両者が含まれた。TEE の大部分は非重篤であり，試験終了までに回復した。両群で最も発現頻度が高かった TEE は門脈血栓症であった（エルトロンボパグ投与群 2%，プラセボ群 1%未満）。治療開始と TEE の事象の間に特別な時間的な関係は認められなかった。低アルブミン値（35 g/L 以下）または MELD スコア 10 以上であった患者では，よりアルブミン値が高かった患者と比べて TEE の危険性が 2 倍高かった。60 歳以上の患者では，より若年の患者と比べて TEE の危険性が 2 倍高かった。これらの患者では，期待される有益性と危険性を比較し慎重に検討した場合に限って，エルトロンボパグを投与する。TEE の徴候及び症状を厳密に監視する。

慢性肝疾患患者に侵襲的治療の準備として 1 日 1 回 75 mg を 2 週間投与すると，TEE の危険性が増大することが知られている。エルトロンボパグを投与した成人慢性肝疾患患者 143 例中 6 例（4%）に TEE（すべて門脈系）が発現し，プラセボ群 145 例中 2 例（1%）に TEE が発現した（門脈系 1 例，心筋梗塞 1 例）。エルトロンボパグ投与群の 6 例中 5 例は，エルトロンボパグの最終投与後 30 日以内で，血小板数 200,000/μl 超のときに血栓性合併症を発現した。侵襲的治療の準備として慢性肝疾患患者の血小板減少症を治療する場合，エルトロンボパグの適応はない。

ITP におけるエルトロンボパグの臨床試験では血小板数が低値，正常範囲内で血栓塞栓性事象が認められた。遺伝性（第 V 因子ライデン等）または後天性（ATIII 欠損症，抗リン脂質抗体症候群等）の危険因子，高齢，長期間の寝たきり状態，悪性腫瘍，避妊薬及びホルモン補充療法，手術／外傷，肥満，及び喫煙等の血栓塞栓症の危険因子を有する患者にエルトロンボパグを投与する場合は注意を要する。血小板数を厳密に監視し，目標値を上回った場合はエルトロンボパグを減量するか，投与を中止する。原因にかかわらず血栓塞栓性事象（TEE）の危険性がある患者ではリスクベネフィットバランスを検討する。

期待される有益性が特定されている門脈血栓症の危険性を上回らない限り，肝機能障害（Child-Pugh スコア 5 以上）を伴う ITP 患者にはエルトロンボパグを投与しない。肝機能障害を有する患者に対して投与が適切であると考えられる場合は，慎重に投与する。

エルトロンボパグの投与中止後の出血

ITP 患者ではエルトロンボパグの投与中止後，血小板減少症が再発する可能性がある。エルトロンボパグの投与中止後，血小板数は大部分の患者で 2 週間以内に投与開始前値に戻り，出血の危険性が高くなり，出血をきたす場合もある。抗凝血剤または抗血小板剤の投与中にエルトロンボパグを中止するとこの危険性が増大する。エルトロンボパグの投与を中止したら，最新の治療ガイドラインに従って ITP の治療を再開することが望ましい。さらに医学的管理として抗凝血剤及び抗血小板剤の中止，抗凝固活性の中和，または血小板輸血等がある。エルトロンボパグの投与中止後 4 週間は週 1 回血小板数を測定しなければならない。

HCV の臨床試験で，ペグインターフェロン，リバビリン，及びエルトロンボパグの中止後に，重篤及び死に至る例を含め，胃腸出血の発現頻度が上昇した。治療中止後は患者に胃腸出血の徴候または症状がないか観察する。

骨髄レチクリン形成及び骨髄線維症の危険性

エルトロンボパグは骨髄でレチクリン線維の形成または進行の危険性を増大させる可能性がある。他のトロンボポエチン受容体（TPO-R）作動薬と同様，この所見の関連性はまだ確立していない。

エルトロンボパグの投与を開始する前に，末梢血塗抹標本を詳細に検査し，投与開始時の細胞形態学的異常を確認する。用量が安定後，白血球（WBC）分類を含む全血球計算（FBC）を月 1 回実施する。未成熟または異型細胞が認められた場合，末梢血塗抹標本を検査して新たな形態学的異常または悪化（涙滴及び有核赤血球，未成熟白血球等）あるいは血球減少症を検討する。新たな形態学的異常または悪化あるいは血球減少症が認められた場合，エルトロンボパグの投与を中止し，線維染色を含む骨髄生検の実施を検討する。

既存の骨髄異形成症候群（MDS）の進行

TPO-R 作動薬はトロンボポイエチン前駆細胞の増殖，分化，及び血小板産生を誘発する増殖因子である。TPO-R は主に骨髄細胞系列の細胞表面に発現する。TPO-R 作動薬は MDS 等の既存の造血器悪性腫瘍の進行を促進する可能性が懸念される。

MDS 患者に TPO-R 作動薬を投与した臨床試験で，芽球細胞数の一過性の増加例が認められ，MDS が急性骨髄性白血病（AML）に進行した症例が報告された。

成人及び高齢者における ITP または SAA の診断は，血小板減少症を呈する他の疾患を除外して確定する。特に MDS の診断は除外しなければならない。特に 60 歳を超える患者，全身症状または末梢血の芽球増加等の異常徴候がある患者では，疾患及び治療の経過を通じて，骨髄穿刺及び生検の実施を考慮する。

化学療法による血小板減少症，MDS 等他の血小板減少症におけるエルトロンボパグ投与の有効性及び安全性は確立していない。臨床試験以外では，MDS または承認された適応症以外の原因による血小板減少症の治療としてエルトロンボパグを投与しないこと。

SAA 患者における細胞遺伝学的異常及び MDS/AML への進行

SAA 患者において細胞遺伝学的異常の発現が知られている。エルトロンボパグが SAA 患者の細胞遺伝学的異常の危険性を増大させるかは不明である。エルトロンボパグを用いた SAA の第 II 相臨床試験で，新たな細胞遺伝学的異常は患者の 19%（8/43 例［このうち 5 例は第 7 染色体の変化］）に認められた。試験開始から細胞遺伝学的異常までの期間は 2.9 ヵ月であった。

SAA にエルトロンボパグを投与した臨床試験で，患者の 4%（5/133 例）が MDS と診断された。エルトロンボパグの投与開始から診断までの期間の中央値は 3 ヵ月であった。

免疫抑制療法による前治療が無効であった，または多数の前治療を受けていた SAA 患者については，エルトロンボパグの投与開始前，投与開始後 3 ヵ月，及びその後は 6 ヵ月に骨髄穿刺で細胞遺伝学的検査をすることが推奨される。新たな細胞遺伝学的異常が検出された場合は，エルトロンボパグの継続が適切であるか評価しなければならない。

眼の変化

げっ歯類を用いたエルトロンボパグの毒性試験で白内障が認められた。血小板減少症を伴い，インターフェロン療法を受けている HCV 患者を対象とした比較試験（n=1,439）で，既存の白内障の進行または偶発的な白内障がエルトロンボパグ投与群の 8%及びプラセボ群の 5%で報告された。インターフェロン，リバビリン，及びエルトロンボパグを投与した HCV 患者で網膜出血（大部分はグレード 1 または 2）が報告されている（エルトロンボパグ投与群の 2%及びプラセボ群の 2%）。出血は網膜の表面（網膜前），網膜の下（網膜下），または網膜組織内に発生した。定期的に眼科検査を行うことが推奨される。

QT/QTc 延長

健康被験者にエルトロンボパグを 1 日 150 mg 投与した QTc 試験では，心臓再分極に対して臨床的に有意な作用は示されなかった。ITP 患者及び血小板減少症を伴う HCV 患者の臨床試験で QTc 間隔延長が報告されている。この QTc 間隔延長事象の臨床的意義は不明である。

エルトロンボパグの効果の消失

推奨用量範囲でエルトロンボパグを投与して効果が得られない，あるいは血小板数を維持できない場合，骨髄レチクリンの増加等の原因を検討する。

小児

ITP に関する上記の警告及び注意は小児患者にも適用される。

[redacted]

GLOBAL DATA SHEET

Eltrombopag

[redacted]

以下，P2～P53まで削除

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROMACTA safely and effectively. See full prescribing information for PROMACTA.

PROMACTA® (eltrombopag) tablets, for oral use
PROMACTA® (eltrombopag) for oral suspension
Initial U.S. Approval: 2008

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C

RISK OF HEPATOTOXICITY

See full prescribing information for complete boxed warning.

In patients with chronic hepatitis C, PROMACTA in combination with interferon and ribavirin may increase the risk of hepatic decompensation. (5.1)

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended. (5.2)

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

Boxed Warning	10/2016
Warnings and Precautions, Hepatotoxicity (5.2)	10/2016
Warnings and Precautions, Cataracts (5.4)	10/2016

----------INDICATIONS AND USAGE----------

PROMACTA is a thrombopoietin receptor agonist indicated for the treatment of:

- thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Limitations of Use: PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. (1.1)

- thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.

Limitations of Use: PROMACTA should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection. (1.2)

- patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Take on an empty stomach (1 hour before or 2 hours after a meal). (2.4)
- **Chronic ITP:** Initiate PROMACTA at 50 mg once daily for most adult and pediatric patients 6 years and older and at 25 mg once daily for pediatric patients aged 1 to 5 years. Dose reductions are needed for patients with hepatic impairment and some patients of East Asian ancestry. Adjust to maintain platelet count greater than or equal to 50 x 10^9/L. Do not exceed 75 mg per day. (2.1, 8.6, 8.8)
- **Chronic Hepatitis C-associated Thrombocytopenia:** Initiate PROMACTA at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg. (2.2)
- **Severe Aplastic Anemia:** Initiate PROMACTA at 50 mg once daily for most patients. Reduce initial dose in patients with hepatic impairment or patients of East Asian ancestry. Adjust to maintain platelet count greater than 50 x 10^9/L. Do not exceed 150 mg per day. (2.3, 8.6, 8.8)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg (3)
- For oral suspension: 25 mg (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Monitor liver function before and during therapy. (5.2)
- Thrombotic/Thromboembolic Complications: Portal vein thrombosis has been reported in patients with chronic liver disease receiving PROMACTA. Monitor platelet counts regularly. (5.3)

----------ADVERSE REACTIONS----------

- In adult patients with ITP, the most common adverse reactions (greater than or equal to 5% and greater than placebo) were: nausea, diarrhea, upper respiratory tract infection, vomiting, increased ALT, myalgia, and urinary tract infection. (6.1)
- In pediatric patients age 1 year and older with ITP, the most common adverse reactions (greater than or equal to 10% and greater than placebo) were upper respiratory tract infection and nasopharyngitis. (6.1)
- In patients with chronic hepatitis C-associated thrombocytopenia, the most common adverse reactions (greater than or equal to 10% and greater than placebo) were: anemia, pyrexia, fatigue, headache, nausea, diarrhea, decreased appetite, influenza-like illness, asthenia, insomnia, cough, pruritus, chills, myalgia, alopecia, and peripheral edema. (6.1)
- In patients with severe aplastic anemia, the most common adverse reactions (greater than or equal to 20%) were: nausea, fatigue, cough, diarrhea, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Take PROMACTA at least 2 hours before or 4 hours after any medications or products containing polyvalent cations such as antacids, calcium-rich foods, and mineral supplements. (2.4, 7.1)

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

- Pregnancy: Based on animal data, PROMACTA may cause fetal harm. (8.1)
- Nursing Mothers: A decision should be made to discontinue PROMACTA or nursing, taking into account the importance of PROMACTA to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C
1 INDICATIONS AND USAGE
1.1 Treatment of Thrombocytopenia in Patients with Chronic ITP
1.2 Treatment of Thrombocytopenia in Patients with Hepatitis C Infection
1.3 Treatment of Severe Aplastic Anemia
2 DOSAGE AND ADMINISTRATION
2.1 Chronic Immune (Idiopathic) Thrombocytopenia
2.2 Chronic Hepatitis C-associated Thrombocytopenia
2.3 Severe Aplastic Anemia
2.4 Administration
3 DOSAGE FORMS AND STRENGTHS
3.1 Tablets
3.2 For Oral Suspension
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hepatic Decompensation in Patients with Chronic Hepatitis C
5.2 Hepatotoxicity
5.3 Thrombotic/Thromboembolic Complications
5.4 Cataracts
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Polyvalent Cations (Chelation)
7.2 Transporters
7.3 Protease Inhibitors
7.4 Peginterferon alfa-2a/b Therapy
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
8.8 Ethnicity
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
12.6 Assessment of Risk of QT/QTc Prolongation
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Pharmacology and/or Toxicology
14 CLINICAL STUDIES
14.1 Chronic ITP
14.2 Chronic Hepatitis C-associated Thrombocytopenia
14.3 Severe Aplastic Anemia
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 Tablets
16.2 For Oral Suspension
17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C

RISK OF HEPATOTOXICITY

In patients with chronic hepatitis C, PROMACTA® in combination with interferon and ribavirin may increase the risk of hepatic decompensation *[see Warnings and Precautions (5.1)]*.

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Treatment of Thrombocytopenia in Patients with Chronic ITP

PROMACTA is indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Limitations of Use: PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.

1.2 Treatment of Thrombocytopenia in Patients with Hepatitis C Infection

PROMACTA is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.

Limitations of Use:

- PROMACTA should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.
- Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection.

1.3 Treatment of Severe Aplastic Anemia

PROMACTA is indicated for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Chronic Immune (Idiopathic) Thrombocytopenia

Use the lowest dose of PROMACTA to achieve and maintain a platelet count greater than or equal to 50 x 10^9/L as necessary to reduce the risk for bleeding. Dose adjustments are based upon the platelet count response. Do not use PROMACTA to normalize platelet counts *[see Warnings and Precautions (5.3)]*. In clinical trials, platelet counts generally increased within 1 to 2 weeks after starting PROMACTA and decreased within 1 to 2 weeks after discontinuing PROMACTA *[see Clinical Studies (14.1)]*.

Initial Dose Regimen: *Adult and Pediatric Patients 6 Years and Older with ITP:* Initiate PROMACTA at a dose of 50 mg once daily, except in patients who are of East Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean) or who have mild to severe hepatic impairment (Child-Pugh Class A, B, C).

For patients of East Asian ancestry with ITP, initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)]*.

For patients with ITP and mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

For patients of East Asian ancestry with ITP and hepatic impairment (Child-Pugh Class A, B, C), consider initiating PROMACTA at a reduced dose of 12.5 mg once daily *[see Clinical Pharmacology (12.3)]*.

Pediatric Patients with ITP Aged 1 to 5 Years: Initiate PROMACTA at a dose of 25 mg once daily *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)]*.

Monitoring and Dose Adjustment: After initiating PROMACTA, adjust the dose to achieve and maintain a platelet count greater than or equal to 50 x 10^9/L as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA and modify the dosage regimen of PROMACTA based on platelet counts as outlined in Table 1. During therapy with PROMACTA, assess CBCs with differentials, including platelet counts, weekly until a stable platelet count has been achieved. Obtain CBCs with differentials, including platelet counts, monthly thereafter.

When switching between the oral suspension and tablet, assess platelet counts weekly for 2 weeks, and then follow standard monthly monitoring.

Table 1. Dose Adjustments of PROMACTA in Patients with Chronic Immune (Idiopathic) Thrombocytopenia

Platelet Count Result	Dose Adjustment or Response
<50 x 10^9/L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 75 mg/day. For patients taking 12.5 mg once daily, increase the dose to 25 mg daily before increasing the dose amount by 25 mg.
≥200 x 10^9/L to ≤400 x 10^9/L at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. For patients taking 25 mg once daily, decrease the dose to 12.5 mg once daily.
>400 x 10^9/L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
>400 x 10^9/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

In patients with ITP and hepatic impairment (Child-Pugh Class A, B, C), after initiating PROMACTA or after any subsequent dosing increase, wait 3 weeks before increasing the dose.

Modify the dosage regimen of concomitant ITP medications, as medically appropriate, to avoid excessive increases in platelet counts during therapy with PROMACTA. Do not administer more than one dose of PROMACTA within any 24-hour period.

Discontinuation: Discontinue PROMACTA if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy with PROMACTA at the maximum daily dose of 75 mg. Excessive platelet count responses, as outlined in Table 1, or important liver test abnormalities also necessitate discontinuation of PROMACTA *[see Warnings and Precautions (5.2)]*. Obtain CBCs with differentials, including platelet counts, weekly for at least 4 weeks following discontinuation of PROMACTA.

2.2 Chronic Hepatitis C-associated Thrombocytopenia

Use the lowest dose of PROMACTA to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin. Dose adjustments are based upon the platelet count response. Do not use PROMACTA to normalize platelet counts *[see Warnings and Precautions (5.3)]*. In clinical trials, platelet counts generally began to rise within the first week of treatment with PROMACTA *[see Clinical Studies (14.2)]*.

Initial Dose Regimen: Initiate PROMACTA at a dose of 25 mg once daily.

Monitoring and Dose Adjustment: Adjust the dose of PROMACTA in 25-mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Monitor platelet counts every week prior to starting antiviral therapy.

During antiviral therapy, adjust the dose of PROMACTA to avoid dose reductions of peginterferon. Monitor CBCs with differentials, including platelet counts, weekly during antiviral therapy until a stable platelet count is achieved. Monitor platelet counts monthly thereafter. Do not exceed a dose of 100 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA.

For specific dosage instructions for peginterferon or ribavirin, refer to their respective prescribing information.

Table 2. Dose Adjustments of PROMACTA in Adults with Thrombocytopenia due to Chronic Hepatitis C

Platelet Count Result	Dose Adjustment or Response
$<50 \times 10^9$/L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 100 mg/day.
$\geq 200 \times 10^9$/L to $\leq 400 \times 10^9$/L at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
$>400 \times 10^9$/L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $<150 \times 10^9$/L, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
$>400 \times 10^9$/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

Discontinuation: The prescribing information for pegylated interferon and ribavirin include recommendations for antiviral treatment discontinuation for treatment futility. Refer to pegylated interferon and ribavirin prescribing information for discontinuation recommendations for antiviral treatment futility.

PROMACTA should be discontinued when antiviral therapy is discontinued. Excessive platelet count responses, as outlined in Table 2, or important liver test abnormalities also necessitate discontinuation of PROMACTA *[see Warnings and Precautions (5.2)]*.

2.3 Severe Aplastic Anemia

Use the lowest dose of PROMACTA to achieve and maintain a hematologic response. Dose adjustments are based upon the platelet count. Hematologic response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting PROMACTA *[see Clinical Studies (14.3)]*.

Initial Dose Regimen: Initiate PROMACTA at a dose of 50 mg once daily.

For patients with severe aplastic anemia of East Asian ancestry or those with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.6, 8.8), Clinical Pharmacology (12.3)]*.

Monitoring and Dose Adjustment: Adjust the dose of PROMACTA in 50-mg increments every 2 weeks as necessary to achieve the target platelet count greater than or equal to 50 x 10^9/L as necessary. Do not exceed a dose of 150 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA and modify the dosage regimen of PROMACTA based on platelet counts as outlined in Table 3.

Table 3. Dose Adjustments of PROMACTA in Patients with Severe Aplastic Anemia

Platelet Count Result	Dose Adjustment or Response
<50 x 10^9/L following at least 2 weeks of PROMACTA	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥200 x 10^9/L to ≤400 x 10^9/L at any time	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>400 x 10^9/L	Stop PROMACTA for 1 week. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a dose reduced by 50 mg.
>400 x 10^9/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of PROMACTA may be reduced by 50% *[see Clinical Studies (14.3)]*. If counts remain stable after 8 weeks at the reduced dose, then discontinue PROMACTA and monitor blood counts. If platelet counts drop to less than 30 x 10^9/L, hemoglobin to less than 9 g/dL, or ANC to less than 0.5 x 10^9/L, PROMACTA may be reinitiated at the previous effective dose.

Discontinuation: If no hematologic response has occurred after 16 weeks of therapy with PROMACTA, discontinue therapy. If new cytogenetic abnormalities are observed, consider discontinuation of PROMACTA *[see Adverse Reactions (6.1)]*. Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of PROMACTA *[see Warnings and Precautions (5.2)]*.

2.4 Administration

Preparation of the Oral Suspension: Prior to use of the oral suspension, ensure patients or caregivers receive training on proper dosing, preparation, and administration of PROMACTA for oral suspension.

Administer the oral suspension immediately after preparation. **Discard any suspension not administered within 30 minutes after preparation.**

Prepare the suspension with water only. NOTE: Do not use hot water to prepare the suspension.

For details on preparation and administration of the suspension, see **Instructions for Use**.

Administration of Tablets and Oral Suspension: Take PROMACTA on an empty stomach (1 hour before or 2 hours after a meal) *[see Clinical Pharmacology (12.3)]*. Take PROMACTA at least 2 hours before or 4 hours

after other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium-fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Do not crush tablets and mix with food or liquids.

Prepare the oral suspension with water only.

3 DOSAGE FORMS AND STRENGTHS

3.1 Tablets

- 12.5-mg tablets — round, biconvex, white, film-coated tablets debossed with GS MZ1 and 12.5 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 12.5 mg of eltrombopag free acid.
- 25-mg tablets — round, biconvex, orange, film-coated tablets debossed with GS NX3 and 25 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 25 mg of eltrombopag free acid.
- 50-mg tablets — round, biconvex, blue, film-coated tablets debossed with GS UFU and 50 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 50 mg of eltrombopag free acid.
- 75-mg tablets — round, biconvex, pink, film-coated tablets debossed with GS FFS and 75 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 75 mg of eltrombopag free acid.
- 100-mg tablets — round, biconvex, green, film-coated tablets debossed with GS 1L5. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 100 mg of eltrombopag free acid.

3.2 For Oral Suspension

25-mg packet — contains a reddish-brown to yellow powder for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Decompensation in Patients with Chronic Hepatitis C

In patients with chronic hepatitis C, PROMACTA in combination with interferon and ribavirin may increase the risk of hepatic decompensation. In two controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, ascites and encephalopathy occurred more frequently on the arm receiving treatment with PROMACTA plus antivirals (7%) than the placebo plus antivirals arm (4%). Patients with low albumin levels (less than 3.5 g/dL) or Model for End-Stage Liver Disease (MELD) score greater than or equal to 10 at baseline had a greater risk for hepatic decompensation on the arm receiving treatment with PROMACTA plus antivirals. Discontinue PROMACTA if antiviral therapy is discontinued.

5.2 Hepatotoxicity

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity *[see Adverse Reactions (6.1)]*. Measure serum ALT, AST, and bilirubin prior to initiation of PROMACTA, every 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose. PROMACTA inhibits UDP-glucuronosyltransferase (UGT)1A1 and organic anion-transporting polypeptide (OATP)1B1, which may lead to indirect hyperbilirubinemia. If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until resolved or stabilized. Discontinue PROMACTA if ALT levels increase to greater than or equal to 3 x ULN in patients with normal liver function or greater than or equal to 3 x baseline (or greater than 5 x ULN, whichever is the lower) in patients with pre-treatment elevations in transaminases and are:

- progressively increasing, or
- persistent for greater than or equal to 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

If the potential benefit for reinitiating treatment with PROMACTA is considered to outweigh the risk for hepatotoxicity, then consider cautiously reintroducing PROMACTA and measure serum liver tests weekly during the dose adjustment phase. Hepatotoxicity may reoccur if PROMACTA is reinitiated. If liver test abnormalities persist, worsen, or recur, then permanently discontinue PROMACTA.

Isolated cases of severe liver injury were identified in clinical trials. The elevation of liver laboratory values occurred approximately three months after initiation of PROMACTA. In all cases, the event resolved following PROMACTA discontinuation.

5.3 Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts.

Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). To minimize the risk for thrombotic/thromboembolic complications, do not use PROMACTA in an attempt to normalize platelet counts. Follow the dose adjustment guidelines to achieve and maintain target platelet counts *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

In two controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, 3% (31/955) treated with PROMACTA experienced a thrombotic event compared with 1% (5/484) on placebo. The majority of events were of the portal venous system (1% in patients treated with PROMACTA versus less than 1% for placebo).

In a controlled trial in patients with chronic liver disease and thrombocytopenia not related to ITP undergoing elective invasive procedures (N = 292), the risk of thrombotic events was increased in patients treated with 75 mg of PROMACTA once daily. Seven thrombotic complications (six patients) were reported in the group that received PROMACTA and three thrombotic complications were reported in the placebo group (two patients). All of the thrombotic complications reported in the group that received PROMACTA were portal vein thrombosis (PVT). Symptoms of PVT included abdominal pain, nausea, vomiting, and diarrhea. Five of the six patients in the group that received PROMACTA experienced a thrombotic complication within 30 days of completing treatment with PROMACTA and at a platelet count above 200 x 10^9/L. The risk of portal venous thrombosis was increased in thrombocytopenic patients with chronic liver disease treated with 75 mg of PROMACTA once daily for 2 weeks in preparation for invasive procedures.

5.4 Cataracts

In the three controlled clinical trials in adults with chronic ITP, cataracts developed or worsened in 15 (7%) patients who received 50 mg of PROMACTA daily and 8 (7%) placebo-group patients. In the extension trial, cataracts developed or worsened in 11% of patients who underwent ocular examination prior to therapy with PROMACTA. In the two controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, cataracts developed or worsened in 8% of patients treated with PROMACTA and 5% of patients treated with placebo.

Cataracts were observed in toxicology studies of eltrombopag in rodents *[see Nonclinical Toxicology (13.2)]*. Perform a baseline ocular examination prior to administration of PROMACTA and, during therapy with PROMACTA, regularly monitor patients for signs and symptoms of cataracts.

6 ADVERSE REACTIONS

The following serious adverse reactions associated with PROMACTA are described in other sections.

- Hepatic Decompensation in Patients with Chronic Hepatitis C *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Thrombotic/Thromboembolic Complications *[see Warnings and Precautions (5.3)]*
- Cataracts *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Chronic Immune (Idiopathic) Thrombocytopenia: *Adults:* In clinical trials, hemorrhage was the most common serious adverse reaction and most hemorrhagic reactions followed discontinuation of PROMACTA. Other serious adverse reactions included thrombotic/thromboembolic complications *[see Warnings and Precautions (5.3)]*. The data described below reflect exposure of PROMACTA to patients with chronic ITP aged 18 to 85 years, of whom 66% were female, in three placebo-controlled trials and one open-label extension trial *[see Clinical Studies (14.1)]*. PROMACTA was administered to 330 patients for at least 6 months and 218 patients for at least 1 year.

Table 4 presents the most common adverse drug reactions (experienced by greater than or equal to 3% of patients receiving PROMACTA) from the three placebo-controlled trials, with a higher incidence in PROMACTA versus placebo.

Table 4. Adverse Reactions (≥3%) from Three Placebo-controlled Trials in Adults with Chronic Immune (Idiopathic) Thrombocytopenia

Adverse Reaction	PROMACTA 50 mg n = 241 (%)	Placebo n = 128 (%)
Nausea	9	3
Diarrhea	9	7
Upper respiratory tract infection	7	6
Vomiting	6	<1
Increased ALT	5	3
Myalgia	5	2
Urinary tract infection	5	3
Oropharyngeal pain	4	3
Increased AST	4	2
Pharyngitis	4	2
Back pain	3	2
Influenza	3	2
Paresthesia	3	2
Rash	3	2

In the three controlled clinical chronic ITP trials, alopecia, musculoskeletal pain, blood alkaline phosphatase increased, and dry mouth were the adverse reactions reported in 2% of patients treated with PROMACTA and in no patients who received placebo.

Among 302 patients with chronic ITP who received PROMACTA in the single-arm extension trial, the adverse reactions occurred in a pattern similar to that seen in the placebo-controlled trials. Table 5 presents the most

common treatment-related adverse reactions (experienced by greater than or equal to 3% of patients receiving PROMACTA) from the extension trial.

Table 5. Treatment-related Adverse Reactions (≥3%) from Extension Trial in Adults with Chronic Immune (Idiopathic) Thrombocytopenia

Adverse Reaction	PROMACTA 50 mg n = 302 (%)
Headache	10
ALT increased	5
AST increased	5
Cataract	5
Fatigue	5
Blood bilirubin increased	4
Nausea	4
Hyperbilirubinemia	3
Diarrhea	3

In the three controlled chronic ITP trials, serum liver test abnormalities (predominantly Grade 2 or less in severity) were reported in 11% and 7% of patients for PROMACTA and placebo, respectively. Four patients (1%) treated with PROMACTA and three patients in the placebo group (2%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seventeen of the patients treated with PROMACTA in the controlled trials with hepatobiliary laboratory abnormalities were re-exposed to PROMACTA in the extension trial. Eight of these patients again experienced liver test abnormalities (less than or equal to Grade 3) resulting in discontinuation of PROMACTA in one patient. In the extension chronic ITP trial, six additional patients had PROMACTA discontinued due to liver test abnormalities (less than or equal to Grade 3).

In the three controlled chronic ITP trials, cataracts developed or worsened in 7% of patients treated with PROMACTA and 7% of patients in the placebo group. All patients had documented, preexisting risk factors for cataractogenesis including corticosteroid use. In the extension trial, cataracts developed or worsened in 11% of patients who underwent ocular examination prior to therapy with PROMACTA. Seventy-two percent of patients had preexisting risk factors, including corticosteroid use.

In clinical trials in patients with chronic ITP, one patient treated with PROMACTA (<1%) experienced drug-induced liver injury *[see Warnings and Precautions (5.2)]*.

In a placebo-controlled trial of PROMACTA in patients with chronic liver disease and thrombocytopenia not related to ITP, six patients treated with PROMACTA and one patient in the placebo group developed portal vein thromboses *[see Warnings and Precautions (5.3)]*.

Pediatric Patients: The data described below reflect median exposure to PROMACTA of 91 days for 107 pediatric patients (aged 1 to 17 years) with chronic ITP, of whom 53% were female, across the randomized phase of two placebo-controlled trials.

Table 6 presents the most common adverse drug reactions (experienced by greater than or equal to 3% of pediatric patients 1 year and older receiving PROMACTA) across the two placebo-controlled trials, with a higher incidence for PROMACTA versus placebo.

Table 6. Adverse Reactions (≥3%) with a Higher Incidence for PROMACTA versus Placebo from Two Placebo-controlled Trials in Pediatric Patients 1 Year and Older with Chronic Immune (Idiopathic) Thrombocytopenia

Adverse Reaction	PROMACTA n = 107 (%)	Placebo n = 50 (%)
Upper respiratory tract infection	17	6
Nasopharyngitis	12	4
Cough	9	0
Diarrhea	9	2
Pyrexia	9	8
Rhinitis	9	6
Abdominal pain	8	4
Oropharyngeal pain	8	2
Toothache	6	0
ALT increased[a]	6	0
Rash	5	2
AST increased	4	0
Rhinorrhea	4	0

[a] Includes adverse reactions or laboratory abnormalities >3 x ULN.

In the two controlled clinical chronic ITP trials, cataracts developed or worsened in 2 (1%) patients treated with PROMACTA. Both patients had received chronic oral corticosteroids, a risk factor for cataractogenesis.

Chronic Hepatitis C-associated Thrombocytopenia: In the two placebo-controlled trials, 955 patients with chronic hepatitis C-associated thrombocytopenia received PROMACTA. Table 7 presents the most common adverse drug reactions (experienced by greater than or equal to 10% of patients receiving PROMACTA compared with placebo).

Table 7. Adverse Reactions (≥10% and Greater than Placebo) from Two Placebo-controlled Trials in Adults with Chronic Hepatitis C

Adverse Reaction	PROMACTA + Peginterferon/Ribavirin n = 955 (%)	Placebo + Peginterferon/Ribavirin n = 484 (%)
Anemia	40	35
Pyrexia	30	24
Fatigue	28	23
Headache	21	20
Nausea	19	14
Diarrhea	19	11
Decreased appetite	18	14
Influenza-like illness	18	16
Asthenia	16	13
Insomnia	16	15
Cough	15	12
Pruritus	15	13
Chills	14	9
Myalgia	12	10
Alopecia	10	6
Peripheral edema	10	5

Rash was reported in 9% and 7% of patients receiving PROMACTA and placebo, respectively.

In the two controlled clinical trials in patients with chronic hepatitis C, hyperbilirubinemia was reported in 8% of patients receiving PROMACTA compared with 3% for placebo. Total bilirubin greater than or equal to 1.5 x ULN was reported in 76% and 50% of patients receiving PROMACTA and placebo, respectively. ALT or AST greater than or equal to 3 x ULN was reported in 34% and 38% of patients for PROMACTA and placebo, respectively.

In the two controlled clinical trials in patients with chronic hepatitis C, cataracts developed or worsened in 8% of patients treated with PROMACTA and 5% of patients treated with placebo.

In clinical trials in patients with chronic hepatitis C, 11 patients treated with PROMACTA (1%) experienced drug-induced liver injury *[see Warnings and Precautions (5.2)]*.

Severe Aplastic Anemia: In the single-arm, open-label trial, 43 patients with severe aplastic anemia received PROMACTA. Eleven patients (26%) were treated for greater than 6 months and 7 patients (16%) were treated for greater than 1 year. The most common adverse reactions (greater than or equal to 20%) were nausea, fatigue, cough, diarrhea, and headache.

Table 8. Adverse Reactions (≥10%) from One Open-label Trial in Adults with Severe Aplastic Anemia

Adverse Reaction	PROMACTA (n = 43) (%)
Nausea	33
Fatigue	28
Cough	23
Diarrhea	21
Headache	21
Pain in extremity	19
Dyspnea	14
Pyrexia	14
Dizziness	14
Oropharyngeal pain	14
Febrile neutropenia	14
Abdominal pain	12
Ecchymosis	12
Muscle spasms	12
Transaminases increased	12
Arthralgia	12
Rhinorrhea	12

Rash was reported in 7% of patients; cataract was reported in 2% of patients.

In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight patients had a new cytogenetic abnormality reported on therapy, including 5 patients who had complex changes in chromosome 7.

6.2 Postmarketing Experience

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

Vascular Disorders: Thrombotic microangiopathy with acute renal failure.

Skin and Subcutaneous Tissue Disorders: Skin discoloration including hyperpigmentation and skin yellowing.

7 DRUG INTERACTIONS

7.1 Polyvalent Cations (Chelation)

Eltrombopag chelates polyvalent cations (such as iron, calcium, aluminum, magnesium, selenium, and zinc) in foods, mineral supplements, and antacids. In a clinical trial, administration of PROMACTA with a polyvalent cation-containing antacid decreased plasma eltrombopag systemic exposure by approximately 70% *[see Clinical Pharmacology (12.3)]*.

Take PROMACTA at least 2 hours before or 4 hours after any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements to avoid significant reduction in absorption of PROMACTA due to chelation *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

7.2 Transporters

Coadministration of PROMACTA with the OATP1B1 and breast cancer resistance protein (BCRP) substrate, rosuvastatin, to healthy adult subjects increased plasma rosuvastatin $AUC_{0\text{-}INF}$ by 55% and C_{max} by 103% *[see Clinical Pharmacology (12.3)]*.

Use caution when concomitantly administering PROMACTA and drugs that are substrates of OATP1B1 (e.g., atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, olmesartan, pitavastatin, pravastatin, rosuvastatin, repaglinide, rifampin, simvastatin acid, SN-38 [active metabolite of irinotecan], valsartan) or BCRP (e.g., imatinib, irinotecan, lapatinib, methotrexate, mitoxantrone, rosuvastatin, sulfasalazine, topotecan). Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 or BCRP and consider reduction of the dose of these drugs, if appropriate. In clinical trials with PROMACTA, a dose reduction of rosuvastatin by 50% was recommended.

7.3 Protease Inhibitors

HIV Protease Inhibitors: In a drug interaction trial, coadministration of PROMACTA with lopinavir/ritonavir (LPV/RTV) decreased plasma eltrombopag exposure by 17% *[see Clinical Pharmacology (12.3)]*. No dose adjustment is recommended when PROMACTA is coadministered with LPV/RTV. Drug interactions with other HIV protease inhibitors have not been evaluated.

Hepatitis C Virus (HCV) Protease Inhibitors: Coadministration of PROMACTA with either boceprevir or telaprevir did not affect eltrombopag or protease inhibitor exposure significantly *[see Clinical Pharmacology (12.3)]*. No dose adjustments are recommended. Drug interactions with other HCV protease inhibitors have not been evaluated.

7.4 Peginterferon alfa-2a/b Therapy

Coadministration of peginterferon alfa-2a (PEGASYS®) or -2b (PEGINTRON®) did not affect eltrombopag exposure in two randomized, double-blind, placebo-controlled trials with adult patients with chronic hepatitis C *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of eltrombopag use in pregnancy. In animal reproduction and developmental toxicity studies, there was evidence of embryolethality and reduced fetal weights at maternally toxic doses. PROMACTA should be used in pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In an early embryonic development study, female rats received oral eltrombopag at doses of 10, 20, or 60 mg/kg/day (0.8, 2, and 6 times, respectively, the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Increased pre- and post-implantation loss and reduced fetal weight were observed at the highest dose which also caused maternal toxicity.

Eltrombopag was administered orally to pregnant rats at 10, 20, or 60 mg/kg/day (0.8, 2, and 6 times, respectively, the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Decreased fetal weights (6% to 7%) and a slight increase in the presence of cervical ribs were observed at the highest dose which also caused maternal toxicity. However, no evidence of major structural malformations was observed.

Pregnant rabbits were treated with oral eltrombopag doses of 30, 80, or 150 mg/kg/day (0.04, 0.3, and 0.5 times, respectively, the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.02, 0.1, and 0.3 times, respectively, the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). No evidence of fetotoxicity, embryolethality, or teratogenicity was observed.

In a pre- and post-natal developmental toxicity study in pregnant rats (F0), no adverse effects on maternal reproductive function or on the development of the offspring (F1) were observed at doses up to 20 mg/kg/day

(2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and similar to the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Eltrombopag was detected in the plasma of offspring (F1). The plasma concentrations in pups increased with dose following administration of drug to the F0 dams.

8.3 Nursing Mothers

It is not known whether eltrombopag is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PROMACTA, a decision should be made whether to discontinue nursing or to discontinue PROMACTA taking into account the importance of PROMACTA to the mother.

8.4 Pediatric Use

The safety and efficacy of PROMACTA in pediatric patients 1 year and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials *[see Adverse Reactions (6.2), Clinical Studies (14.2)]*. The pharmacokinetics of eltrombopag have been evaluated in 168 pediatric patients 1 year and older with ITP dosed once daily *[see Clinical Pharmacology (12.3)]*. See *Dosage and Administration (2.1)* for dosing recommendations for pediatric patients 1 year and older. The safety and efficacy of PROMACTA in pediatric patients younger than 1 year with ITP have not yet been established.

The safety and efficacy of PROMACTA in pediatric patients with thrombocytopenia associated with chronic hepatitis C and severe aplastic anemia have not been established.

8.5 Geriatric Use

Of the 106 patients in two randomized clinical trials of PROMACTA 50 mg in chronic ITP, 22% were 65 years of age and over, while 9% were 75 years of age and over. In the two randomized clinical trials of PROMACTA in patients with chronic hepatitis C and thrombocytopenia, 7% were 65 years of age and over, while fewer than 1% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients in the placebo-controlled trials, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

Hepatic impairment influences the exposure of PROMACTA *[see Clinical Pharmacology (12.3)]*.

Reduce the initial dose of PROMACTA in patients with chronic ITP (adult and pediatric patients 6 years and older only) or severe aplastic anemia who also have hepatic impairment (Child-Pugh Class A, B, C) *[see Dosage and Administration (2.1, 2.3), Warnings and Precautions (5.2)]*. No dosage adjustment is necessary for patients with chronic hepatitis C and hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No adjustment in the initial dose of PROMACTA is needed for patients with renal impairment *[see Clinical Pharmacology (12.3)]*. Closely monitor patients with impaired renal function when administering PROMACTA.

8.8 Ethnicity

Patients of East Asian ethnicity (i.e., Japanese, Chinese, Taiwanese, and Korean) exhibit higher eltrombopag exposures. A reduction in the initial dose of PROMACTA is recommended for patients of East Asian ancestry with ITP (adult and pediatric patients 6 years and older only) or severe aplastic anemia *[see Dosage and Administration (2.1, 2.3)]*. No dose reduction is needed in patients of East Asian ethnicity with chronic hepatitis C *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications.

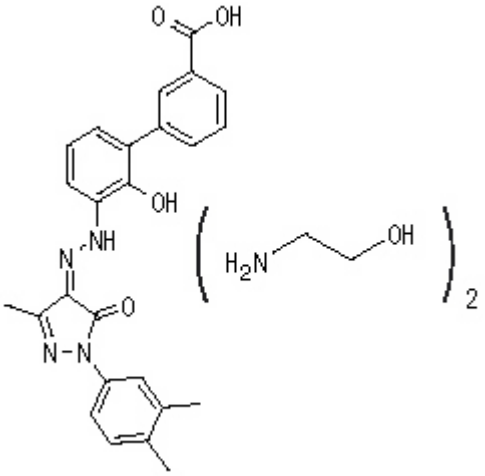
In one report, a subject who ingested 5,000 mg of PROMACTA had a platelet count increase to a maximum of 929 x 10^9/L at 13 days following the ingestion. The patient also experienced rash, bradycardia, ALT/AST elevations, and fatigue. The patient was treated with gastric lavage, oral lactulose, intravenous fluids, omeprazole, atropine, furosemide, calcium, dexamethasone, and plasmapheresis; however, the abnormal platelet count and liver test abnormalities persisted for 3 weeks. After 2 months' follow-up, all events had resolved without sequelae.

In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in accordance with dosing and administration recommendations *[see Dosage and Administration (2.1, 2.2)]*.

11 DESCRIPTION

PROMACTA (eltrombopag) tablets contain eltrombopag olamine, a small molecule thrombopoietin (TPO) receptor agonist for oral administration. Eltrombopag interacts with the transmembrane domain of the TPO receptor (also known as cMpl) leading to increased platelet production.

Eltrombopag olamine is a biphenyl hydrazone. The chemical name for eltrombopag olamine is 3'-{(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid - 2-aminoethanol (1:2). It has the molecular formula $C_{25}H_{22}N_4O_4 \bullet 2(C_2H_7NO)$. The molecular weight is 564.65 for eltrombopag olamine and 442.5 for eltrombopag free acid. Eltrombopag olamine has the following structural formula:



Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to 7.4, and is sparingly soluble in water.

PROMACTA (eltrombopag) tablets contain eltrombopag olamine in the amount equivalent to 12.5 mg, 25 mg, 50 mg, 75 mg, or 100 mg of eltrombopag free acid. The inactive ingredients of PROMACTA tablets are: **Tablet Core:** magnesium stearate, mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate. **Coating:** hypromellose (12.5-mg, 25-mg, 50-mg, and 75-mg tablets) or polyvinyl alcohol and talc (100-mg tablet), polyethylene glycol 400, titanium dioxide, polysorbate 80 (12.5-mg tablet), FD&C Yellow No. 6 aluminum lake (25-mg tablet), FD&C Blue No. 2 aluminum lake (50-mg tablet), Iron Oxide Red and Iron Oxide Black (75-mg tablet), or Iron Oxide Yellow and Iron Oxide Black (100-mg tablet).

PROMACTA (eltrombopag) for oral suspension packets contain a reddish-brown to yellow powder which produces a reddish-brown suspension when reconstituted with water. Each 25-mg packet delivers eltrombopag olamine equivalent to 25 mg of eltrombopag free acid. The inactive ingredients of PROMACTA for oral suspension are mannitol, sucralose, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eltrombopag is an orally bioavailable, small-molecule TPO-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells.

12.3 Pharmacokinetics

Absorption: Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Based on urinary excretion and biotransformation products eliminated in feces, the oral absorption of drug-related material following administration of a single 75-mg solution dose was estimated to be at least 52%.

An open-label, randomized, crossover trial was conducted to assess the effect of food on the bioavailability of eltrombopag. A standard high-fat breakfast significantly decreased plasma eltrombopag $AUC_{0\text{-}INF}$ by approximately 59% and C_{max} by 65% and delayed T_{max} by 1 hour. The calcium content of this meal may have also contributed to this decrease in exposure.

In a second trial, administration of a single 25-mg dose of eltrombopag for oral suspension to adults with a high-calcium, moderate-fat, moderate-calorie meal reduced plasma eltrombopag $AUC_{0\text{-}INF}$ by 75% (90% CI: 71%, 88%) and C_{max} by 79% (90% CI: 76%, 82%). Administration of a single 25-mg dose of eltrombopag for oral suspension 2 hours after the high-calcium meal reduced plasma eltrombopag $AUC_{0\text{-}INF}$ by 47% (90% CI: 40%, 53%) and C_{max} by 48% (90% CI: 40%, 54%). Administration of a single 25-mg dose of eltrombopag for oral suspension 2 hours before the high-calcium meal reduced plasma eltrombopag $AUC_{0\text{-}INF}$ by 20% (90% CI: 9%, 29%) and C_{max} by 14% (90% CI: 2%, 25%).

In a relative bioavailability trial in adults, the eltrombopag for oral suspension delivered 22% higher plasma $AUC_{0\text{-}INF}$ than the tablet formulation.

Distribution: The concentration of eltrombopag in blood cells is approximately 50% to 79% of plasma concentrations based on a radiolabel study. *In vitro* studies suggest that eltrombopag is highly bound to human plasma proteins (greater than 99%). Eltrombopag is a substrate of BCRP, but is not a substrate for P-glycoprotein (P-gp) or OATP1B1.

Metabolism: Absorbed eltrombopag is extensively metabolized, predominantly through pathways including cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or cysteine. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for the oxidative metabolism of eltrombopag. UGT1A1 and UGT1A3 are responsible for the glucuronidation of eltrombopag.

Elimination: The predominant route of eltrombopag excretion is via feces (59%), and 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for approximately 20% of the dose; unchanged eltrombopag is not detectable in urine. The plasma elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26 to 35 hours in patients with ITP.

Drug Interactions: *Polyvalent Cation-containing Antacids:* In a clinical trial, coadministration of 75 mg of PROMACTA with a polyvalent cation-containing antacid (1,524 mg aluminum hydroxide, 1,425 mg magnesium carbonate, and sodium alginate) to 26 healthy adult subjects decreased plasma eltrombopag $AUC_{0\text{-}INF}$ and C_{max} by approximately 70%. The contribution of sodium alginate to this interaction is not known.

Cytochrome P450 Enzymes (CYPs): In a clinical trial, PROMACTA 75 mg once daily was administered for 7 days to 24 healthy male subjects did not show inhibition or induction of the metabolism of a combination of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam) in humans. Probe substrates for CYP2C8 were not evaluated in this trial.

Rosuvastatin: In a clinical trial, coadministration of 75 mg of PROMACTA once daily for 5 days with a single 10-mg dose of the OATP1B1 and BCRP substrate, rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin $AUC_{0\text{-}INF}$ by 55% and C_{max} by 103%.

Protease Inhibitors: HIV Protease Inhibitors: In a clinical trial, coadministration of repeat-dose lopinavir 400 mg/ritonavir 100 mg twice daily with a single dose of PROMACTA 100 mg to 40 healthy adult subjects decreased plasma eltrombopag $AUC_{0\text{-}INF}$ by 17%.

HCV Protease Inhibitors: In a clinical trial, coadministration of repeat-dose telaprevir 750 mg every 8 hours or boceprevir 800 mg every 8 hours with a single dose of PROMACTA 200 mg to healthy adult subjects did not alter plasma telaprevir, boceprevir, or eltrombopag $AUC_{0\text{-}INF}$ or C_{max} to a significant extent.

Cyclosporine: In a drug interaction trial, coadministration of a single dose of PROMACTA 50 mg with a single dose of an OATP and BCRP inhibitor cyclosporine 200 mg in healthy adult subjects decreased plasma eltrombopag $AUC_{0\text{-}INF}$ by 18% (90% CI: 8%, 28%) and C_{max} by 25% (90% CI: 15%, 35%). In the same clinical trial, coadministration of a single dose of PROMACTA 50 mg with a single dose of cyclosporine 600 mg in healthy adult subjects decreased plasma eltrombopag $AUC_{0\text{-}INF}$ by 24% (90% CI: 14%, 32%) and C_{max} by 39% (90% CI: 30%, 47%).

Pegylated Interferon alfa-2a + Ribavirin and Pegylated Interferon alfa-2b + Ribavirin: The pharmacokinetics of eltrombopag in both the presence and absence of pegylated interferon alfa-2a and -2b therapy were evaluated using a population pharmacokinetic analysis in 635 patients with chronic hepatitis C. The population PK model estimates of clearance indicate no significant difference in eltrombopag clearance in the presence of pegylated interferon alfa plus ribavirin therapy.

In vitro Studies: *In vitro*, CYP1A2, CYP2C8, UGT1A1, and UGT1A3 are involved in the metabolism of eltrombopag. *In vitro*, eltrombopag inhibits the following metabolic or transporter systems: CYP2C8, CYP2C9, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15, OATP1B1, and BCRP.

Specific Populations: *Ethnicity:* Based on two population PK analyses of eltrombopag concentrations in patients with ITP or chronic hepatitis C, East Asian (i.e., Japanese, Chinese, Taiwanese, Korean) subjects exhibited 50% to 55% higher eltrombopag plasma concentrations compared with non-East Asian subjects *[see Dosage and Administration (2.1, 2.3)]*.

An approximately 40% higher systemic eltrombopag exposure in healthy African-American subjects was noted in at least one clinical pharmacology trial. The effect of African-American ethnicity on exposure and related safety and efficacy of eltrombopag has not been established.

Hepatic Impairment: In a pharmacokinetic trial, the disposition of a single 50-mg dose of PROMACTA in patients with mild, moderate, and severe hepatic impairment was compared with subjects with normal hepatic function. The degree of hepatic impairment was based on Child-Pugh score. Plasma eltrombopag $AUC_{0\text{-}INF}$ was 41% higher in patients with mild hepatic impairment (Child-Pugh Class A) compared with subjects with normal hepatic function. Plasma eltrombopag $AUC_{0\text{-}INF}$ was approximately 2-fold higher in patients with moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C). The half-life of eltrombopag was prolonged 2-fold in these patients. This clinical trial did not evaluate protein-binding effects.

Chronic Liver Disease: A population PK analysis in thrombocytopenic patients with chronic liver disease following repeat doses of eltrombopag demonstrated that mild hepatic impairment resulted in an 87% to 110% higher plasma eltrombopag $AUC_{(0\text{-}\tau)}$ and patients with moderate hepatic impairment had approximately 141% to 240% higher plasma eltrombopag $AUC_{(0\text{-}\tau)}$ values compared with patients with normal hepatic function. The half-life of eltrombopag was prolonged 3-fold in patients with mild hepatic impairment and 4-fold in patients with moderate hepatic impairment. This clinical trial did not evaluate protein-binding effects.

Chronic Hepatitis C: A population PK analysis in 28 healthy adults and 635 patients with chronic hepatitis C demonstrated that patients with chronic hepatitis C treated with PROMACTA had higher plasma $AUC_{(0\text{-}\tau)}$

values as compared with healthy subjects, and $AUC_{(0-\tau)}$ increased with increasing Child-Pugh score. Patients with chronic hepatitis C and mild hepatic impairment had approximately 100% to 144% higher plasma $AUC_{(0-\tau)}$ compared with healthy subjects. This clinical trial did not evaluate protein-binding effects.

Renal Impairment: The disposition of a single 50-mg dose of PROMACTA in patients with mild (creatinine clearance [CrCl] of 50 to 80 mL/min), moderate (CrCl of 30 to 49 mL/min), and severe (CrCl less than 30 mL/min) renal impairment was compared with subjects with normal renal function. Average total plasma eltrombopag AUC_{0-INF} was 32% to 36% lower in subjects with mild to moderate renal impairment and 60% lower in subjects with severe renal impairment compared with healthy subjects. The effect of renal impairment on unbound (active) eltrombopag exposure has not been assessed.

Pediatric Patients: The pharmacokinetics of eltrombopag have been evaluated in 168 pediatric patients 1 year and older with ITP dosed once daily in two trials. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. East Asian pediatric patients with ITP had approximately 43% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared with non-East Asian patients.

Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} in pediatric patients aged 12 to 17 years was similar to that observed in adults. The pharmacokinetic parameters of eltrombopag in pediatric patients with ITP are shown in Table 9.

Table 9. Geometric Mean (95% CI) Steady-state Plasma Eltrombopag Pharmacokinetic Parameters[a] in Patients with ITP (Normalized to a Once-daily 50-mg Dose)

Age	C_{max}[b] (mcg/mL)	$AUC_{(0-\tau)}$[b] (mcg·hr/mL)
Adults (n = 108)	7.03 (6.44, 7.68)	101 (91.4, 113)
12 to 17 years (n = 62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n = 68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n = 38)	11.6 (10.4, 12.9)	162 (139, 187)

[a] PK parameters presented as geometric mean (95% CI).
[b] Based on population PK post-hoc estimates.

12.6 Assessment of Risk of QT/QTc Prolongation

There is no indication of a QT/QTc prolonging effect of PROMACTA at doses up to 150 mg daily for 5 days. The effects of PROMACTA at doses up to 150 mg daily for 5 days (supratherapeutic doses) on the QT/QTc interval were evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400 mg, single oral dose) crossover trial in healthy adult subjects. Assay sensitivity was confirmed by significant QTc prolongation by moxifloxacin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Eltrombopag does not stimulate platelet production in rats, mice, or dogs because of unique TPO receptor specificity. Data from these animals do not fully model effects in humans.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day).

Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure based on C_{max} in patients

with ITP at 75 mg/day and 7 times the human clinical exposure based on C_{max} in patients with chronic hepatitis C at 100 mg/day). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (less than 3-fold increase in mutation frequency).

Eltrombopag did not affect female fertility in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and similar to the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day).

13.2 Animal Pharmacology and/or Toxicology

Treatment-related cataracts were detected in rodents in a dose- and time-dependent manner. At greater than or equal to 6 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 3 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day, cataracts were observed in mice after 6 weeks and in rats after 28 weeks of dosing. At greater than or equal to 4 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing *[see Warnings and Precautions (5.4)]*.

Renal tubular toxicity was observed in studies up to 14 days in duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75, and 150 mg/kg/day. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.6 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day. No similar effects were observed in mice after 13 weeks at exposures greater than those associated with renal changes in the 2-year study, suggesting that this effect is both dose- and time-dependent.

14 CLINICAL STUDIES

14.1 Chronic ITP

Adults: The efficacy and safety of PROMACTA in adult patients with chronic ITP were evaluated in three randomized, double-blind, placebo-controlled trials and in an open-label extension trial.

Trials 1 and 2: In Trials 1 and 2, patients who had completed at least one prior ITP therapy and who had a platelet count less than 30 x 10^9/L were randomized to receive either PROMACTA or placebo daily for up to 6 weeks, followed by 6 weeks off therapy. During the trials, PROMACTA or placebo was discontinued if the platelet count exceeded 200 x 10^9/L.

The median age of the patients was 50 years and 60% were female. Approximately 70% of the patients had received at least 2 prior ITP therapies (predominantly corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine) and 40% of the patients had undergone splenectomy. The median baseline platelet counts (approximately 18 x 10^9/L) were similar among all treatment groups.

Trial 1 randomized 114 patients (2:1) to PROMACTA 50 mg or placebo. Trial 2 randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of PROMACTA, 30 mg, 50 mg, or 75 mg each administered daily.

The efficacy of PROMACTA in this trial was evaluated by response rate, defined as a shift from a baseline platelet count of less than 30 x 10^9/L to greater than or equal to 50 x 10^9/L at any time during the treatment period (Table 10).

Table 10. Trials 1 and 2 Platelet Count Response (≥50 x 10^9/L) Rates in Adults with Chronic Immune (Idiopathic) Thrombocytopenia

Trial	PROMACTA 50 mg Daily	Placebo
1	43/73 (59%)[a]	6/37 (16%)
2	19/27 (70%)[a]	3/27 (11%)

[a] *P* value <0.001 for PROMACTA versus placebo.

The platelet count response to PROMACTA was similar among patients who had or had not undergone splenectomy. In general, increases in platelet counts were detected 1 week following initiation of PROMACTA and the maximum response was observed after 2 weeks of therapy. In the placebo and 50-mg–dose groups of PROMACTA, the trial drug was discontinued due to an increase in platelet counts to greater than 200 x 10^9/L in 3% and 27% of the patients, respectively. The median duration of treatment with the 50-mg dose of PROMACTA was 42 days in Trial 1 and 43 days in Trial 2.

Of 7 patients who underwent hemostatic challenges, additional ITP medications were required in 3 of 3 placebo group patients and 0 of 4 patients treated with PROMACTA. Surgical procedures accounted for most of the hemostatic challenges. Hemorrhage requiring transfusion occurred in one placebo group patient and no patients treated with PROMACTA.

Trial 3: In this trial, 197 patients were randomized (2:1) to receive either PROMACTA 50 mg once daily (n = 135) or placebo (n = 62) for 6 months, during which time the dose of PROMACTA could be adjusted based on individual platelet counts. Patients were allowed to taper or discontinue concomitant ITP medications after being treated with PROMACTA for 6 weeks. Patients were permitted to receive rescue treatments at any time during the trial as clinically indicated.

The median ages of the patients treated with PROMACTA and placebo were 47 years and 52.5 years, respectively. Approximately half of the patients treated with PROMACTA and placebo (47% and 50%, respectively) were receiving concomitant ITP medication (predominantly corticosteroids) at randomization and had baseline platelet counts less than or equal to15 x 10^9/L (50% and 48%, respectively). A similar percentage of patients treated with PROMACTA and placebo (37% and 34%, respectively) had a prior splenectomy.

The efficacy of PROMACTA in this trial was evaluated by the odds of achieving a platelet count greater than or equal to 50 x 10^9/L and less than or equal to 400 x 10^9/L for patients receiving PROMACTA relative to placebo and was based on patient response profiles throughout the 6-month treatment period. In 134 patients who completed 26 weeks of treatment, a sustained platelet response (platelet count greater than or equal to 50 x 10^9/L and less than or equal to 400 x 10^9/L for 6 out of the last 8 weeks of the 26-week treatment period in the absence of rescue medication at any time) was achieved by 60% of patients treated with PROMACTA, compared with 10% of patients treated with placebo (splenectomized patients: PROMACTA 51%, placebo 8%; non-splenectomized patients: PROMACTA 66%, placebo 11%). The proportion of responders in the group of patients treated with PROMACTA was between 37% and 56% compared with 7% and 19% in the placebo treatment group for all on-therapy visits. Patients treated with PROMACTA were significantly more likely to achieve a platelet count between 50 x 10^9/L and 400 x 10^9/L during the entire 6-month treatment period compared with those patients treated with placebo.

Outcomes of treatment are presented in Table 11 for all patients enrolled in the trial.

Table 11. Outcomes of Treatment from Trial 3 in Adults with Chronic Immune (Idiopathic) Thrombocytopenia

Outcome	PROMACTA N = 135	Placebo N = 62
Mean number of weeks with platelet counts ≥50 x 10^9/L	11.3	2.4
Requiring rescue therapy, n (%)	24 (18)	25 (40)

Among 94 patients receiving other ITP therapy at baseline, 37 (59%) of 63 patients treated with PROMACTA and 10 (32%) of 31 patients in the placebo group discontinued concomitant therapy at some time during the trial.

Extension Trial: Patients who completed any prior clinical trial with PROMACTA were enrolled in an open-label, single-arm trial in which attempts were made to decrease the dose or eliminate the need for any concomitant ITP medications. PROMACTA was administered to 302 patients; 218 patients completed 1 year, 180 patients completed 2 years, 107 patients completed 3 years, 75 patients completed 4 years, 34 patients completed 5 years, and 18 patients completed 6 years of therapy. The median baseline platelet count was 19 x 10^9/L prior to administration of PROMACTA. Median platelet counts at 1, 2, 3, 4, 5, 6, and 7 years on study were 85 x 10^9/L, 85 x 10^9/L, 105 x 10^9/L, 64 x 10^9/L, 75 x 10^9/L, 119 x 10^9/L, and 76 x 10^9/L, respectively.

Pediatric Patients: The efficacy and safety of PROMACTA in pediatric patients 1 year and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials. The trials differed in time since ITP diagnosis: at least 6 months versus at least 12 months. During the trials, doses could be increased every 2 weeks to a maximum of 75 mg once daily. The dose of PROMACTA was reduced if the platelet count exceeded 200 x 10^9/L and interrupted and reduced if it exceeded 400 x 10^9/L.

Trial 4: Patients refractory or relapsed to at least one prior ITP therapy with a platelet count less than 30 x 10^9/L (n = 92) were stratified by age and randomized (2:1) to PROMACTA (n = 63) or placebo (n = 29). The starting dose for patients aged 6 to 17 years was 50 mg once daily for those at least 27 kg and 37.5 mg once daily for those less than 27 kg, administered as oral tablets. A reduced dose of 25 mg once daily was used for East Asian patients aged 6 to 17 years regardless of weight. The starting dose for patients aged 1 to 5 years was 1.2 mg/kg once daily (0.8 mg/kg once daily for East Asian patients) administered as oral suspension.

The 13-week, randomized, double-blind period was followed by a 24-week, open-label period where patients from both arms were eligible to receive PROMACTA.

The median age of the patients was 9 years and 48% were female. Approximately 62% of patients had a baseline platelet count less than or equal to 15 x 10^9/L, a characteristic that was similar between treatment arms. The percentage of patients with at least 2 prior ITP therapies (predominantly corticosteroids and immunoglobulins) was 73% in the group treated with PROMACTA and 90% in the group treated with placebo. Four patients in the group treated with PROMACTA had undergone splenectomy.

The efficacy of PROMACTA in this trial was evaluated by the proportion of subjects on PROMACTA achieving platelet counts ≥50 x 10^9/L (in the absence of rescue therapy) for at least 6 out of 8 weeks between Weeks 5 to 12 of the randomized, double-blind period (Table 12).

Table 12. Trial 4 Platelet Count Response (≥50 x 10^9/L without Rescue) for 6 out of 8 Weeks (between Weeks 5 to 12) Overall and by Age Cohort in Pediatric Patients 1 Year and Older with Chronic Immune (Idiopathic) Thrombocytopenia

Age Cohort	PROMACTA	Placebo
Overall	26/63 (41%)[a]	1/29 (3%)
12 to 17 years	10/24 (42%)	1/10 (10%)
6 to 11 years	11/25 (44%)	0/13 (0%)
1 to 5 years	5/14 (36%)	0/6 (0%)

[a] *P* value = <0.001 for PROMACTA versus placebo.

More pediatric patients treated with PROMACTA (75%) compared with placebo (21%) had at least one platelet count greater than or equal to 50 x 10^9/L during the first 12 weeks of randomized treatment in absence of rescue therapy. Fewer pediatric patients treated with PROMACTA required rescue treatment during the randomized, double-blind period compared with placebo-treated patients (19% [12/63] versus 24% [7/29]). In the patients who achieved a platelet response (≥50 x 10^9/L without rescue) for 6 out of 8 weeks (between weeks 5 to 12), 62% (16/26) had an initial response in the first 2 weeks after starting PROMACTA.

Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the trial. Among 15 patients receiving other ITP therapy at baseline, 53% (8/15) reduced (n = 1) or discontinued (n = 7) concomitant therapy, mainly corticosteroids, without needing rescue therapy.

Trial 5: Patients refractory or relapsed to at least one prior ITP therapy with a platelet count less than 30 x 10^9/L (n = 67) were stratified by age and randomized (2:1) to PROMACTA (n = 45) or placebo (n = 22). The starting dose for patients aged 12 to 17 years was 37.5 mg once daily regardless of weight or race. The starting dose for patients aged 6 to 11 years was 50 mg once daily for those greater than or equal to 27 kg and 25 mg once daily for those less than 27 kg, administered as oral tablets. Reduced doses of 25 mg (for those greater than or equal to 27 kg) and 12.5 mg (for those less than 27 kg), each once daily, were used for East Asian patients in this age range. The starting dose for patients aged 1 to 5 years was 1.5 mg/kg once daily (0.8 mg/kg once daily for East Asian patients) administered as oral suspension.

The 7-week, randomized, double-blind period was followed by an open-label period of up to 24 weeks where patients from both arms were eligible to receive PROMACTA.

The median age of the patients was 10 years and 60% were female. Approximately 51% of patients had a baseline platelet count less than or equal to 15 x 10^9/L. The percentage of patients with at least 2 prior ITP therapies (predominantly corticosteroids and immunoglobulins) was 84% in the group treated with PROMACTA and 86% in the group treated with placebo. Five patients in the group treated with PROMACTA had undergone splenectomy.

The efficacy of PROMACTA in this trial was evaluated by the proportion of patients achieving platelet counts greater than or equal to 50 x 10^9/L (in absence of rescue therapy) at least once between Weeks 1 and 6 of the randomized, double-blind period (Table 13). Platelet response to PROMACTA was consistent across the age cohorts.

Table 13. Trial 5 Platelet Count Response (≥50 x 10^9/L without Rescue) Rates in Pediatric Patients 1 Year and Older with Chronic Immune (Idiopathic) Thrombocytopenia

	PROMACTA	Placebo
Overall	28/45 (62%)[a]	7/22 (32%)
12 to 17 years	10/16 (62%)	0/8 (0%)
6 to 11 years	12/19 (63%)	3/9 (33%)
1 to 5 years	6/10 (60%)	4/5 (80%)

[a] *P* value = 0.011 for PROMACTA versus placebo.

Fewer pediatric patients treated with PROMACTA required rescue treatment during the randomized, double-blind period compared with placebo-treated patients (13% [6/45] versus 50% [11/22]).

Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the trial. Among 13 patients receiving other ITP therapy at baseline, 46% (6/13) reduced (n = 3) or discontinued (n = 3) concomitant therapy, mainly corticosteroids, without needing rescue therapy.

14.2 Chronic Hepatitis C-associated Thrombocytopenia

The efficacy and safety of PROMACTA for the treatment of thrombocytopenia in adult patients with chronic hepatitis C were evaluated in two randomized, double-blind, placebo-controlled trials. Trial 1 utilized peginterferon alfa-2a (PEGASYS®) plus ribavirin for antiviral treatment and Trial 2 utilized peginterferon alfa-2b (PEGINTRON®) plus ribavirin. In both trials, patients with a platelet count of less than 75 x 10^9/L were enrolled and stratified by platelet count, screening HCV RNA, and HCV genotype. Patients were excluded if they had evidence of decompensated liver disease with Child-Pugh score greater than 6 (class B and C), history of ascites, or hepatic encephalopathy. The median age of the patients in both trials was 52 years, 63% were male, and 74% were Caucasian. Sixty-nine percent of patients had HCV genotypes 1, 4, 6, with the remainder genotypes 2 and 3. Approximately 30% of patients had been previously treated with interferon and ribavirin. The majority of patients (90%) had bridging fibrosis and cirrhosis, as indicated by noninvasive testing. A similar proportion (95%) of patients in both treatment groups had Child-Pugh Class A (score 5 to 6) at baseline. A similar proportion of patients (2%) in both treatment groups had baseline international normalized ratio (INR) greater than 1.7. Median baseline platelet counts (approximately 60 x 10^9/L) were similar in both treatment groups. The trials consisted of 2 phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label PROMACTA to increase the platelet count to a threshold of greater than or equal to 90 x 10^9/L for Trial 1 and greater than or equal to 100 x 10^9/L for Trial 2. PROMACTA was administered at an initial dose of 25 mg once daily for 2 weeks and increased in 25-mg increments over 2- to 3-week periods to achieve the optimal platelet count to initiate antiviral therapy. The maximal time patients could receive open-label PROMACTA was 9 weeks. If threshold platelet counts were achieved, patients were randomized (2:1) to the same dose of PROMACTA at the end of the pre-treatment phase or to placebo. PROMACTA was administered in combination with pegylated interferon and ribavirin per their respective prescribing information for up to 48 weeks.

The efficacy of PROMACTA for both trials was evaluated by sustained virologic response (SVR) defined as the percentage of patients with undetectable HCV-RNA at 24 weeks after completion of antiviral treatment. The median time to achieve the target platelet count greater than or equal to 90 x 10^9/L was approximately 2 weeks. Ninety-five percent of patients were able to initiate antiviral therapy.

In both trials, a significantly greater proportion of patients treated with PROMACTA achieved SVR (see Table 14). The improvement in the proportion of patients who achieved SVR was consistent across subgroups based on baseline platelet count (less than 50 x 10^9/L versus greater than or equal to 50 x 10^9/L). In patients with high baseline viral loads (greater than or equal to 800,000), the SVR rate was 18% (82/452) for PROMACTA versus 8% (20/239) for placebo.

Table 14. Trials 1 and 2 Sustained Virologic Response in Adults with Chronic Hepatitis C

Pre-antiviral Treatment Phase	Trial 1[a] N = 715		Trial 2[b] N = 805	
% Patients who achieved target platelet counts and initiated antiviral therapy[c]	95%		94%	
Antiviral Treatment Phase	**PROMACTA N = 450 %**	**Placebo N = 232 %**	**PROMACTA N = 506 %**	**Placebo N = 253 %**
Overall SVR[d]	23	14	19	13
HCV Genotype 2,3	35	24	34	25
HCV Genotype 1,4,6	18	10	13	7

[a] PROMACTA given in combination with peginterferon alfa-2a (180 mcg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,200 mg daily in 2 divided doses orally).

[b] PROMACTA given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,400 mg daily in 2 divided doses orally).

[c] Target platelet count was $\geq 90 \times 10^9$/L for Trial 1 and $\geq 100 \times 10^9$/L for Trial 2.

[d] *P* value <0.05 for PROMACTA versus placebo.

The majority of patients treated with PROMACTA (76%) maintained a platelet count greater than or equal to 50×10^9/L compared with 19% for placebo. A greater proportion of patients on PROMACTA did not require any antiviral dose reduction as compared with placebo (45% versus 27%).

14.3 Severe Aplastic Anemia

PROMACTA was studied in a single-arm, single-center, open-label trial in 43 patients with severe aplastic anemia who had an insufficient response to at least one prior immunosuppressive therapy and who had a platelet count less than or equal to 30×10^9/L. PROMACTA was administered at an initial dose of 50 mg once daily for 2 weeks and increased over 2-week periods up to a maximum dose of 150 mg once daily. The efficacy of PROMACTA in the study was evaluated by the hematologic response assessed after 12 weeks of treatment. Hematologic response was defined as meeting 1 or more of the following criteria: 1) platelet count increases to 20×10^9/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) hemoglobin increase by greater than 1.5 g/dL, or a reduction in greater than or equal to 4 units of RBC transfusions for 8 consecutive weeks; 3) ANC increase of 100% or an ANC increase greater than 0.5×10^9/L. PROMACTA was discontinued after 16 weeks if no hematologic response was observed. Patients who responded continued therapy in an extension phase of the trial.

The treated population had median age of 45 years (range: 17 to 77 years) and 56% were male. At baseline, the median platelet count was 20×10^9/L, hemoglobin was 8.4 g/dL, ANC was 0.58×10^9/L, and absolute reticulocyte count was 24.3×10^9/L. Eighty-six percent of patients were RBC transfusion dependent and 91% were platelet transfusion dependent. The majority of patients (84%) received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

Table 15 presents the efficacy results.

Table 15. Hematologic Response in Patients with Severe Aplastic Anemia

Outcome	PROMACTA N = 43
Response rate[a], n (%) 95% CI (%)	17 (40) (25, 56)
Median of duration of response in months (95% CI)	NR[b] (3.0, NR[b])

[a] Includes single- and multi-lineage.
[b] NR = Not reached due to few events (relapsed).

In the 17 responders, the platelet transfusion-free period ranged from 8 to 1,096 days with a median of 200 days, and the RBC transfusion-free period ranged from 15 to 1,082 days with a median of 208 days.

In the extension phase, 8 patients achieved a multi-lineage response; 4 of these patients subsequently tapered off treatment with PROMACTA and maintained the response (median follow up: 8.1 months, range: 7.2 to 10.6 months).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Tablets

- The 12.5-mg tablets are round, biconvex, white, film-coated tablets debossed with GS MZ1 and 12.5 on one side and are available in bottles of 30: NDC 0078-0684-15.
- The 25-mg tablets are round, biconvex, orange, film-coated tablets debossed with GS NX3 and 25 on one side and are available in bottles of 30: NDC 0078-0685-15.
- The 50-mg tablets are round, biconvex, blue, film-coated tablets debossed with GS UFU and 50 on one side and are available in bottles of 30: NDC 0078-0686-15.
- The 75-mg tablets are round, biconvex, pink, film-coated tablets debossed with GS FFS and 75 on one side and are available in bottles of 30: NDC 0078-0687-15.
- The 100-mg tablets are round, biconvex, green, film-coated tablets debossed with GS 1L5 and are available in bottles of 30: NDC 0078-0688-15. This product contains a desiccant.

Store at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*. Do not remove desiccant if present. Dispense in original bottle.

16.2 For Oral Suspension

The 25-mg for oral suspension is a reddish-brown to yellow powder in unit-dose packets, co-packaged in a kit with a 40-cc reconstitution vessel, an oral dosing syringe, and a threaded closure with syringe-port capability.

Each kit (NDC 0078-0697-61) contains 30 packets: NDC 0078-0697-19.

Store at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Following reconstitution, the product should be administered immediately but may be stored for a maximum period of 30 minutes between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Throw away (discard) the mixture if not used within 30 minutes.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Prior to treatment, patients should fully understand and be informed of the following risks and considerations for PROMACTA:

Risks

Hepatotoxicity

- Therapy with PROMACTA may be associated with hepatobiliary laboratory abnormalities *[see Warnings and Precautions (5.2)]*.
- Advise patients with chronic hepatitis C and cirrhosis that they may be at risk for hepatic decompensation when receiving PROMACTA with alfa interferon therapy *[see Warnings and Precautions (5.1)]*.
- Advise patients that they should report any of the following signs and symptoms of liver problems to their healthcare provider right away *[see Warnings and Precautions (5.2)]*.
  - yellowing of the skin or the whites of the eyes (jaundice)
  - unusual darkening of the urine
  - unusual tiredness
  - right upper stomach area pain
  - confusion
  - swelling of the stomach area (abdomen)

Risk of Bleeding Upon PROMACTA Discontinuation

- Advise patients that thrombocytopenia and risk of bleeding may reoccur upon discontinuing PROMACTA, particularly if PROMACTA is discontinued while the patient is on anticoagulants or antiplatelet agents. Advise patients that during therapy with PROMACTA, they should continue to avoid situations or medications that may increase the risk for bleeding.

Thrombotic/Thromboembolic Complications

- Advise patients that too much PROMACTA may result in excessive platelet counts and a risk for thrombotic/thromboembolic complications *[see Warnings and Precautions (5.3)]*.

Cataracts

- Advise patients to have a baseline ocular examination prior to administration of PROMACTA and be monitored for signs and symptoms of cataracts during therapy *[see Warnings and Precautions (5.4)]*.

Drug Interactions

- Advise patients to take PROMACTA at least 2 hours before or 4 hours after foods, mineral supplements, and antacids which contain polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc *[see Dosage and Administration (2.4), Drug Interactions (7.1)]*.

Administration of PROMACTA

- For patients with chronic ITP, therapy with PROMACTA is administered to achieve and maintain a platelet count greater than or equal to 50 x 10^9/L as necessary to reduce the risk for bleeding *[see Indications and Usage (1.1)]*.
- For patients with chronic hepatitis C, therapy with PROMACTA is administered to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin *[see Indications and Usage (1.2)]*.
- Prior to use of the oral suspension, ensure patients or caregivers receive training on proper dosing, preparation, and administration *[see Dosage and Administration (2.4)]*.
- Inform patients or caregivers how many packets to administer to get the full dose *[see Instructions for Use]*.

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MEDICATION GUIDE

PROMACTA® (pro-MAC-ta) (eltrombopag) tablets	**PROMACTA® (pro-MAC-ta) (eltrombopag) for oral suspension**

What is the most important information I should know about PROMACTA?

PROMACTA can cause serious side effects, including:

Liver problems. If you have chronic hepatitis C virus, and take PROMACTA with interferon and ribavirin treatment, PROMACTA may increase your risk of liver problems. Tell your healthcare provider right away if you have any of these signs and symptoms of liver problems:

- yellowing of the skin or the whites of the eyes (jaundice)
- unusual darkening of the urine
- unusual tiredness
- right upper stomach area (abdomen) pain
- confusion
- swelling of the stomach area (abdomen)

See "What are the possible side effects of PROMACTA?" for other side effects of PROMACTA.

What is PROMACTA?

PROMACTA is a prescription medicine used to treat adults and children 1 year of age and older with low blood platelet counts due to chronic immune (idiopathic) thrombocytopenia (ITP), when other medicines to treat ITP or surgery to remove the spleen have not worked well enough.

PROMACTA is also used to treat people with:

- low blood platelet counts due to chronic hepatitis C virus (HCV) infection before and during treatment with interferon.
- severe aplastic anemia (SAA) when other medicines to treat SAA have not worked well enough.

PROMACTA is used to try to raise platelet counts in order to lower your risk for bleeding.

PROMACTA is not used to make platelet counts normal.

PROMACTA is for treatment of certain people with low platelet counts caused by chronic ITP, chronic HCV, or SAA, not low platelet counts caused by other conditions or diseases.

It is not known if PROMACTA is safe and effective when used with other antiviral medicines that are approved to treat chronic hepatitis C.

It is not known if PROMACTA is safe and effective in children with chronic hepatitis C or severe aplastic anemia or in children younger than 1 year with ITP.

What should I tell my healthcare provider before taking PROMACTA?

Before you take PROMACTA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have or had a blood clot
- have a history of cataracts
- have had surgery to remove your spleen (splenectomy)
- have bleeding problems
- are Asian and you are of Chinese, Japanese, Taiwanese, or Korean ancestry. You may need a lower dose of PROMACTA.
- are pregnant or plan to become pregnant. It is not known if PROMACTA will harm an unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if PROMACTA passes into your breast milk. You and your healthcare provider should decide whether you will take PROMACTA or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. PROMACTA may affect the way certain medicines work. Certain other medicines may affect the way PROMACTA works.

Especially tell your healthcare provider if you take:

- certain medicines used to treat high cholesterol, called "statins".
- a blood thinner medicine.

Certain medicines may keep PROMACTA from working correctly. Take PROMACTA at least 2 hours before or 4 hours

after taking these products:

- antacid medicine used to treat stomach ulcers or heartburn
- multivitamins or products that contain iron, calcium, aluminum, magnesium, selenium, and zinc which may be found in mineral supplements

Ask your healthcare provider if you are not sure if your medicine is one that is listed above.

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

How should I take PROMACTA?

- Take PROMACTA exactly as your healthcare provider tells you to take it. Your healthcare provider will prescribe the dose of PROMACTA tablets or PROMACTA oral suspension that is right for you.
- If your healthcare provider prescribes PROMACTA oral suspension, see “Instructions for Use” that comes with your medicine for instructions on how to prepare and take your dose.
- Do not stop taking PROMACTA without talking with your healthcare provider first. Do not change your dose or schedule for taking PROMACTA unless your healthcare provider tells you to change it.
- Take PROMACTA on an empty stomach, either 1 hour before or 2 hours after eating food.
- Take PROMACTA at least 2 hours before or 4 hours after eating dairy products and calcium-fortified juices.
- **Take PROMACTA tablets whole. Do not crush PROMACTA tablets and mix with food or liquids.**
  If you miss a dose of PROMACTA, wait and take your next scheduled dose. Do not take more than one dose of PROMACTA in one day.
- If you take too much PROMACTA, you may have a higher risk of serious side effects. Call your healthcare provider right away.
- Your healthcare provider will check your platelet count during your treatment with PROMACTA and change your dose of PROMACTA as needed.
- Tell your healthcare provider about any bruising or bleeding that happens while you take and after you stop taking PROMACTA.

What should I avoid while taking PROMACTA?

Avoid situations and medicines that may increase your risk of bleeding.

What are the possible side effects of PROMACTA?
PROMACTA may cause serious side effects, including:

- See **“What is the most important information I should know about PROMACTA?”**
- **Abnormal liver function tests.** Your healthcare provider will order blood tests to check your liver before you start taking PROMACTA and during your treatment. In some cases treatment with PROMACTA may need to be stopped due to changes in your liver function tests.
- **High platelet counts and higher risk for blood clots.** Your risk of getting a blood clot is increased if your platelet count is too high during treatment with PROMACTA. Your risk of getting a blood clot may also be increased during treatment with PROMACTA if you have normal or low platelet counts. You may have severe problems or die from some forms of blood clots, such as clots that travel to the lungs or that cause heart attacks or strokes. Your healthcare provider will check your blood platelet counts, and change your dose or stop PROMACTA if your platelet counts get too high. Tell your healthcare provider right away if you have signs and symptoms of a blood clot in the leg, such as swelling, pain, or tenderness in your leg.

  People with chronic liver disease may be at risk for a type of blood clot in the stomach area. Tell your healthcare provider right away if you have stomach area pain that may be a symptom of this type of blood clot.
- **New or worsened cataracts (a clouding of the lens in the eye).** New or worsened cataracts have happened in people taking PROMACTA. Your healthcare provider will check your eyes before and during your treatment with PROMACTA. Tell your healthcare provider about any changes in your eyesight while taking PROMACTA.

The most common side effects of PROMACTA in adults when used to treat chronic ITP are:

- nausea
- diarrhea
- upper respiratory tract infection. Symptoms may include runny nose, stuffy nose, and sneezing
- vomiting
- muscle aches
- urinary tract infection. Symptoms may include frequent or urgent need to urinate, low fever in some people, pain or burning with urination.
- pain or swelling (inflammation) in your throat or mouth (oropharyngeal pain and pharyngitis)
- abnormal liver function tests
- back pain
- ”flu”-like symptoms (influenza) including fever, headache, tiredness, cough, sore throat, and body aches
- skin tingling, itching, or burning
- rash

The most common side effects of PROMACTA in children 1 year and older when used to treat chronic ITP are:

- upper respiratory tract infection. Symptoms may include runny nose, stuffy nose, and sneezing.
- pain or swelling (inflammation) in your nose or throat (nasopharyngitis)
- cough
- diarrhea
- fever
- runny, stuffy nose (rhinitis)
- stomach (abdominal) pain
- pain or swelling (inflammation) in your throat or mouth (oropharyngeal pain)
- toothache
- rash
- abnormal liver function tests

The most common side effects when PROMACTA is used in combination with other medicines to treat chronic HCV are:

- low red blood cell count (anemia)
- fever
- tiredness
- headache
- nausea
- diarrhea
- decreased appetite
- “flu”-like symptoms (influenza) including fever, headache, tiredness, cough, sore throat, and body aches
- feeling weak
- trouble sleeping
- cough
- itching
- chills
- muscle aches
- hair loss
- swelling in your ankles, feet, and legs

The most common side effects when PROMACTA is used to treat severe aplastic anemia are:

- nausea
- feeling tired
- cough
- diarrhea
- headache

Laboratory tests may show abnormal changes to the cells in your bone marrow.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of PROMACTA. For more information, ask your healthcare provider or pharmacist.

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

How should I store PROMACTA tablets and oral suspension?

Tablets:

- Store PROMACTA tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep PROMACTA tightly closed in the bottle given to you.
- The PROMACTA bottle may contain a desiccant pack to help keep your medicine dry. Do not remove the desiccant pack from the bottle.

For oral suspension:

- Store PROMACTA for oral suspension at room temperature between 68°F to 77°F (20°C to 25°C).
- After mixing, PROMACTA should be taken right away but may be stored for no more than 30 minutes between 68°F to 77°F (20°C to 25°C). Throw away (discard) the mixture if not used within 30 minutes.

Keep PROMACTA and all medicines out of the reach of children.

General information about the safe and effective use of PROMACTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PROMACTA for a condition for which it was not prescribed. Do not give PROMACTA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about PROMACTA that is written for health professionals.

What are the ingredients in PROMACTA?

Tablets:

Active ingredient: eltrombopag olamine.

Inactive ingredients:

- **Tablet Core:** magnesium stearate, mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate.
- **Coating:** hypromellose (12.5-mg, 25-mg, 50-mg, and 75-mg tablets) or polyvinyl alcohol and talc (100-mg tablet), polyethylene glycol 400, titanium dioxide, polysorbate 80 (12.5-mg tablet), and FD&C Yellow No. 6 aluminum lake (25-mg tablet), FD&C Blue No. 2 aluminum lake (50-mg tablet), Iron Oxide Red and Iron Oxide Black (75-mg tablet), or Iron Oxide Yellow and Iron Oxide Black (100-mg tablet).

For oral suspension:

Active ingredient: eltrombopag olamine.

Inactive ingredients: mannitol, sucralose, xanthan gum.

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For more information about PROMACTA, go to www.PROMACTA.com or call 1-888-669-6682.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised July 2017

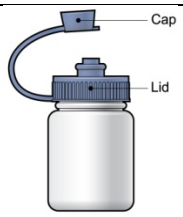
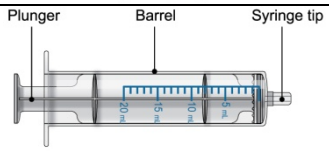
INSTRUCTIONS FOR USE
PROMACTA® (pro-MAC-ta)
(eltrombopag)
for oral suspension

Read all the Instructions for Use and follow the steps below to mix and give a dose of PROMACTA for oral suspension.

Important:

- **Do not take PROMACTA for oral suspension or give it to someone else until you have been shown how to properly give PROMACTA for oral suspension.** Your healthcare provider or nurse will show you how to prepare and give a dose of PROMACTA for oral suspension properly.
- **PROMACTA for oral suspension must be mixed with cool or cold water only.** Do not use hot water to prepare the oral suspension.
- Give the dose of suspension right away after mixing with water. **If medicine is not given within 30 minutes, you will have to mix a new dose.** Throw away (discard) the unused mixture into the trash. Do not pour it down the drain.
    - If PROMACTA for oral suspension comes in contact with your skin, wash the skin right away with soap and water. Call your healthcare provider if you have a skin reaction or if you have any questions. If you spill any powder or liquid, follow the clean up instructions in **Step 12**.
- Contact your healthcare provider or pharmacist if you have any questions about how to mix or give PROMACTA to the child or if you damage or lose any of the supplies in your kit.
- After you have used all 30 packets, throw all the remaining supplies (mixing bottle, lid with cap, and oral dosing syringe) away in the trash.

Each PROMACTA for oral suspension kit contains the following supplies:

30 packets of PROMACTA for oral suspension	
1 Reusable mixing bottle with lid and cap	
1 Reusable 20-mL oral dosing syringe	

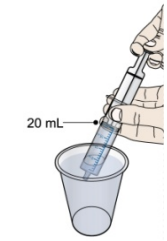
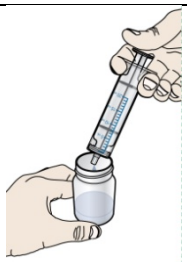
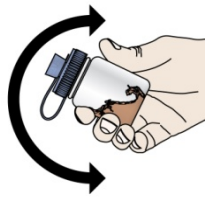
You will need the following to give a single dose of PROMACTA for oral suspension.

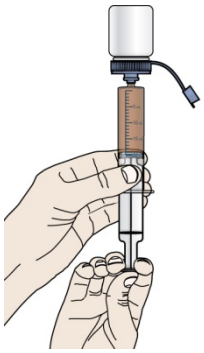
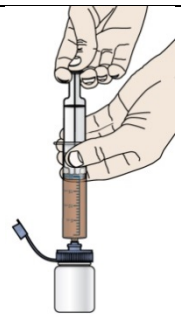
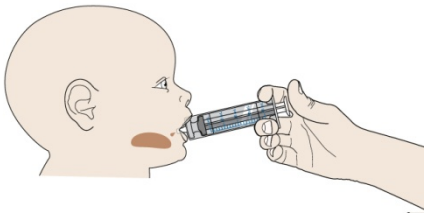
From the kit:

- prescribed number of packets
- 1 reusable mixing bottle with lid and cap. NOTE: Due to its small size, the cap may pose a danger of choking to small children.
- 1 reusable 20-mL oral dosing syringe

Not included in the kit:

- 1 clean glass or cup filled with drinking water
- scissors to cut packet
- paper towels or disposable cloth
- disposable gloves (optional)

How do I prepare a dose of PROMACTA for oral suspension?	
Step 1. Make sure that the mixing bottle, cap, lid and oral dosing syringe are dry before use. Remove the lid from the mixing bottle. • Prepare a clean, flat work surface. • Wash and dry your hands before preparing the medicine.	
Step 2. Fill the oral dosing syringe with 20 mL of drinking water from the glass or cup. • Start with the plunger pushed all the way into the syringe. • Put the tip of the oral dosing syringe all the way into the water and pull back on the plunger to the 20 mL mark on the barrel of the oral dosing syringe.	
Step 3. Place the oral dosing syringe into the open mixing bottle. Empty water into open mixing bottle by slowly pushing the plunger all the way into the oral dosing syringe.	
Step 4. Take only the prescribed number of packets for one dose out of the kit. You may need to use more than one packet to prepare the entire dose. • 12.5-mg dose (1 packet); Note: See Step 9 for instructions on how to give a 12.5-mg dose. • 25-mg dose (1 packet) • 50-mg dose (2 packets) • 75-mg dose (3 packets)	
Step 5. Add the prescribed number of packets to the mixing bottle. • Tap the top of each packet to make sure the contents fall to the bottom. • Cut off the top of the packet with scissors and empty the entire contents of the packet into the mixing bottle. • Make sure not to spill the powder outside the mixing bottle.	
Step 6. Screw the lid tightly onto the mixing bottle. Make sure the cap is pushed onto the lid.	
Step 7. Gently and slowly shake the mixing bottle back and forth for at least 20 seconds to mix the water with the powder. • To prevent the mixture from foaming, do not shake the mixing bottle hard.	
How should I give a dose of PROMACTA for oral suspension?	
Step 8. Make sure the plunger is pushed all the way into the oral dosing syringe. Pull cap off the mixing bottle lid and insert the tip of the oral dosing syringe into the hole in the lid.	

Step 9. Transfer the mixture into the oral dosing syringe. The liquid will be dark brown in color. • Turn the mixing bottle upside down along with the oral dosing syringe. • Pull back the plunger: o to the 10 mL mark on the oral dosing syringe for a **12.5-mg dose only** **OR** o until all the medicine is in the oral dosing syringe (25-mg, 50-mg, or 75-mg dose).	
Step 10. Return the mixing bottle to the upright position and remove the oral dosing syringe from the mixing bottle.	
Step 11. Giving a dose of PROMACTA for oral suspension to a child. • Place the tip of the oral dosing syringe into the inside of the child's cheek. • Slowly push the plunger all the way down to give the entire dose. Make sure the child has time to swallow the medicine.	
How should I clean up?	
Step 12. Carefully clean up any spill of the powder or suspension with a damp paper towel or disposable cloth. • To avoid possibly staining your skin, consider using disposable gloves. • Throw away (discard) used paper towel or disposable cloth and gloves in the trash.	
Step 13. Clean the mixing supplies. • **Do not reuse any of the mixture remaining in the mixing bottle.** • Throw away (discard) any mixture remaining in the mixing bottle in the trash. Do not pour down the drain. • Remove the plunger from the oral dosing syringe. • Rinse the mixing bottle, lid, oral dosing syringe, and plunger under running water and air dry. The mixing bottle may become stained from the medicine. This is normal. • Wash hands with soap and water.	

How should I store PROMACTA for oral suspension?

- Store PROMACTA for oral suspension at room temperature between 68°F to 77°F (20°C to 25°C).
- After mixing, PROMACTA should be taken right away but may be stored for no more than 30 minutes between 68°F to 77°F (20°C to 25°C). Throw away (discard) the mixture if not used within 30 minutes.

Keep PROMACTA and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: July 2017

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 12.5 mg film-coated tablets
Revolade 25 mg film-coated tablets
Revolade 50 mg film-coated tablets
Revolade 75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Revolade 12.5 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 12.5 mg eltrombopag.

Revolade 25 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

Revolade 50 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.

Revolade 75 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Revolade 12.5 mg film-coated tablets
Round, biconvex, white film-coated tablet (approximately 7.9 mm in diameter) debossed with 'GS MZ1' and '12.5' on one side.

Revolade 25 mg film-coated tablets
Round, biconvex, white film-coated tablet (approximately 10.3 mm in diameter) debossed with 'GS NX3' and '25' on one side.

Revolade 50 mg film-coated tablets
Round, biconvex, brown film-coated tablet (approximately 10.3 mm in diameter) debossed with 'GS UFU' and '50' on one side.

Revolade 75 mg film-coated tablets
Round, biconvex, pink film-coated tablet (approximately 10.3 mm in diameter) debossed with 'GS FFS' and '75' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revolade is indicated for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (see sections 4.4 and 5.1).

Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation (see section 5.1).

4.2 Posology and method of administration

Eltrombopag treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of haematological diseases or the management of chronic hepatitis C and its complications.

Posology

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts.

The powder for oral suspension may lead to higher eltrombopag exposure than the tablet formulation (see section 5.2). When switching between the tablet and powder for oral suspension formulations, platelet counts should be monitored weekly for 2 weeks.

Chronic immune (idiopathic) thrombocytopenia

The lowest dose of eltrombopag to achieve and maintain a platelet count ≥ 50,000/µl should be used. Dose adjustments are based upon the platelet count response. Eltrombopag must not be used to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation.

Adults and paediatric population aged 6 to 17 years
The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2).

Paediatric population aged 1 to 5 years
The recommended starting dose of eltrombopag is 25 mg once daily.

Monitoring and dose adjustment

After initiating eltrombopag, the dose must be adjusted to achieve and maintain a platelet count ≥ 50,000/µl as necessary to reduce the risk for bleeding. A daily dose of 75 mg must not be exceeded.

Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in Table 1. During therapy with eltrombopag full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥ 50,000/µl for at least 4 weeks) has been achieved. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

Table 1 Dose adjustments of eltrombopag in ITP patients

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day*.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
> 250,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg.

* - For patients taking 25 mg eltrombopag once every other day, increase dose to 25 mg once daily.
♦ - For patients taking 25 mg eltrombopag once daily, consideration should be given to dosing at 12.5 mg once daily or alternatively a dose of 25 mg once every other day.

Eltrombopag can be administered in addition to other ITP medicinal products. The dose regimen of concomitant ITP medicinal products should be modified, as medically appropriate, to avoid excessive increases in platelet counts during therapy with eltrombopag.

It is necessary to wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment.

The standard eltrombopag dose adjustment, either decrease or increase, would be 25 mg once daily.

Discontinuation

Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag therapy at 75 mg once daily.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. In non-splenectomised patients this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see section 4.4).

Chronic hepatitis C (HCV) associated thrombocytopenia

When eltrombopag is given in combination with antivirals reference should be made to the full summary of product characteristics of the respective coadministered medicinal products for comprehensive details of relevant safety information or contraindications.

In clinical studies, platelet counts generally began to increase within 1 week of starting eltrombopag. The aim of treatment with eltrombopag should be to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level that prevents the risk of bleeding complications, normally around 50,000-75,000/µl. Platelet counts > 75,000/µl should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

Initial dose regimen

Eltrombopag should be initiated at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East Asian ancestry or patients with mild hepatic impairment (see section 5.2).

Monitoring and dose adjustment

The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate anti-viral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided (see Table 2).

During antiviral therapy, the dose of eltrombopag should be adjusted as necessary to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding (see Table 2). Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved, normally around 50,000-75,000/µl. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter. Dose reductions on the daily dose by 25 mg should be considered if platelet counts exceed the required target. It is recommended to wait for 2 weeks to assess the effects of this and any subsequent dose adjustments.

A dose of 100 mg eltrombopag once daily must not be exceeded.

Table 2 Dose adjustments of eltrombopag in HCV patients during antiviral therapy

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
≥ 50,000/µl to ≤ 100,000/µl	Use lowest dose of eltrombopag as necessary to avoid dose reductions of peginterferon
> 100,000/µl to ≤ 150,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
> 150,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg*.

* - For patients taking 25 mg eltrombopag once daily, consideration should be given to reinitiating dosing at 25 mg every other day.
♦ - On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

Discontinuation

If after 2 weeks of eltrombopag therapy at 100 mg the required platelet level to initiate antiviral therapy is not achieved, eltrombopag should be discontinued.

Eltrombopag treatment should be terminated when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation.

Severe aplastic anaemia

Initial dose regimen

Eltrombopag should be initiated at a dose of 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2). The treatment should not be initiated when the patients have existing cytogenetic abnormalities of chromosome 7.

Monitoring and dose adjustment

Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting eltrombopag (see section 5.1). The dose of eltrombopag should be adjusted in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥ 50,000/µl. For patients taking 25 mg once daily, the dose should be increased to 50 mg daily before increasing the dose amount by 50 mg. A dose of 150 mg daily must not be exceeded. Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dosage regimen of eltrombopag modified based on platelet counts as outlined in Table 3.

Table 3 Dose adjustments of eltrombopag in patients with severe aplastic anaemia

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag to maintain platelet counts.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/µl	Stop eltrombopag; for at least one week. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 50 mg.

Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders

For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of eltrombopag may be reduced by 50%.

If counts remain stable after 8 weeks at the reduced dose, then eltrombopag must be discontinued and blood counts monitored. If platelet counts drop to < 30,000/µl, haemoglobin to < 9 g/dL or ANC < 0.5 x 10^9/L, eltrombopag may be reinitiated at the previous effective dose.

Discontinuation

If no haematological response has occurred after 16 weeks of therapy with eltrombopag, therapy should be discontinued. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate (see sections 4.4 and 4.8). Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of eltrombopag (see section 4.8).

<u>*Special populations*</u>

Renal impairment

No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section 5.2).

Hepatic impairment

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see section 4.4).

If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 3 weeks should be observed before increasing the dose.

No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤ 6). Chronic HCV patients and severe aplastic anaemia patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily (see section 5.2). After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 2 weeks should be observed before increasing the dose.

There is an increased risk for adverse events, including hepatic decompensation and thromboembolic events, in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections 4.4 and 4.8).

Elderly

There are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see section 5.2).

There are limited data on the use of eltrombopag in HCV and SAA patients aged over 75 years. Caution should be exercised in these patients (see section 4.4).

East Asian patients

For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), including those with hepatic impairment, eltrombopag should be initiated at a dose of 25 mg once daily (see section 5.2).

Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

Paediatric population

Revolade is not recommended for use in children under the age of one year with chronic ITP due to insufficient data on safety and efficacy. The safety and efficacy of eltrombopag has not been established in children and adolescents (< 18 years) with chronic HCV related thrombocytopenia or SAA. No data are available.

<u>Method of administration</u>

Oral use.
The tablets should be taken at least two hours before or four hours after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc) (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to eltrombopag or to any of the excipients, listed in section 6.1.

4.4 Special warnings and precautions for use

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤ 35 g/L or model for end stage liver disease (MELD) score ≥ 10, when treated with eltrombopag in combination with interferon-based therapy. In addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35g/L) compared with the group overall. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.

Combination with direct acting antiviral agents

Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection.

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function and severe hepatotoxicity, which might be life-threatening. In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed (see section 4.8).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies in adults with chronic ITP, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality. In two placebo-controlled studies in paediatric patients (aged 1 to 17 years) with chronic ITP, ALT ≥ 3 times the upper limit of normal (x ULN) was reported in 4.7% and 0% of the eltrombopag and placebo groups, respectively.

In 2 controlled clinical studies in patients with HCV, ALT or AST ≥ 3 x ULN was reported in 34% and 38% of the eltrombopag and placebo groups, respectively. Most patients receiving eltrombopag in combination with peginterferon / ribavirin therapy will experience indirect hyperbilirubinaemia. Overall, total bilirubin ≥ 1.5 x ULN was reported in 76% and 50% of the eltrombopag and placebo groups, respectively.

Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinaemia. If bilirubin is elevated fractionation should be performed. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥ 3 x ULN in patients with normal liver function, or ≥ 3 x baseline or > 5 x ULN, whichever is the lower, in patients with pre-treatment elevations in transaminases) and are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Caution is required when administering eltrombopag to patients with hepatic disease. In ITP and SAA patients a lower starting dose of eltrombopag should be used. Close monitoring is required when administering to patients with hepatic impairment (see section 4.2).

Hepatic decompensation (use with interferon)

Hepatic decompensation in patients with chronic hepatitis C: Monitoring is required in patients with low albumin levels (≤ 35 g/L) or with MELD score ≥ 10 at baseline.

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤ 35 g/L) or MELD score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. In addition, the benefits of treatment in terms of the proportion achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35 g/L) compared with the group overall. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon summary of product characteristics should be referenced for discontinuation criteria. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/Thromboembolic complications

In controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy (n=1,439), 38 out of 955 subjects (4%) treated with eltrombopag and 6 out of 484 subjects (1%) in the placebo group experienced thromboembolic events (TEEs). Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus < 1% for placebo). No specific temporal relationship between start of treatment and event of TEE were observed. Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1%) subjects in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count > 200,000/µl and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In eltrombopag clinical trials in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels (see section 4.2). The risk-benefit balance should be considered in patients at risk of thromboembolic events (TEEs) of any aetiology.

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, caution is required when administering eltrombopag to patients with hepatic impairment (see sections 4.2 and 4.8).

<u>Bleeding following discontinuation of eltrombopag</u>

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increases the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of eltrombopag.

In HCV clinical trials, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding.

<u>Bone marrow reticulin formation and risk of bone marrow fibrosis</u>

Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin receptor (TPO-R) agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, full blood count (FBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression of existing myelodysplastic syndrome (MDS)

TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For TPO-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS.

In clinical studies with a TPO-R agonist in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported.

The diagnosis of ITP or SAA in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms, or abnormal signs such as increased peripheral blast cells.

The effectiveness and safety of eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia or MDS. Eltrombopag should not be used outside of clinical trials for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than the approved indications.

Cytogenetic abnormalities and progression to MDS/AML in patients with SAA

Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II SAA clinical study with eltrombopag, the incidence of new cytogenetic abnormalities was observed in 19% of patients [8/43 (where 5 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In clinical trials with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment.

For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate.

Ocular changes

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n=1,439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8% of the eltrombopag group and 5% of the placebo group. Retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2% of the eltrombopag group and 2% of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended.

QT/QTc prolongation

A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarisation. QTc interval prolongation has been reported in clinical trials of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

Loss of response to eltrombopag

A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

Paediatric population

The above warnings and precautions for ITP also apply to the paediatric population.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter. *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103% (90% confidence interval [CI]: 82%, 126%) and $AUC_{0-\infty}$ 55% (90% CI: 42%, 69%). Interactions are also expected with other HMG-CoA reductase inhibitors, including atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 5.2).

OATP1B1 and BCRP substrates

Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution (see section 5.2).

Cytochrome P450 substrates

In studies utilising human liver microsomes, eltrombopag (up to 100 μM) showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates. Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates are co-administered (see section 5.2).

HCV protease inhibitors

Dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir. Co-administration of a single dose of eltrombopag 200 mg with telaprevir 750 mg every 8 hours did not alter plasma telaprevir exposure.

Co-administration of a single dose of eltrombopag 200 mg with boceprevir 800 mg every 8 hours did not alter plasma boceprevir $AUC_{(0-\tau)}$, but increased C_{max} by 20%, and decreased C_{min} by 32%. The clinical relevance of the decrease in C_{min} has not been established, increased clinical and laboratory monitoring for HCV suppression is recommended.

Effects of other medicinal products on eltrombopag

Ciclosporin

In vitro studies demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg ciclosporin (a BCRP inhibitor) (see section 5.2). Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count (see section 4.2). Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with ciclosporin. Eltrombopag dose may need to be increased based on these platelet counts.

Polyvalent cations (chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62%, 76%). Eltrombopag should be taken at least two hours before or four hours after any products such as antacids, dairy products or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption due to chelation (see sections 4.2 and 5.2).

Food interaction

The administration of eltrombopag tablet or powder for oral suspension with a high-calcium meal (e.g. a meal that included dairy products) significantly reduced plasma eltrombopag $AUC_{0-\infty}$ and C_{max}. In contrast, the administration of eltrombopag 2 hours before or 4 hours after a high-calcium meal or with low-calcium food [< 50 mg calcium] did not alter plasma eltrombopag exposure to a clinically significant extent (see sections 4.2 and 5.2).

Lopinavir/ritonavir

Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of single dose eltrombopag 100 mg with repeat dose LPV/RTV 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{(0-\infty)}$ by 17% (90% CI: 6.6%, 26.6%). Therefore, caution should be used when co-administration of eltrombopag with LPV/RTV takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

CYP1A2 and CYP2C8 inhibitors and inducers

Eltrombopag is metabolised through multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3 (see section 5.2). Medicinal products that inhibit or induce a single enzyme are unlikely to significantly affect plasma eltrombopag concentrations; whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag concentrations.

HCV protease inhibitors

Results of a drug-drug pharmacokinetic (PK) interaction study show that co-administration of repeat doses of boceprevir 800 mg every 8 hours or telaprevir 750 mg every 8 hours with a single dose of eltrombopag 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with eltrombopag in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Revolade is not recommended during pregnancy.

Women of childbearing potential / Contraception in males and females

Revolade is not recommended in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether eltrombopag/metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk (see section 5.3); therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue/abstain from Revolade therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Fertility was not affected in male or female rats at exposures that were comparable to those in humans. However a risk for humans cannot be ruled out (see section 5.3).

4.7 Effects on ability to drive and use machines

Eltrombopag has negligible influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of eltrombopag, including dizziness and lack of alertness, should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

In 4 controlled and 2 uncontrolled clinical studies, 530 chronic adult ITP patients were treated with eltrombopag. The mean duration of exposure to eltrombopag was 260 days. The most important serious adverse reactions were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included: headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral oedema.

In 2 controlled clinical studies, 171 chronic paediatric ITP patients were treated with eltrombopag. The median duration of exposure was 171 days. The profile of adverse reactions was comparable to that seen in adults with some additional adverse reactions, marked ♦ in the table below. The most common adverse reactions in paediatric ITP patients 1 year and older (≥ 3% and greater than placebo) were upper respiratory tract infection, nasopharyngitis, cough, diarrhoea, pyrexia, rhinitis, abdominal pain, oropharyngeal pain, toothache, rash, increased AST and rhinorrhoea.

In 2 controlled clinical studies 955 thrombocytopenic patients with HCV infection were treated with eltrombopag. The median duration of exposure was 183 days. The most important serious adverse reactions identified were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included: headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral oedema.

The safety of eltrombopag in severe aplastic anaemia was assessed in a single-arm, open-label trial (N=43) in which 12 patients (28%) were treated for > 6 months and 9 patients (21%) were treated for > 1 year. The most important serious adverse reactions were febrile neutropenia and sepsis/infection. The most common adverse reactions occurring in at least 10% of patients included: headache, dizziness, insomnia, cough, dyspnoea, oropharyngeal pain, rhinorrhoea, nausea, diarrhoea, abdominal pain, transaminases increased, ecchymosis, arthralgia, muscle spasms, pain in extremity, fatigue, febrile neutropenia, and pyrexia.

List of adverse reactions

The adverse reactions in the adult ITP studies (N=550), paediatric ITP studies (N=107), the HCV studies (N=955), the SAA studies (N=43) and post-marketing reports are listed below by MedDRA system organ class and by frequency.

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)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data)

ITP study population

Infections and infestations

Very common Nasopharyngitis♦, upper respiratory tract infection♦

Common Rhinitis♦

Uncommon Pharyngitis, Urinary tract infection, Influenza, Oral herpes, Pneumonia, Sinusitis, Tonsillitis, Respiratory tract infection, Gingivitis, Skin infection

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Uncommon Rectosigmoid cancer

Blood and lymphatic system disorders

Uncommon Anaemia, Anisocytosis, Eosinophilia, Haemolytic anaemia, Leukocytosis, Myelocytosis, Thrombocytopenia, Haemoglobin increased, Band neutrophil count increased, Haemoglobin decreased, Myelocyte present, Platelet count increased, White blood cell count decreased

Immune system disorders

Uncommon Hypersensitivity

Metabolism and nutrition disorders

Uncommon Anorexia, Hypokalaemia, Decreased appetite, Gout, Hypocalcaemia, Blood uric acid increased

Psychiatric disorders

Uncommon Sleep disorder, Depression, Apathy, Mood altered, Tearfulness

Nervous system disorders

Common Paraesthesia

Uncommon Hypoaesthesia, Somnolence, Migraine, Tremor, Balance disorder, Dysaesthesia, Hemiparesis, Migraine with aura, Neuropathy peripheral, Peripheral sensory neuropathy, Speech disorder, Toxic neuropathy, Vascular headache

Eye disorders

Common Dry eye

Uncommon Vision blurred, Lenticular opacities, Astigmatism, Cataract cortical, Eye pain, Lacrimation increased, Retinal haemorrhage, Retinal pigment epitheliopathy, Visual acuity reduced, Visual impairment, Visual acuity tests abnormal, Blepharitis and Keratoconjunctivitis sicca

Ear and labyrinth disorders

Uncommon Ear pain, Vertigo

Cardiac disorders

Uncommon Tachycardia, Acute myocardial infarction, Cardiovascular disorder, Cyanosis, Sinus tachycardia, Electrocardiogram QT prolonged

Vascular disorders

Uncommon Deep vein thrombosis, Embolism, Hot flush, Thrombophlebitis superficial, Flushing, Haematoma

Respiratory, thoracic and mediastinal disorders

Common Cough♦, Oropharyngeal pain♦, Rhinorrhoea♦

Uncommon Pulmonary embolism, Pulmonary infarction, Nasal discomfort, Oropharyngeal blistering, Oropharyngeal pain, Sinus disorder, Sleep apnoea syndrome

Gastrointestinal disorders

Common Nausea, Diarrhoea*, Mouth ulceration, Toothache♦
* Very common in paediatric ITP

Uncommon Dry mouth, Vomiting, Abdominal pain, Glossodynia, Mouth haemorrhage, Abdominal tenderness, Faeces discoloured, Flatulence, Food poisoning, Frequent bowel movements, Haematemesis, Oral discomfort

Hepatobiliary disorders

Common Alanine aminotransferase increased*, Aspartate aminotransferase increased*, Hyperbilirubinaemia, Hepatic function abnormal

Uncommon Cholestasis, Hepatic lesion, Hepatitis, Drug-induced liver injury

*Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

Skin and subcutaneous tissue disorders

Common Rash, Alopecia

Uncommon Hyperhidrosis, Pruritus generalised, Urticaria, Dermatosis, Petechiae, Cold sweat, Erythema, Melanosis, Pigmentation disorder, Skin discolouration, Skin exfoliation

Musculoskeletal and connective tissue disorders

Common Myalgia, Muscle spasm, Musculoskeletal pain, Bone pain, Back pain

Uncommon Muscular weakness

Renal and urinary disorders

Uncommon Renal failure, Leukocyturia, Lupus nephritis, Nocturia, Proteinuria, Blood urea increased, Blood creatinine increased, Urine protein/creatinine ratio increased

Reproductive system and breast disorders

Common Menorrhagia

General disorders and administration site conditions

Common Pyrexia♦

Uncommon Chest pain, Feeling hot, Vessel puncture site haemorrhage, Asthenia, Feeling jittery, Inflammation of wound, Malaise, Pyrexia, Sensation of foreign body

Investigations

Uncommon Blood albumin increased, Blood alkaline phosphatase increased, Protein total increased, Blood albumin decreased, pH urine increased

Injury, poisoning and procedural complications

Uncommon Sunburn

♦ Additional adverse reactions observed in paediatric studies (aged 1to 17 years).

HCV study population (in combination with anti-viral interferon and ribavirin therapy)

Infections and infestations

Common Urinary tract infection, Upper respiratory tract infection, Bronchitis, Nasopharyngitis, Influenza, Oral herpes, Gastroenteritis, Pharyngitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Common Hepatic neoplasm malignant

Blood and lymphatic system disorders

Very common Anaemia
Common Lymphopenia, Haemolytic anaemia

Metabolism and nutrition disorders

Very common Decreased appetite
Common Hyperglycaemia, Abnormal loss of weight

Psychiatric disorders

Very common Insomnia
Common Depression, Anxiety, Sleep disorder, Confusional state, Agitation

Nervous system disorders

Very common Headache
Common Dizziness, Disturbance in attention, Dysgeusia, Hepatic encephalopathy, Lethargy, Memory impairment, Paraesthesia

Eye disorders

Common Cataract, Retinal exudates, Dry Eye, Ocular icterus, Retinal haemorrhage

Ear and labyrinth disorders

Common Vertigo

Cardiac disorders

Common Palpitations

Respiratory, thoracic and mediastinal disorders

Very common Cough
Common Dyspnoea, Oropharyngeal pain, Dyspnoea exertional, Productive cough

Gastrointestinal disorders

Very common Nausea, Diarrhoea
Common Vomiting, Ascites, Abdominal pain, Abdominal pain upper, Dyspepsia, Dry mouth, Constipation, Abdominal distension, Toothache, Stomatitis, Gastrooesophagal reflux disease, Haemorrhoids, Abdominal discomfort, Gastritis, Varices oesophageal, Aphthous stomatitis, Oesophageal varices haemorrhage

Hepatobiliary disorders

Common Hyperbilirubinaemia, Jaundice, Portal vein thrombosis, Hepatic failure, Drug-induced liver injury

Skin and subcutaneous tissue disorders

Very common Pruritus, Alopecia
Common Rash, Dry skin, Eczema, Rash pruritic, Erythema, Hyperhidrosis, Pruritus generalised, Night sweats, Skin lesion
Not known Skin discolouration, Skin hyperpigmentation

Musculoskeletal and connective tissue disorder

Very common Myalgia
Common Arthralgia, Muscle spasms, Back pain, Pain in extremity, Musculoskeletal pain, Bone pain

Renal and urinary disorders

Uncommon Dysuria

General disorders and administration site conditions

Very common Pyrexia, Fatigue, Influenza like illness, Asthenia, Chills, Oedema peripheral
Common Irritability, Pain, Malaise, Injection site reaction, Non-cardiac chest pain, Oedema, Injection site rash, Chest discomfort, Injection site pruritus

Investigations

Common Blood bilirubin increased, Weight decreased, White blood cell count decreased, Haemoglobin decreased, Neutrophil count decreased, International normalised ratio increased, Activated partial thromboplastin time prolonged, Blood glucose increased, Blood albumin decreased, Electrocardiogram QT prolonged

SAA study population

Blood and lymphatic system disorders

Common Neutropenia, Splenic infarction

Metabolism and nutrition disorders

Common Iron overload, Decreased appetite, Hypoglycaemia, Increased appetite

Psychiatric disorders

Very common Insomnia

Common Anxiety, Depression

Nervous system disorders

Very common Headache, Dizziness

Common Syncope

Eye disorders

Common Dry eye, Eye pruritus, Cataract, Ocular icterus, Vision blurred, Visual impairment, Vitreous floaters

Respiratory, thoracic and mediastinal disorders

Very common Cough. Dyspnoea, Oropharyngeal Pain, Rhinorrhoea

Common Epistaxis

Gastrointestinal disorders

Very common Abdominal pain, Diarrhoea, Nausea

Common Gingival bleeding, Oral mucosal blistering, Oral pain, Vomiting, Abdominal discomfort, Abdominal pain, Constipation, Abdominal distension, Dysphagia, Faeces discoloured, Swollen tongue, Gastrointestinal motility disorder, Flatulence

Hepatobiliary disorders

Very common Transaminases increased

Common Blood bilirubin increased (hyperbilirubinemia), Jaundice

Not known Drug-induced liver injury*

* Cases of Drug-induced liver injury have been reported in patients with ITP and HCV

Skin and subcutaneous tissue disorders

Very common Ecchymosis

Common Petechiae, Rash, Pruritus, Urticaria, Skin lesion, Rash Macular

Not known Skin discolouration, Skin hyperpigmentation

Musculosketal and connective tissue disorders

Very common Arthralgia, Muscle spasms, Pain in extremity

Common Back pain, Myalgia, Bone pain

Renal and urinary disorders

Common Chromaturia

General disorders and administration site conditions

Very common Fatigue, Febrile neutropenia, Pyrexia

Common Asthenia, Oedema peripheral, Chills, Malaise

Investigations

Common Blood creatine phosphokinase increased

Description of selected adverse reactions

Thrombotic/Thromboembolic events (TEEs)

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving eltrombopag (n=446), 17 subjects experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n=6), pulmonary embolism (n=6), acute myocardial infarction (n=2), cerebral infarction (n=2), embolism (n=1) (see section 4.4).

In a placebo-controlled study (n=288, Safety population), following 2 weeks treatment in preparation for invasive procedures, 6 of 143 (4%) adult patients with chronic liver disease receiving eltrombopag experienced 7 TEEs of the portal venous system and 2 of 145 (1%) subjects in the placebo group experienced 3 TEEs. Five of the 6 patients treated with eltrombopag experienced the TEE at a platelet count > 200,000/µl

No specific risk factors were identified in those subjects who experienced a TEE with the exception of platelet counts ≥ 200,000/µl (see section 4.4).

In controlled studies in thrombocytopenic patients with HCV (n=1,439), 38 out of 955 subjects (4%) treated with eltrombopag experienced a TEE and 6 out of 484 subjects (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus < 1% for placebo) (see section 4.4). Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients.

Hepatic decompensation (use with interferon)

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤ 35 g/L) or MELD score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation (see section 4.4).

Thrombocytopenia following discontinuation of treatment

In the 3 controlled clinical ITP studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% and 8% of the eltrombopag and placebo groups, respectively (see section 4.4).

Increased bone marrow reticulin

Across the programme, no patients had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In a small number of ITP patients, eltrombopag treatment was discontinued due to bone marrow reticulin (see section 4.4).

Cytogenetic abnormalities

In the single-arm, open-label trial in SAA, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight (19%) patients had a new cytogenetic abnormality reported, including 5 patients who had changes in chromosome 7. In the two ongoing studies (ELT116826 and ELT116643), cytogenetic abnormalities have been detected in 4/28 (14%) and 4/62 (6%) subjects in each study.

Haematologic malignancies

In the single-arm, open label trial in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) subject has been diagnosed with MDS or AML in each study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consideration should be given to oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Platelet counts should be closely monitored. Treatment with eltrombopag should be reinitiated in accordance with dosing and administration recommendations (see section 4.2).

In the clinical studies there was one report of overdose where the subject ingested 5000 mg of eltrombopag. Reported adverse reactions included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. Liver enzymes measured between Days 2 and 18 after ingestion peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin, The platelet counts were 672,000/µl on day 18 after ingestion and the maximum platelet count was 929,000/µl. All events were resolved without sequelae following treatment.

Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics. ATC code: B02BX 05.

Mechanism of action

TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-R. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation from bone marrow progenitor cells.

Clinical efficacy and safety

Chronic immune (idiopathic) thrombocytopenia (ITP) studies

Two Phase III, randomised, double-blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of eltrombopag in adult patients with previously treated chronic ITP. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year.

Double-blind placebo-controlled studies

RAISE: 197 ITP patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medicinal products at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6-month treatment period based on individual platelet counts. All patients initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment, 15 to 28% of eltrombopag treated patients were maintained on ≤ 25 mg and 29 to 53% received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥ 3 prior ITP therapies and 36% had a prior splenectomy.

Median platelet counts at baseline were 16,000/µl for both treatment groups and in the eltrombopag group were maintained above 50,000/µl at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained < 30,000/µl throughout the study.

Platelet count response between 50,000-400,000/µl in the absence of rescue treatment was achieved by significantly more patients in the eltrombopag treated group during the 6 month treatment period, $p < 0.001$. Fifty-four percent of the eltrombopag-treated patients and 13% of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52% and 16% of patients responding at the end of the 6-month treatment period.

Table 4: Secondary efficacy results from RAISE

	Eltrombopag N=135	Placebo N=62
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥ 50,000-400,000/µl, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥ 75% of assessments in the target range (50,000 to 400,000/µl), n (%)	51 (38)	4 (7)
p-value [a]	< 0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
p-value [a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
p-value [a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
p-value [a]	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%)[b]	37 (59)	10 (32)
p-value [a]	0.016	

a Logistic regression model adjusted for randomisation stratification variables

b 21 out of 63 (33%) patients treated with eltrombopag who were taking an ITP medicinal product at baseline permanently discontinued all baseline ITP medicinal products.

At baseline, more than 70% of ITP patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20% reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50% from Day 15 to the end of treatment throughout the 6 month treatment period.

TRA100773B: The primary efficacy endpoint was the proportion of responders, defined as ITP patients who had an increase in platelet counts to ≥ 50,000/µl at Day 43 from a baseline of < 30,000/µl; patients who withdrew prematurely due to a platelet count > 200,000/µl were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated chronic ITP were randomised 2:1 eltrombopag (n=76) to placebo (n=38).

Table 5: Efficacy results from TRA100773B

	Eltrombopag N=74	Placebo N=38
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥ 50,000/µl after up to 42 days of dosing (compared to a baseline count of < 30,000/µl), n (%)	43 (59)	6 (16)
p-value[a]	< 0.001	
Key secondary endpoints		
Patients with a Day 43 bleeding assessment, n	51	30
Bleeding (WHO Grades 1-4) n (%)	20 (39)	18 (60)
p-value[a]	0.029	

a – Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medicinal product use, splenectomy status and baseline platelet count (≤ 15,000/µl, > 15,000/µl) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP patients with baseline platelet count ≤ 15,000/µl the median platelet counts did not reach the target level (> 50,000/µl), although in both studies 43% of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42% of patients with baseline platelet count ≤ 15,000/µl treated with eltrombopag responded at the end of the 6 month treatment period. Forty-two to 60% of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

An open label, repeat dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

Eltrombopag was administered to 302 ITP patients in the open-label extension study EXTEND (TRA105325), 218 patients completed 1 year, 180 completed 2 years, 107 completed 3 years, 75 completed 4 years, 34 completed 5 years and 18 completed 6 years. The median baseline platelet count was 19,000/µl prior to eltrombopag administration. Median platelet counts at 1, 2, 3, 4, 5, 6 and 7 years on study were 85,000/µl, 85,000/µl, 105,000/µl, 64,000/µl, 75,000/µl, 119,000/µl and 76,000/µl, respectively.

Clinical studies comparing eltrombopag to other treatment options (e.g. splenectomy) have not been conducted. The long-term safety of eltrombopag should be considered prior to starting therapy.

Paediatric population (aged 1 to 17 years)

The safety and efficacy of eltrombopag in paediatric subjects has been investigated in two studies.

TRA115450 (PETIT2): The primary endpoint was a sustained response, defined as the proportion of subjects receiving eltrombopag, compared to placebo, achieving platelet counts ≥ 50,000/µl for at least 6 out of 8 weeks (in the absence of rescue therapy), between weeks 5 to 12 during the double-blind randomised period. Subjects were diagnosed with chronic ITP for at least 1 year and were refractory or relapsed to at least one prior ITP therapy or unable to continue other ITP treatments for a medical reason and had platelet count < 30,000/µl. Ninety-two subjects were randomised by three age cohort strata (2:1) to eltrombopag (n=63) or placebo (n=29). The dose of eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of eltrombopag subjects (40%) compared with placebo subjects (3%) achieved the primary endpoint (Odds Ratio: 18.0 [95% CI: 2.3, 140.9] p < 0.001) which was similar across the three age cohorts (Table 6).

Table 6: Sustained platelet response rates by age cohort in paediatric subjects with chronic ITP

	Eltrombopag n/N (%) [95% CI]	Placebo n/N (%) [95% CI]
Cohort 1 (12 to 17 years)	9/23 (39%) [20%, 61%]	1/10 (10%) [0%, 45%]
Cohort 2 (6 to 11 years)	11/26 (42%) [23%, 63%]	0/13 (0%) [N/A]
Cohort 3 (1 to 5 years)	5/14 (36%) [13%, 65%]	0/6 (0%) [N/A]

Statistically fewer eltrombopag subjects required rescue treatment during the randomised period compared to placebo subjects (19% [12/63] vs. 24% [7/29], p=0.032).

At baseline, 71% of subjects in the eltrombopag group and 69% in the placebo group reported any bleeding (WHO Grades 1-4). At Week 12, the proportion of eltrombopag subjects reporting any bleeding was decreased to half of baseline (36 %). In comparison, at Week 12, 55% of placebo subjects reported any bleeding.

Subjects were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the study and 53% (8/15) of subjects were able to reduce (n=1) or discontinue (n=7) baseline ITP therapy, mainly corticosteroids, without needing rescue therapy.

TRA108062 (PETIT): The primary endpoint was the proportion of subjects achieving platelet counts ≥ 50,000/µl at least once between weeks 1 and 6 of the randomised period. Subjects were refractory or relapsed to at least one prior ITP therapy with a platelet count < 30,000/µl (n=67). During the randomised period of the study, subjects were randomised by 3 age cohort strata (2:1) to eltrombopag (n=45) or placebo (n=22). The dose of eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of eltrombopag subjects (62%) compared with placebo subjects (32%) met the primary endpoint (Odds Ratio: 4.3 [95% CI: 1.4, 13.3] p=0.011).

Sustained response was seen in 50% of the initial responders during 20 out of 24 weeks in the PETIT 2 study and 15 out of 24 weeks in the PETIT study.

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomised, double-blind, placebo-controlled studies. ENABLE 1 utilised peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilised peginterferon alfa-2b plus ribavirin. Patients did not receive direct acting antiviral agents. In both studies, patients with a platelet count of < 75,000/µl were enrolled and stratified by platelet count (< 50,000/µl and ≥ 50,000/µl to < 75,000/µl), screening HCV RNA (< 800,000 IU/ml and ≥ 800,000 IU/ml), and HCV genotype (genotype 2/3, and genotype 1/4/6).

Baseline disease characteristics were similar in both studies and were consistent with compensated cirrhotic HCV patient population. The majority of patients were HCV genotype 1 (64%) and had bridging fibrosis/cirrhosis. Thirty-one percent of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet count was 59,500/µl in both treatment groups: 0.8%, 28% and 72% of the patients recruited had platelet counts < 20,000/µl, < 50.000/µl and ≥ 50,000/µl respectively.

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, subjects received open-label eltrombopag to increase the platelet count to ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. The median time to achieve the target platelet count ≥ 90,000/µl (ENABLE 1) or ≥ 100,000/µl (ENABLE 2) was 2 weeks.

The primary efficacy endpoint for both studies was sustained virologic response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period.

In both HCV studies, a significantly greater proportion of patients treated with eltrombopag (n=201, 21%) achieved SVR compared to those treated with placebo (n=65, 13%) (see Table 7). The improvement in the proportion of patients who achieved SVR was consistent across all subgroups in the randomisation strata (baseline platelet counts (< 50,000 vs. > 50,000), viral load (< 800,000 IU/ml vs. ≥ 800,000 IU/ml) and genotype (2/3 vs. 1/4/6)).

Table 7: Virologic response in HCV patients in ENABLE 1 and ENABLE 2

	Pooled Data		**ENABLE 1[a]**		**ENABLE 2[b]**	
Patients achieving target platelet counts & initiating antiviral therapy [c]	1,439/1,520 (95%)		680/715 (95%)		759/805 (94%)	
	Eltrombopag	**Placebo**	**Eltrombopag**	**Placebo**	**Eltrombopag**	**Placebo**
Total number of patients entering Antiviral Treatment Phase	**n=956**	**n=485**	**n=450**	**n=232**	**n=506**	**n=253**
	% patients achieving virologic response					
Overall SVR [d]	21	13	23	14	19	13
HCV RNA Genotype						
Genotype 2/3	35	25	35	24	34	25
Genotype 1/4/6[e]	15	8	18	10	13	7
Albumin levels [f]						
≤ 35g/L	11	8				
> 35g/L	25	16				
MELD score[f]						
≥ 10	18	10				
< 10	23	17				

a Eltrombopag given in combination with peginterferon alfa-2a (180 mcg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1200 mg daily in 2 divided doses orally)

b Eltrombopag given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for 48 weeks for genotype 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1400 mg orally in 2 divided doses)

c Target platelet count was ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. For ENABLE 1, 682 patients were randomised to the antiviral treatment phase; however 2 subjects then withdrew consent prior to receiving antiviral therapy.

d *p*-value < 0.05 for eltrombopag versus placebo

e 64% subjects participating in ENABLE 1 and ENABLE 2 were genotype 1

f Post-hoc analyses

Other secondary findings of the studies included the following; significantly fewer patients treated with eltrombopag prematurely discontinued antiviral therapy compared to placebo (45% vs. 60%, p=< 0.0001). A greater proportion of patients on eltrombopag did not require any antiviral dose reduction as compared to placebo (45% versus 27%). Eltrombopag treatment delayed and reduced the number of peginterferon dose reductions.

Severe aplastic anaemia

Eltrombopag was studied in a single-arm, single-centre open-label trial in 43 patients with severe aplastic anaemia with refractory thrombocytopenia following at least one prior immunosuppressive therapy (IST) and who had a platelet count ≤ 30,000/µl.

The majority of subjects, 33 (77%), were considered to have 'primary refractory disease', defined as having no prior adequate response to IST in any lineage. The remaining 10 subjects had insufficient platelet response to prior therapies. All 10 had received at least 2 prior IST regimens and 50% had received at least 3 prior IST regimens. Patients with diagnosis of Fanconi anaemia, infection not responding to appropriate therapy, PNH clone size in neutrophils of ≥50%, where excluded from participation.

At baseline the median platelet count was 20,000/µl, haemoglobin was 8.4 g/dL, ANC was 0.58 x 10^9/L and absolute reticulocyte count was 24.3 x10^9/L. Eighty-six percent of patients were RBC transfusion dependent, and 91% were platelet transfusion dependent. The majority of patients (84%) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

The primary endpoint was haematological response assessed after 12 weeks of eltrombopag treatment. Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20,000/µl above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by > 1.5g/dL, or a reduction in ≥ 4 units of red blood cell (RBC) transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% or an ANC increase > 0.5 x 10^9/L.

The haematological response rate was 40% (17/43 patients; 95% CI 25, 56), the majority were unilineage responses (13/17, 76%) whilst there were 3 bilineage and 1 trilineage responses at week 12. Eltrombopag was discontinued after 16 weeks if no haematological response or transfusion independence was observed. Patients who responded continued therapy in an extension phase of the study. A total of 14 patients entered the extension phase of the trial. Nine of these patients achieved a multi-lineage response, 4 of the 9 remain on treatment and 5 tapered off treatment with eltrombopag and maintained the response (median follow up: 20.6 months, range: 5.7 to 22.5 months). The remaining 5 patients discontinued treatment, three due to relapse at the month 3 extension visit.

During treatment with eltrombopag 59% (23/39) became platelet transfusion independent (28 days without platelet transfusion) and 27% (10/37) became RBC transfusion independent (56 days without RBC transfusion). The longest platelet transfusion free period for non-responders was 27 days (median). The longest platelet transfusion free period for responders was 287 days (median). The longest RBC transfusion free period for non-responders was 29 days (median). The longest RBC transfusion free period for responders was 266 days (median).

Over 50% of responders who were transfusion dependent at baseline, had > 80% reduction in both platelet and RBC transfusion requirements compared to baseline.

Preliminary results from a supportive study (Study ELT116826), an ongoing non-randomised, phase II, single-arm, open-label study in refractory SAA subjects, showed consistent results. Data are limited to 21 out of the planned 60 patients with haematological responses reported by 52% of patients at 6 months. Multilineage responses were reported by 45% of patients.

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 patients with ITP in Studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for ITP patients are presented (Table 8).

Table 8: Geometric mean (95% confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	$AUC_{(0-\tau)}$[a], µg.h/ml	C_{max}[a], µg/ml
30 mg	28	47 (39, 58)	3.78 (3.18, 4.49)
50 mg	34	108 (88, 134)	8.01 (6.73, 9.53)
75 mg	26	168 (143, 198)	12.7 (11.0, 14.5)

a - $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates.

Plasma eltrombopag concentration-time data collected in 590 subjects with HCV enrolled in Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from patients with HCV enrolled in the Phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma eltrombopag C_{max} and $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in the Phase 3 studies are presented for each dose studied in Table 9.

Table 9 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

Eltrombopag dose (once daily)	**N**	**$AUC_{(0-\tau)}$ (µg.h/ml)**	**C_{max} (µg/ml)**
25 mg	330	118 (109, 128)	6.40 (5.97, 6.86)
50 mg	119	166 (143, 192)	9.08 (7.96, 10.35)
75 mg	45	301 (250, 363)	16.71 (14.26, 19.58)
100 mg	96	354 (304, 411)	19.19 (16.81, 21.91)

Data presented as geometric mean (95% CI).
$AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each patient.

Absorption and bioavailability

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see section 4.2). In a relative bioavailability study in adults, the eltrombopag powder for oral suspension delivered 22% higher plasma $AUC_{(0-\infty)}$ than the tablet formulation. The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52%.

Distribution

Eltrombopag is highly bound to human plasma proteins (> 99.9%), predominantly to albumin. Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Biotransformation

Eltrombopag is primarily metabolised through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64% of plasma radiocarbon $AUC_{0-\infty}$. Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

Elimination

Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59%) with 31% of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20% of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

Pharmacokinetic interactions

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes *in vitro*. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag.

Approximately 21% of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section 4.5).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section 4.5). In clinical studies with eltrombopag, a dose reduction of statins by 50% was recommended. The co-administration of 200 mg ciclosporin (a BCRP inhibitor) decreased the C_{max} and the AUC_{inf} of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg ciclosporin decreased the C_{max} and the AUC_{inf} of eltrombopag by 39% and 24%, respectively.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see sections 4.2 and 4.5).

Administration of a single 50 mg dose of eltrombopag in tablet form with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 59% and mean C_{max} by 65%.

Administration of a single 25 mg dose of eltrombopag as powder for oral suspension with a high-calcium, moderate fat and moderate calorie meal reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 75% and mean C_{max} by 79%. This decrease of exposure was attenuated when a single 25 mg dose of eltrombopag powder for oral suspension was administered 2 hours before a high-calcium meal (mean $AUC_{0-\infty}$ was decreased by 20% and mean C_{max} by 14%).

Food low in calcium (< 50 mg calcium) including fruit, lean ham, beef and unfortified (no added calcium, magnesium or iron) fruit juice, unfortified soya milk and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5).

Special patient populations

Renal impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with renal impairment. Following administration of a single 50 mg-dose, the $AUC_{0-\infty}$ of eltrombopag was 32% to 36% lower in subjects with mild to moderate renal impairment, and 60% lower in subjects with severe renal impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2). The efficacy and safety of eltrombopag has not been established in subjects with both moderate to severe renal impairment and hepatic impairment.

Hepatic impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with hepatic impairment. Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 41% higher in subjects with mild hepatic impairment and 80% to 93% higher in subjects with moderate to severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 714 patients with hepatic impairment (673 patients with HCV and 41 patients with chronic liver disease of other aetiology). Of the 714 patients, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with severe hepatic impairment. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 111% (95% CI: 45% to 283%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values and patients with moderate hepatic impairment had approximately 183% (95% CI: 90% to 459%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values.

Therefore, eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see sections 4.2 and 4.4). For patients with HCV initiate eltrombopag at a dose of 25 mg once daily (see section 4.2).

Race

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East Asians) and 88 patients with ITP (18 East Asians). Based on estimates from the population pharmacokinetic analysis, East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 49% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients who were predominantly Caucasian (see section 4.2).

The influence of East Asian ethnicity (such as Chinese, Japanese, Taiwanese, Korean, and Thai) on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (145 East Asians and 69 Southeast Asians). Based on estimates from the population pharmacokinetic analysis, East Asian patients had approximately 55% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian (see section 4.2).

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 23% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients, without adjustment for body weight differences.

The influence of gender on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 635 patients with HCV (260 females). Based on model estimate, female HCV patient had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients.

Age

The influence of age on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects, 673 patients with HCV, and 41 patients with chronic liver disease of other aetiology ranging from 19 to 74 years old. There are no PK data on the use of eltrombopag in patients ≥ 75 years. Based on model estimate, elderly (≥ 65 years) patients had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see section 4.2).

Paediatric population (aged 1 to 17 years)

The pharmacokinetics of eltrombopag have been evaluated in 168 paediatric ITP subjects dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT-2. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. The effects of race and sex on plasma eltrombopag CL/F estimates were consistent between paediatric and adult patients. East Asian paediatric ITP patients had approximately 43% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients. Female paediatric ITP patients had approximately 25% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to male patients.

The pharmacokinetic parameters of eltrombopag in paediatric subjects with ITP are shown in Table 10.

Table 10 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in paediatric subjects with ITP (50 mg once daily dosing regimen)

Age	**C_{max} (µg/ml)**	**$AUC_{(0-\tau)}$ (µg.hr/ml)**
12 to 17 years (n=62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n=68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n=38)	11.6 (10.4, 12.9)	162 (139, 187)

Data presented as geometric mean (95%CI). $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates

5.3 Preclinical safety data

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥ 6 times the human clinical exposure in adult ITP patients at 75 mg/day and 3 times the human clinical exposure in adult HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥ 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. At non-tolerated doses in pre-weaning juvenile rats dosed from Days 4-32 (approximately equating to a 2-year old human at the end of the dosing period), ocular opacities were observed (histology not performed) at 9 times the maximum human clinical exposure in pediatric ITP patients at 75 mg/day, based on AUC. However, cataracts were not observed in juvenile rats given tolerated doses at 5 times the human clinical exposure in pediatric ITP patients, based on AUC. Cataracts have not been observed in adult dogs after 52 weeks of dosing at 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2 year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterised by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 or 0.8 times the human clinical exposure based on AUC in adult or paediatric ITP patients at 75 mg/day and 0.6 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times the human clinical exposure in adult ITP patients and 3 and 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) and in dogs (52 weeks) at 4 or 2 times the human clinical exposure in adult ITP patients and 3 or 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times or equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

At poorly tolerated doses in rats and dogs (> 10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and> 4 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times human clinical exposure in adult or paediatric ITP patients at 75 mg/day and ≤ 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Endosteal hyperostosis was observed in a 28 week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times or 4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two in vivo assays in rats (micronucleus and unscheduled DNA synthesis, 10 times or 8 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day, based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (< 3-fold increase in mutation frequency). These *in vitro* and *in vivo* findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure in adult or adolescent (12-17 years old) ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.3 to 0.5 times the human clinical exposure in ITP patients at 75 mg/day and HCV patients at 100 mg/day, based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see section 4.6). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioral or reproductive function of the offspring (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) or ocular phototoxicity (≥ 4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg. This was measured by delayed phototoxic index. Nevertheless, a potential risk of photoallergy cannot be ruled out since no specific preclinical study could be performed.

There are no findings in juvenile rats to suggest a greater risk of toxicity with eltrombopag treatment in paediatric vs. adult ITP patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Revolade 12.5 mg film-coated tablets
Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

Tablet coating
Hypromellose
Macrogol 400
Polysorbate 80
Titanium dioxide (E171)

Revolade 25 mg film-coated tablets
Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

Tablet coating
Hypromellose
Macrogol 400
Polysorbate 80
Titanium dioxide (E171)

Revolade 50 mg film-coated tablets
Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

Tablet coating
Hypromellose
Iron oxide red (E172)
Iron oxide yellow (E172)
Macrogol 400
Titanium dioxide (E171)

Revolade 75 mg film-coated tablets
Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

Tablet coating
Hypromellose
Iron oxide red (E172)
Iron oxide black (E172)
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Film-coated tablets
Aluminum blisters (PA/Alu/PVC/Alu) in a carton containing 14 or 28 film-coated tablets and multipacks containing 84 (3 packs of 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

Revolade 12.5 mg film-coated tablets
EU/1/10/612/010
EU/1/10/612/011
EU/1/10/612/012

Revolade 25 mg film-coated tablets
EU/1/10/612/001
EU/1/10/612/002
EU/1/10/612/003

Revolade 50 mg film-coated tablets
EU/1/10/612/004
EU/1/10/612/005
EU/1/10/612/006

Revolade 75 mg film-coated tablets
EU/1/10/612/007
EU/1/10/612/008
EU/1/10/612/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 March 2010
Date of latest renewal: 15 January 2015

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

Revolade 25 mg powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains eltrombopag olamine equivalent to 25 mg of eltrombopag.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension

Reddish-brown to yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revolade is indicated for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (see sections 4.4 and 5.1).

Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation (see section 5.1).

4.2 Posology and method of administration

Eltrombopag treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of haematological diseases or the management of chronic hepatitis C and its complications.

<u>Posology</u>

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts.

The powder for oral suspension may lead to higher eltrombopag exposure than the tablet formulation (see section 5.2). When switching between the tablet and powder for oral suspension formulations, platelet counts should be monitored weekly for 2 weeks.

Chronic immune (idiopathic) thrombocytopenia

The lowest dose of eltrombopag to achieve and maintain a platelet count ≥ 50,000/µl should be used. Dose adjustments are based upon the platelet count response. Eltrombopag must not be used to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation.

Adults and paediatric population aged 6 to 17 years
The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2).

Paediatric population aged 1 to 5 years
The recommended starting dose of eltrombopag is 25 mg once daily.

Monitoring and dose adjustment

After initiating eltrombopag, the dose must be adjusted to achieve and maintain a platelet count ≥ 50,000/µl as necessary to reduce the risk for bleeding. A daily dose of 75 mg must not be exceeded.

Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in Table 1. During therapy with eltrombopag full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥ 50,000/µl for at least 4 weeks) has been achieved. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

Table 1 Dose adjustments of eltrombopag in ITP patients

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day*.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
> 250,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg.

* - For patients taking 25 mg eltrombopag once every other day, increase dose to 25 mg once daily.
♦ - For patients taking 25 mg eltrombopag once daily, consideration should be given to dosing at 12.5 mg once daily or alternatively a dose of 25 mg once every other day.

Eltrombopag can be administered in addition to other ITP medicinal products. The dose regimen of concomitant ITP medicinal products should be modified, as medically appropriate, to avoid excessive increases in platelet counts during therapy with eltrombopag.

It is necessary to wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment.

The standard eltrombopag dose adjustment, either decrease or increase, would be 25 mg once daily.

Discontinuation

Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag therapy at 75 mg once daily.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. In non-splenectomised patients this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see section 4.4).

Chronic hepatitis C (HCV) associated thrombocytopenia

When eltrombopag is given in combination with antivirals reference should be made to the full summary of product characteristics of the respective coadministered medicinal products for comprehensive details of relevant safety information or contraindications.

In clinical studies, platelet counts generally began to increase within 1 week of starting eltrombopag. The aim of treatment with eltrombopag should be to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level that prevents the risk of bleeding complications, normally around 50,000-75,000/µl. Platelet counts > 75,000/µl should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

Initial dose regimen

Eltrombopag should be initiated at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East Asian ancestry or patients with mild hepatic impairment (see section 5.2).

Monitoring and dose adjustment

The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate anti-viral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided (see Table 2).

During antiviral therapy, the dose of eltrombopag should be adjusted as necessary to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding (see Table 2). Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved, normally around 50,000-75,000/µl. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter. Dose reductions on the daily dose by 25 mg should be considered if platelet counts exceed the required target. It is recommended to wait for 2 weeks to assess the effects of this and any subsequent dose adjustments.

A dose of 100 mg eltrombopag once daily must not be exceeded.

Table 2 Dose adjustments of eltrombopag in HCV patients during antiviral therapy

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
≥ 50,000/µl to ≤ 100,000/µl	Use lowest dose of eltrombopag as necessary to avoid dose reductions of peginterferon
> 100,000/µl to ≤ 150,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
> 150,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg*.

* - For patients taking 25 mg eltrombopag once daily, consideration should be given to reinitiating dosing at 25 mg every other day.
♦ - On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

Discontinuation

If after 2 weeks of eltrombopag therapy at 100 mg the required platelet level to initiate antiviral therapy is not achieved, eltrombopag should be discontinued.

Eltrombopag treatment should be terminated when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation.

Severe aplastic anaemia

Initial dose regimen

Eltrombopag should be initiated at a dose of 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2). The treatment should not be initiated when the patients have existing cytogenetic abnormalities of chromosome 7.

Monitoring and dose adjustment

Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting eltrombopag (see section 5.1). The dose of eltrombopag should be adjusted in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥ 50,000/µl. For patients taking 25 mg once daily, the dose should be increased to 50 mg daily before increasing the dose amount by 50 mg. A dose of 150 mg daily must not be exceeded. Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dosage regimen of eltrombopag modified based on platelet counts as outlined in Table 3.

Table 3 Dose adjustments of eltrombopag in patients with severe aplastic anaemia

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag to maintain platelet counts.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/µl	Stop eltrombopag; for at least one week. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 50 mg.

Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders

For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of eltrombopag may be reduced by 50%.

If counts remain stable after 8 weeks at the reduced dose, then eltrombopag must be discontinued and blood counts monitored. If platelet counts drop to < 30,000/µl, haemoglobin to < 9 g/dL or ANC < 0.5 x 10^9/L, eltrombopag may be reinitiated at the previous effective dose.

Discontinuation

If no haematological response has occurred after 16 weeks of therapy with eltrombopag, therapy should be discontinued. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate (see sections 4.4 and 4.8). Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of eltrombopag (see section 4.8).

Special populations

Renal impairment

No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section 5.2).

Hepatic impairment

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see section 4.4).

If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 3 weeks should be observed before increasing the dose.

No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤ 6). Chronic HCV patients and severe aplastic anaemia patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily (see section 5.2). After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 2 weeks should be observed before increasing the dose.

There is an increased risk for adverse events, including hepatic decompensation and thromboembolic events, in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections 4.4 and 4.8).

Elderly

There are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see section 5.2).

There are limited data on the use of eltrombopag in HCV and SAA patients aged over 75 years. Caution should be exercised in these patients (see section 4.4).

East Asian patients

For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), including those with hepatic impairment, eltrombopag should be initiated at a dose of 25 mg once daily (see section 5.2).

Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

Paediatric population

Revolade is not recommended for use in children under the age of one year with chronic ITP due to insufficient data on safety and efficacy. The safety and efficacy of eltrombopag has not been established in children and adolescents (< 18 years) with chronic HCV related thrombocytopenia or SAA. No data are available.

Method of administration (see section 6.6)

Oral use.
The suspension should be taken at least two hours before or four hours after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc) (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to eltrombopag or to any of the excipients, listed in section 6.1.

4.4 Special warnings and precautions for use

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤ 35 g/L or model for end stage liver disease (MELD) score ≥ 10, when treated with eltrombopag in combination with interferon-based therapy. In addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35g/L) compared with the group overall. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.

Combination with direct acting antiviral agents

Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection.

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function and severe hepatotoxicity, which might be life-threatening. In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed (see section 4.8).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies in adults with chronic ITP, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality. In two placebo-controlled studies in paediatric patients (aged 1 to 17 years) with chronic ITP, ALT ≥ 3 times the upper limit of normal (x ULN) was reported in 4.7% and 0% of the eltrombopag and placebo groups, respectively.

In 2 controlled clinical studies in patients with HCV, ALT or AST ≥ 3 x ULN was reported in 34% and 38% of the eltrombopag and placebo groups, respectively. Most patients receiving eltrombopag in combination with peginterferon / ribavirin therapy will experience indirect hyperbilirubinaemia. Overall, total bilirubin ≥ 1.5 x ULN was reported in 76% and 50% of the eltrombopag and placebo groups, respectively.

Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinaemia. If bilirubin is elevated fractionation should be performed. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥ 3 x ULN in patients with normal liver function, or ≥ 3 x baseline or > 5 x ULN, whichever is the lower, in patients with pre-treatment elevations in transaminases) and are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Caution is required when administering eltrombopag to patients with hepatic disease. In ITP and SAA patients a lower starting dose of eltrombopag should be used. Close monitoring is required when administering to patients with hepatic impairment (see section 4.2).

Hepatic decompensation (use with interferon)

Hepatic decompensation in patients with chronic hepatitis C: Monitoring is required in patients with low albumin levels (≤ 35 g/L) or with MELD score ≥ 10 at baseline.

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤ 35 g/L) or MELD score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. In addition, the benefits of treatment in terms of the proportion achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35 g/L) compared with the group overall. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon summary of product characteristics should be referenced for discontinuation criteria. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/Thromboembolic complications

In controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy (n=1,439), 38 out of 955 subjects (4%) treated with eltrombopag and 6 out of 484 subjects (1%) in the placebo group experienced thromboembolic events (TEEs). Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus < 1% for placebo). No specific temporal relationship between start of treatment and event of TEE were observed. Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1%) subjects in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count > 200,000/µl and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In eltrombopag clinical trials in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels (see section 4.2). The risk-benefit balance should be considered in patients at risk of thromboembolic events (TEEs) of any aetiology.

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, caution is required when administering eltrombopag to patients with hepatic impairment (see sections 4.2 and 4.8).

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increases the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of eltrombopag.

In HCV clinical trials, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin receptor (TPO-R) agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, full blood count (FBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression of existing myelodysplastic syndrome (MDS)

TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For TPO-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS.

In clinical studies with a TPO-R agonist in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported.

The diagnosis of ITP or SAA in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms, or abnormal signs such as increased peripheral blast cells.

The effectiveness and safety of eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia or MDS. Eltrombopag should not be used outside of clinical trials for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than the approved indications.

Cytogenetic abnormalities and progression to MDS/AML in patients with SAA

Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II SAA clinical study with eltrombopag, the incidence of new cytogenetic abnormalities was observed in 19% of patients [8/43 (where 5 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In clinical trials with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment.

For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate.

Ocular changes

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n=1,439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8% of the eltrombopag group and 5% of the placebo group. Retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2% of the eltrombopag group and 2% of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended.

QT/QTc prolongation

A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarisation. QTc interval prolongation has been reported in clinical trials of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

Loss of response to eltrombopag

A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

Paediatric population

The above warnings and precautions for ITP also apply to the paediatric population.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter. *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103% (90% confidence interval [CI]: 82%, 126%) and $AUC_{0-\infty}$ 55% (90% CI: 42%, 69%). Interactions are also expected with other HMG-CoA reductase inhibitors, including atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 5.2).

OATP1B1 and BCRP substrates

Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution (see section 5.2).

Cytochrome P450 substrates

In studies utilising human liver microsomes, eltrombopag (up to 100 μM) showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates. Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates are co-administered (see section 5.2).

HCV protease inhibitors

Dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir. Co-administration of a single dose of eltrombopag 200 mg with telaprevir 750 mg every 8 hours did not alter plasma telaprevir exposure.

Co-administration of a single dose of eltrombopag 200 mg with boceprevir 800 mg every 8 hours did not alter plasma boceprevir $AUC_{(0-\tau)}$, but increased C_{max} by 20%, and decreased C_{min} by 32%. The clinical relevance of the decrease in C_{min} has not been established, increased clinical and laboratory monitoring for HCV suppression is recommended.

Effects of other medicinal products on eltrombopag

Ciclosporin

In vitro studies demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg ciclosporin (a BCRP inhibitor) (see section 5.2). Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count (see section 4.2). Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with ciclosporin. Eltrombopag dose may need to be increased based on these platelet counts.

Polyvalent cations (chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62%, 76%). Eltrombopag should be taken at least two hours before or four hours after any products such as antacids, dairy products or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption due to chelation (see sections 4.2 and 5.2).

Food interaction

The administration of eltrombopag tablet or powder for oral suspension with a high-calcium meal (e.g. a meal that included dairy products) significantly reduced plasma eltrombopag $AUC_{0-\infty}$ and C_{max}. In contrast, the administration of eltrombopag 2 hours before or 4 hours after a high-calcium meal or with low-calcium food [< 50 mg calcium] did not alter plasma eltrombopag exposure to a clinically significant extent (see sections 4.2 and 5.2).

Lopinavir/ritonavir

Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of single dose eltrombopag 100 mg with repeat dose LPV/RTV 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{(0-\infty)}$ by 17% (90% CI: 6.6%, 26.6%). Therefore, caution should be used when co-administration of eltrombopag with LPV/RTV takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

CYP1A2 and CYP2C8 inhibitors and inducers

Eltrombopag is metabolised through multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3 (see section 5.2). Medicinal products that inhibit or induce a single enzyme are unlikely to significantly affect plasma eltrombopag concentrations; whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag concentrations.

HCV protease inhibitors

Results of a drug-drug pharmacokinetic (PK) interaction study show that co-administration of repeat doses of boceprevir 800 mg every 8 hours or telaprevir 750 mg every 8 hours with a single dose of eltrombopag 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with eltrombopag in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Revolade is not recommended during pregnancy.

Women of childbearing potential / Contraception in males and females

Revolade is not recommended in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether eltrombopag/metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk (see section 5.3); therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue/abstain from Revolade therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Fertility was not affected in male or female rats at exposures that were comparable to those in humans. However a risk for humans cannot be ruled out (see section 5.3).

4.7 Effects on ability to drive and use machines

Eltrombopag has negligible influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of eltrombopag, including dizziness and lack of alertness, should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

In 4 controlled and 2 uncontrolled clinical studies, 530 chronic adult ITP patients were treated with eltrombopag. The mean duration of exposure to eltrombopag was 260 days. The most important serious adverse reactions were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included: headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral oedema.

In 2 controlled clinical studies, 171 chronic paediatric ITP patients were treated with eltrombopag. The median duration of exposure was 171 days. The profile of adverse reactions was comparable to that seen in adults with some additional adverse reactions, marked ♦ in the table below. The most common adverse reactions in paediatric ITP patients 1 year and older (≥ 3% and greater than placebo) were upper respiratory tract infection, nasopharyngitis, cough, diarrhoea, pyrexia, rhinitis, abdominal pain, oropharyngeal pain, toothache, rash, increased AST and rhinorrhoea.

In 2 controlled clinical studies 955 thrombocytopenic patients with HCV infection were treated with eltrombopag. The median duration of exposure was 183 days. The most important serious adverse reactions identified were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included: headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral oedema.

The safety of eltrombopag in severe aplastic anaemia was assessed in a single-arm, open-label trial (N=43) in which 12 patients (28%) were treated for > 6 months and 9 patients (21%) were treated for > 1 year. The most important serious adverse reactions were febrile neutropenia and sepsis/infection. The most common adverse reactions occurring in at least 10% of patients included: headache, dizziness, insomnia, cough, dyspnoea, oropharyngeal pain, rhinorrhoea, nausea, diarrhoea, abdominal pain, transaminases increased, ecchymosis, arthralgia, muscle spasms, pain in extremity, fatigue, febrile neutropenia, and pyrexia.

List of adverse reactions

The adverse reactions in the adult ITP studies (N=550), paediatric ITP studies (N=107), the HCV studies (N=955), the SAA studies (N=43) and post-marketing reports are listed below by MedDRA system organ class and by frequency.

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)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data)

ITP study population

Infections and infestations

Very common Nasopharyngitis♦, upper respiratory tract infection♦

Common Rhinitis♦

Uncommon Pharyngitis, Urinary tract infection, Influenza, Oral herpes, Pneumonia, Sinusitis, Tonsillitis, Respiratory tract infection, Gingivitis, Skin infection

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Uncommon Rectosigmoid cancer

Blood and lymphatic system disorders

Uncommon Anaemia, Anisocytosis, Eosinophilia, Haemolytic anaemia, Leukocytosis, Myelocytosis, Thrombocytopenia, Haemoglobin increased, Band neutrophil count increased, Haemoglobin decreased, Myelocyte present, Platelet count increased, White blood cell count decreased

Immune system disorders

Uncommon Hypersensitivity

Metabolism and nutrition disorders

Uncommon Anorexia, Hypokalaemia, Decreased appetite, Gout, Hypocalcaemia, Blood uric acid increased

Psychiatric disorders

Uncommon Sleep disorder, Depression, Apathy, Mood altered, Tearfulness

Nervous system disorders

Common Paraesthesia

Uncommon Hypoaesthesia, Somnolence, Migraine, Tremor, Balance disorder, Dysaesthesia, Hemiparesis, Migraine with aura, Neuropathy peripheral, Peripheral sensory neuropathy, Speech disorder, Toxic neuropathy, Vascular headache

Eye disorders

Common Dry eye

Uncommon Vision blurred, Lenticular opacities, Astigmatism, Cataract cortical, Eye pain, Lacrimation increased, Retinal haemorrhage, Retinal pigment epitheliopathy, Visual acuity reduced, Visual impairment, Visual acuity tests abnormal, Blepharitis and Keratoconjunctivitis sicca

Ear and labyrinth disorders

Uncommon Ear pain, Vertigo

Cardiac disorders

Uncommon Tachycardia, Acute myocardial infarction, Cardiovascular disorder, Cyanosis, Sinus tachycardia, Electrocardiogram QT prolonged

Vascular disorders

Uncommon Deep vein thrombosis, Embolism, Hot flush, Thrombophlebitis superficial, Flushing, Haematoma

Respiratory, thoracic and mediastinal disorders

Common Cough♦, Oropharyngeal pain♦, Rhinorrhoea♦

Uncommon Pulmonary embolism, Pulmonary infarction, Nasal discomfort, Oropharyngeal blistering, Oropharyngeal pain, Sinus disorder, Sleep apnoea syndrome

Gastrointestinal disorders

Common Nausea, Diarrhoea*, Mouth ulceration, Toothache♦
* Very common in paediatric ITP

Uncommon Dry mouth, Vomiting, Abdominal pain, Glossodynia, Mouth haemorrhage, Abdominal tenderness, Faeces discoloured, Flatulence, Food poisoning, Frequent bowel movements, Haematemesis, Oral discomfort

Hepatobiliary disorders

Common Alanine aminotransferase increased*, Aspartate aminotransferase increased*, Hyperbilirubinaemia, Hepatic function abnormal

Uncommon Cholestasis, Hepatic lesion, Hepatitis, Drug-induced liver injury

*Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

Skin and subcutaneous tissue disorders

Common Rash, Alopecia

Uncommon Hyperhidrosis, Pruritus generalised, Urticaria, Dermatosis, Petechiae, Cold sweat, Erythema, Melanosis, Pigmentation disorder, Skin discolouration, Skin exfoliation

Musculoskeletal and connective tissue disorders

Common Myalgia, Muscle spasm, Musculoskeletal pain, Bone pain, Back pain

Uncommon Muscular weakness

Renal and urinary disorders

Uncommon Renal failure, Leukocyturia, Lupus nephritis, Nocturia, Proteinuria, Blood urea increased, Blood creatinine increased, Urine protein/creatinine ratio increased

Reproductive system and breast disorders

Common Menorrhagia

General disorders and administration site conditions

Common Pyrexia♦

Uncommon Chest pain, Feeling hot, Vessel puncture site haemorrhage, Asthenia, Feeling jittery, Inflammation of wound, Malaise, Pyrexia, Sensation of foreign body

Investigations

Uncommon Blood albumin increased, Blood alkaline phosphatase increased, Protein total increased, Blood albumin decreased, pH urine increased

Injury, poisoning and procedural complications

Uncommon Sunburn

♦ Additional adverse reactions observed in paediatric studies (aged 1to 17 years).

HCV study population (in combination with anti-viral interferon and ribavirin therapy)

Infections and infestations

Common Urinary tract infection, Upper respiratory tract infection, Bronchitis, Nasopharyngitis, Influenza, Oral herpes, Gastroenteritis, Pharyngitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Common Hepatic neoplasm malignant

Blood and lymphatic system disorders

Very common Anaemia
Common Lymphopenia, Haemolytic anaemia

Metabolism and nutrition disorders

Very common Decreased appetite
Common Hyperglycaemia, Abnormal loss of weight

Psychiatric disorders

Very common Insomnia
Common Depression, Anxiety, Sleep disorder, Confusional state, Agitation

Nervous system disorders

Very common Headache
Common Dizziness, Disturbance in attention, Dysgeusia, Hepatic encephalopathy, Lethargy, Memory impairment, Paraesthesia

Eye disorders

Common Cataract, Retinal exudates, Dry Eye, Ocular icterus, Retinal haemorrhage

Ear and labyrinth disorders

Common Vertigo

Cardiac disorders

Common Palpitations

Respiratory, thoracic and mediastinal disorders

Very common Cough
Common Dyspnoea, Oropharyngeal pain, Dyspnoea exertional, Productive cough

Gastrointestinal disorders

Very common Nausea, Diarrhoea
Common Vomiting, Ascites, Abdominal pain, Abdominal pain upper, Dyspepsia, Dry mouth, Constipation, Abdominal distension, Toothache, Stomatitis, Gastrooesophagal reflux disease, Haemorrhoids, Abdominal discomfort, Gastritis, Varices oesophageal, Aphthous stomatitis, Oesophageal varices haemorrhage

Hepatobiliary disorders

Common Hyperbilirubinaemia, Jaundice, Portal vein thrombosis, Hepatic failure, Drug-induced liver injury

Skin and subcutaneous tissue disorders

Very common Pruritus, Alopecia
Common Rash, Dry skin, Eczema, Rash pruritic, Erythema, Hyperhidrosis, Pruritus generalised, Night sweats, Skin lesion
Not known Skin discolouration, Skin hyperpigmentation

Musculoskeletal and connective tissue disorder

Very common Myalgia
Common Arthralgia, Muscle spasms, Back pain, Pain in extremity, Musculoskeletal pain, Bone pain

Renal and urinary disorders

Uncommon Dysuria

General disorders and administration site conditions

Very common Pyrexia, Fatigue, Influenza like illness, Asthenia, Chills, Oedema peripheral
Common Irritability, Pain, Malaise, Injection site reaction, Non-cardiac chest pain, Oedema, Injection site rash, Chest discomfort, Injection site pruritus

Investigations

Common Blood bilirubin increased, Weight decreased, White blood cell count decreased, Haemoglobin decreased, Neutrophil count decreased, International normalised ratio increased, Activated partial thromboplastin time prolonged, Blood glucose increased, Blood albumin decreased, Electrocardiogram QT prolonged

SAA study population

Blood and lymphatic system disorders

Common Neutropenia, Splenic infarction

Metabolism and nutrition disorders

Common Iron overload, Decreased appetite, Hypoglycaemia, Increased appetite

Psychiatric disorders

Very common Insomnia

Common Anxiety, Depression

Nervous system disorders

Very common Headache, Dizziness

Common Syncope

Eye disorders

Common Dry eye, Eye pruritus, Cataract, Ocular icterus, Vision blurred, Visual impairment, Vitreous floaters

Respiratory, thoracic and mediastinal disorders

Very common Cough. Dyspnoea, Oropharyngeal Pain, Rhinorrhoea

Common Epistaxis

Gastrointestinal disorders

Very common Abdominal pain, Diarrhoea, Nausea

Common Gingival bleeding, Oral mucosal blistering, Oral pain, Vomiting, Abdominal discomfort, Abdominal pain, Constipation, Abdominal distension, Dysphagia, Faeces discoloured, Swollen tongue, Gastrointestinal motility disorder, Flatulence

Hepatobiliary disorders

Very common Transaminases increased

Common Blood bilirubin increased (hyperbilirubinemia), Jaundice

Not known Drug-induced liver injury*

* Cases of Drug-induced liver injury have been reported in patients with ITP and HCV

Skin and subcutaneous tissue disorders

Very common Ecchymosis

Common Petechiae, Rash, Pruritus, Urticaria, Skin lesion, Rash Macular

Not known Skin discolouration, Skin hyperpigmentation

Musculosketal and connective tissue disorders

Very common Arthralgia, Muscle spasms, Pain in extremity

Common Back pain, Myalgia, Bone pain

Renal and urinary disorders

Common Chromaturia

General disorders and administration site conditions

Very common Fatigue, Febrile neutropenia, Pyrexia

Common Asthenia, Oedema peripheral, Chills, Malaise

Investigations

Common Blood creatine phosphokinase increased

Description of selected adverse reactions

Thrombotic/Thromboembolic events (TEEs)

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving eltrombopag (n=446), 17 subjects experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n=6), pulmonary embolism (n=6), acute myocardial infarction (n=2), cerebral infarction (n=2), embolism (n=1) (see section 4.4).

In a placebo-controlled study (n=288, Safety population), following 2 weeks treatment in preparation for invasive procedures, 6 of 143 (4%) adult patients with chronic liver disease receiving eltrombopag experienced 7 TEEs of the portal venous system and 2 of 145 (1%) subjects in the placebo group experienced 3 TEEs. Five of the 6 patients treated with eltrombopag experienced the TEE at a platelet count > 200,000/µl

No specific risk factors were identified in those subjects who experienced a TEE with the exception of platelet counts ≥ 200,000/µl (see section 4.4).

In controlled studies in thrombocytopenic patients with HCV (n=1439), 38 out of 955 subjects (4%) treated with eltrombopag experienced a TEE and 6 out of 484 subjects (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus < 1% for placebo) (see section 4.4). Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients.

Hepatic decompensation (use with interferon)

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤ 35 g/L) or MELD score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation (see section 4.4).

Thrombocytopenia following discontinuation of treatment

In the 3 controlled clinical ITP studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% and 8% of the eltrombopag and placebo groups, respectively (see section 4.4).

Increased bone marrow reticulin

Across the programme, no patients had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In a small number of ITP patients, eltrombopag treatment was discontinued due to bone marrow reticulin (see section 4.4).

Cytogenetic abnormalities

In the single-arm, open-label trial in SAA, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight (19%) patients had a new cytogenetic abnormality reported, including 5 patients who had changes in chromosome 7. In the two ongoing studies (ELT116826 and ELT116643), cytogenetic abnormalities have been detected in 4/28 (14%) and 4/62 (6%) subjects in each study.

Haematologic malignancies

In the single-arm, open label trial in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) subject has been diagnosed with MDS or AML in each study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consideration should be given to oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Platelet counts should be closely monitored. Treatment with eltrombopag should be reinitiated in accordance with dosing and administration recommendations (see section 4.2).

In the clinical studies there was one report of overdose where the subject ingested 5000 mg of eltrombopag. Reported adverse reactions included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. Liver enzymes measured between Days 2 and 18 after ingestion peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin, The platelet counts were 672,000/µl on day 18 after ingestion and the maximum platelet count was 929,000/µl. All events were resolved without sequelae following treatment.

Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics. ATC code: B02BX 05.

Mechanism of action

TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-R. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation from bone marrow progenitor cells.

Clinical efficacy and safety

Chronic immune (idiopathic) thrombocytopenia (ITP) studies

Two Phase III, randomised, double-blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of eltrombopag in adult patients with previously treated chronic ITP. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year.

Double-blind placebo-controlled studies

RAISE: 197 ITP patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medicinal products at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6 month treatment period based on individual platelet counts. All patients initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment, 15 to 28% of eltrombopag treated patients were maintained on ≤ 25 mg and 29 to 53% received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥ 3 prior ITP therapies and 36% had a prior splenectomy.

Median platelet counts at baseline were 16,000/µl for both treatment groups and in the eltrombopag group were maintained above 50,000/µl at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained < 30,000/µl throughout the study.

Platelet count response between 50,000-400,000/µl in the absence of rescue treatment was achieved by significantly more patients in the eltrombopag treated group during the 6 month treatment period, $p < 0.001$. Fifty-four percent of the eltrombopag-treated patients and 13% of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52% and 16% of patients responding at the end of the 6-month treatment period.

Table 4: Secondary efficacy results from RAISE

	Eltrombopag N=135	Placebo N=62
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥ 50,000-400,000/µl, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥ 75% of assessments in the target range (50,000 to 400,000/µl), n (%)	51 (38)	4 (7)
p-value [a]	< 0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
p-value [a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
p-value [a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
p-value [a]	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%)[b]	37 (59)	10 (32)
p-value [a]	0.016	

a Logistic regression model adjusted for randomisation stratification variables
b 21 out of 63 (33%) patients treated with eltrombopag who were taking an ITP medicinal product at baseline permanently discontinued all baseline ITP medicinal products.

At baseline, more than 70% of ITP patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20% reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50% from Day 15 to the end of treatment throughout the 6 month treatment period.

TRA100773B: The primary efficacy endpoint was the proportion of responders, defined as ITP patients who had an increase in platelet counts to ≥ 50,000/µl at Day 43 from a baseline of < 30,000/µl; patients who withdrew prematurely due to a platelet count > 200,000/µl were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated chronic ITP were randomised 2:1 eltrombopag (n=76) to placebo (n=38).

Table 5: Efficacy results from TRA100773B

	Eltrombopag N=74	Placebo N=38
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥ 50,000/µl after up to 42 days of dosing (compared to a baseline count of < 30,000/µl), n (%)	43 (59)	6 (16)
p-value[a]	< 0.001	
Key secondary endpoints		
Patients with a Day 43 bleeding assessment, n	51	30
Bleeding (WHO Grades 1-4) n (%)	20 (39)	18 (60)
p-value[a]	0.029	

a – Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medicinal product use, splenectomy status and baseline platelet count (≤ 15,000/µl, > 15,000/µl) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP patients with baseline platelet count ≤ 15,000/µl the median platelet counts did not reach the target level (> 50,000/µl), although in both studies 43% of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42% of patients with baseline platelet count ≤ 15,000/µl treated with eltrombopag responded at the end of the 6 month treatment period. Forty-two to 60% of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

An open label, repeat dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

Eltrombopag was administered to 302 ITP patients in the open-label extension study EXTEND (TRA105325), 218 patients completed 1 year, 180 completed 2 years, 107 completed 3 years, 75 completed 4 years, 34 completed 5 years and 18 completed 6 years. The median baseline platelet count was 19,000/µl prior to eltrombopag administration. Median platelet counts at 1, 2, 3, 4, 5, 6 and 7 years on study were 85,000/µl, 85,000/µl, 105,000/µl, 64,000/µl, 75,000/µl, 119,000/µl and 76,000/µl, respectively.

Clinical studies comparing eltrombopag to other treatment options (e.g. splenectomy) have not been conducted. The long-term safety of eltrombopag should be considered prior to starting therapy.

Paediatric population (aged 1 to 17 years)

The safety and efficacy of eltrombopag in paediatric subjects has been investigated two studies.

TRA115450 (PETIT2): The primary endpoint was a sustained response, defined as the proportion of subjects receiving eltrombopag, compared to placebo, achieving platelet counts ≥50,000/µl for at least 6 out of 8 weeks (in the absence of rescue therapy), between weeks 5 to 12 during the double-blind randomised period. Subjects were diagnosed with chronic ITP for at least 1 year and were refractory or relapsed to at least one prior ITP therapy or unable to continue other ITP treatments for a medical reason and had platelet count < 30,000/µl. Ninety-two subjects were randomised by three age cohort strata (2:1) to eltrombopag (n=63) or placebo (n=29). The dose of eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of eltrombopag subjects (40%) compared with placebo subjects (3%) achieved the primary endpoint (Odds Ratio: 18.0 [95% CI: 2.3, 140.9] p < 0.001) which was similar across the three age cohorts (Table 6).

Table 6: Sustained platelet response rates by age cohort in paediatric subjects with chronic ITP

	Eltrombopag n/N (%) [95% CI]	Placebo n/N (%) [95% CI]
Cohort 1 (12 to 17 years)	9/23 (39%) [20%, 61%]	1/10 (10%) [0%, 45%]
Cohort 2 (6 to 11 years)	11/26 (42%) [23%, 63%]	0/13 (0%) [N/A]
Cohort 3 (1 to 5 years)	5/14 (36%) [13%, 65%]	0/6 (0%) [N/A]

Statistically fewer eltrombopag subjects required rescue treatment during the randomised period compared to placebo subjects (19% [12/63] vs. 24% [7/29], p=0.032).

At baseline, 71% of subjects in the eltrombopag group and 69% in the placebo group reported any bleeding (WHO Grades 1-4). At Week 12, the proportion of eltrombopag subjects reporting any bleeding was decreased to half of baseline (36%). In comparison, at Week 12, 55% of placebo subjects reported any bleeding.

Subjects were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the study and 53% (8/15) of subjects were able to reduce (n=1) or discontinue (n=7) baseline ITP therapy, mainly corticosteroids, without needing rescue therapy.

TRA108062 (PETIT): The primary endpoint was the proportion of subjects achieving platelet counts ≥ 50,000/µl at least once between weeks 1 and 6 of the randomised period. Subjects were refractory or relapsed to at least one prior ITP therapy with a platelet count < 30,000/µl (n=67). During the randomised period of the study, subjects were randomised by 3 age cohort strata (2:1) to eltrombopag (n=45) or placebo (n=22). The dose of eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of eltrombopag subjects (62%) compared with placebo subjects (32%) met the primary endpoint (Odds Ratio: 4.3 [95% CI: 1.4, 13.3] p=0.011).

Sustained response was seen in 50% of the initial responders during 20 out of 24 weeks in the PETIT 2 study and 15 out of 24 weeks in the PETIT Study.

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomised, double-blind, placebo-controlled studies. ENABLE 1 utilised peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilised peginterferon alfa-2b plus ribavirin. Patients did not receive direct acting antiviral agents. In both studies, patients with a platelet count of < 75,000/µl were enrolled and stratified by platelet count (< 50,000/µl and ≥ 50,000/µl to < 75,000/µl), screening HCV RNA (< 800,000 IU/ml and ≥ 800,000 IU/ml), and HCV genotype (genotype 2/3, and genotype 1/4/6).

Baseline disease characteristics were similar in both studies and were consistent with compensated cirrhotic HCV patient population. The majority of patients were HCV genotype 1 (64%) and had bridging fibrosis/cirrhosis. Thirty-one percent of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet count was 59,500/µl in both treatment groups: 0.8%, 28% and 72% of the patients recruited had platelet counts < 20,000/µl, < 50.000/µl and ≥ 50,000/µl respectively.

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, subjects received open-label eltrombopag to increase the platelet count to ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. The median time to achieve the target platelet count ≥ 90,000/µl (ENABLE 1) or ≥ 100,000/µl (ENABLE 2) was 2 weeks.

The primary efficacy endpoint for both studies was sustained virologic response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period.

In both HCV studies, a significantly greater proportion of patients treated with eltrombopag (n=201, 21%) achieved SVR compared to those treated with placebo (n=65, 13%) (see Table 7). The improvement in the proportion of patients who achieved SVR was consistent across all subgroups in the randomisation strata (baseline platelet counts (< 50,000 vs. > 50,000), viral load (< 800,000 IU/ml vs. ≥ 800,000 IU/ml) and genotype (2/3 vs. 1/4/6)).

Table 7: Virologic response in HCV patients in ENABLE 1 and ENABLE 2

	Pooled Data		**ENABLE 1[a]**		**ENABLE 2[b]**	
Patients achieving target platelet counts & initiating antiviral therapy [c]	1,439/1,520 (95%)		680/715 (95%)		759/805 (94%)	
	Eltrombopag	**Placebo**	**Eltrombopag**	**Placebo**	**Eltrombopag**	**Placebo**
Total number of patients entering Antiviral Treatment Phase	**n=956**	**n=485**	**n=450**	**n=232**	**n=506**	**n=253**
	% patients achieving virologic response					
Overall SVR [d]	21	13	23	14	19	13
HCV RNA Genotype						
Genotype 2/3	35	25	35	24	34	25
Genotype 1/4/6[e]	15	8	18	10	13	7
Albumin levels [f]						
≤ 35g/L	11	8				
> 35g/L	25	16				
MELD score[f]						
≥ 10	18	10				
< 10	23	17				

a Eltrombopag given in combination with peginterferon alfa-2a (180 mcg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1200 mg daily in 2 divided doses orally)

b Eltrombopag given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for 48 weeks for genotype 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1400 mg orally in 2 divided doses)

c Target platelet count was ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. For ENABLE 1, 682 patients were randomised to the antiviral treatment phase; however 2 subjects then withdrew consent prior to receiving antiviral therapy.

d *p*-value < 0.05 for eltrombopag versus placebo

e 64% subjects participating in ENABLE 1 and ENABLE 2 were genotype 1

f Post-hoc analyses

Other secondary findings of the studies included the following; significantly fewer patients treated with eltrombopag prematurely discontinued antiviral therapy compared to placebo (45% vs. 60%, p=< 0.0001). A greater proportion of patients on eltrombopag did not require any antiviral dose reduction as compared to placebo (45% versus 27%). Eltrombopag treatment delayed and reduced the number of peginterferon dose reductions.

Severe aplastic anaemia

Eltrombopag was studied in a single-arm, single-centre open-label trial in 43 patients with severe aplastic anaemia with refractory thrombocytopenia following at least one prior immunosuppressive therapy (IST) and who had a platelet count ≤ 30,000/µl.

The majority of subjects, 33 (77%), were considered to have 'primary refractory disease', defined as having no prior adequate response to IST in any lineage. The remaining 10 subjects had insufficient platelet response to prior therapies. All 10 had received at least 2 prior IST regimens and 50% had received at least 3 prior IST regimens. Patients with diagnosis of Fanconi anaemia, infection not responding to appropriate therapy, PNH clone size in neutrophils of ≥50%, where excluded from participation.

At baseline the median platelet count was 20,000/µl, haemoglobin was 8.4 g/dL, ANC was 0.58 x 10^9/L and absolute reticulocyte count was 24.3 x10^9/L. Eighty-six percent of patients were RBC transfusion dependent, and 91% were platelet transfusion dependent. The majority of patients (84%) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

The primary endpoint was haematological response assessed after 12 weeks of eltrombopag treatment. Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20,000/µl above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by > 1.5g/dL, or a reduction in ≥ 4 units of red blood cell (RBC) transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% or an ANC increase > 0.5 x 10^9/L.

The haematological response rate was 40% (17/43 patients; 95 % CI 25, 56), the majority were unilineage responses (13/17, 76%) whilst there were 3 bilineage and 1 trilineage responses at week 12. Eltrombopag was discontinued after 16 weeks if no haematological response or transfusion independence was observed. Patients who responded continued therapy in an extension phase of the study. A total of 14 patients entered the extension phase of the trial. Nine of these patients achieved a multi-lineage response, 4 of the 9 remain on treatment and 5 tapered off treatment with eltrombopag and maintained the response (median follow up: 20.6 months, range: 5.7 to 22.5 months). The remaining 5 patients discontinued treatment, three due to relapse at the month 3 extension visit.

During treatment with eltrombopag 59% (23/39) became platelet transfusion independent (28 days without platelet transfusion) and 27% (10/37) became RBC transfusion independent (56 days without RBC transfusion). The longest platelet transfusion free period for non-responders was 27 days (median). The longest platelet transfusion free period for responders was 287 days (median). The longest RBC transfusion free period for non-responders was 29 days (median). The longest RBC transfusion free period for responders was 266 days (median).

Over 50% of responders who were transfusion dependent at baseline, had >80% reduction in both platelet and RBC transfusion requirements compared to baseline.

Preliminary results from a supportive study (Study ELT116826), an ongoing non-randomised, phase II, single-arm, open-label study in refractory SAA subjects, showed consistent results. Data are limited to 21 out of the planned 60 patients with haematological responses reported by 52% of patients at 6 months. Multilineage responses were reported by 45% of patients.

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 patients with ITP in Studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for ITP patients are presented (Table 8).

Table 8: Geometric mean (95% confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	$AUC_{(0-\tau)}$[a], µg.h/ml	C_{max}[a], µg/ml
30 mg	28	47 (39, 58)	3.78 (3.18, 4.49)
50 mg	34	108 (88, 134)	8.01 (6.73, 9.53)
75 mg	26	168 (143, 198)	12.7 (11.0, 14.5)

a - $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates.

Plasma eltrombopag concentration-time data collected in 590 subjects with HCV enrolled in Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from patients with HCV enrolled in the Phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma eltrombopag C_{max} and $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in the Phase 3 studies are presented for each dose studied in Table 9.

Table 9 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

Eltrombopag dose (once daily)	**N**	**$AUC_{(0-\tau)}$ (µg.h/ml)**	**C_{max} (µg/ml)**
25 mg	330	118 (109, 128)	6.40 (5.97, 6.86)
50 mg	119	166 (143, 192)	9.08 (7.96, 10.35)
75 mg	45	301 (250, 363)	16.71 (14.26, 19.58)
100 mg	96	354 (304, 411)	19.19 (16.81, 21.91)

Data presented as geometric mean (95% CI).
$AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each patient.

Absorption and bioavailability

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see section 4.2). In a relative bioavailability study in adults, the eltrombopag powder for oral suspension delivered 22% higher plasma $AUC_{(0-\infty)}$ than the tablet formulation. The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52%.

Distribution

Eltrombopag is highly bound to human plasma proteins (> 99.9%), predominantly to albumin. Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Biotransformation

Eltrombopag is primarily metabolised through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64% of plasma radiocarbon $AUC_{0-\infty}$. Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

Elimination

Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59%) with 31% of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20% of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

Pharmacokinetic interactions

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes *in vitro*. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag.

Approximately 21% of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section 4.5).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section 4.5). In clinical studies with eltrombopag, a dose reduction of statins by 50% was recommended. The co-administration of 200 mg ciclosporin (a BCRP inhibitor) decreased the C_{max} and the AUC_{inf} of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg ciclosporin decreased the C_{max} and the AUC_{inf} of eltrombopag by 39% and 24%, respectively.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see sections 4.2 and 4.5).

Administration of a single 50 mg dose of eltrombopag in tablet form with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 59% and mean C_{max} by 65%.

Administration of a single 25 mg dose of eltrombopag as powder for oral suspension with a high-calcium, moderate fat and moderate calorie meal reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 75% and mean C_{max} by 79%. This decrease of exposure was attenuated when a single 25 mg dose of eltrombopag powder for oral suspension was administered 2 hours before a high-calcium meal (mean $AUC_{0-\infty}$ was decreased by 20% and mean C_{max} by 14%).

Food low in calcium (< 50 mg calcium) including fruit, lean ham, beef and unfortified (no added calcium, magnesium or iron) fruit juice, unfortified soya milk and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5).

Special patient populations

Renal impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with renal impairment. Following administration of a single 50 mg-dose, the $AUC_{0-\infty}$ of eltrombopag was 32% to 36% lower in subjects with mild to moderate renal impairment, and 60% lower in subjects with severe renal impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2). The efficacy and safety of eltrombopag has not been established in subjects with both moderate to severe renal impairment and hepatic impairment.

Hepatic impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with hepatic impairment. Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 41% higher in subjects with mild hepatic impairment and 80% to 93% higher in subjects with moderate to severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 714 patients with hepatic impairment (673 patients with HCV and 41 patients with chronic liver disease of other aetiology). Of the 714 patients, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with severe hepatic impairment. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 111% (95% CI: 45% to 283%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values and patients with moderate hepatic impairment had approximately 183% (95% CI: 90% to 459%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values.

Therefore, eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see sections 4.2 and 4.4). For patients with HCV initiate eltrombopag at a dose of 25 mg once daily (see section 4.2).

Race

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East Asians) and 88 patients with ITP (18 East Asians). Based on estimates from the population pharmacokinetic analysis, East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 49% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients who were predominantly Caucasian (see section 4.2).

The influence of East Asian ethnicity (such as Chinese, Japanese, Taiwanese, Korean, and Thai) on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (145 East Asians and 69 Southeast Asians). Based on estimates from the population pharmacokinetic analysis, East Asian patients had approximately 55% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian (see section 4.2).

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 23% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients, without adjustment for body weight differences.

The influence of gender on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 635 patients with HCV (260 females). Based on model estimate, female HCV patient had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients.

Age

The influence of age on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects, 673 patients with HCV, and 41 patients with chronic liver disease of other aetiology ranging from 19 to 74 years old. There are no PK data on the use of eltrombopag in patients ≥ 75 years. Based on model estimate, elderly (≥ 65 years) patients had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see section 4.2).

Paediatric Population (aged 1 to 17 years)

The pharmacokinetics of eltrombopag have been evaluated in 168 paediatric ITP subjects dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT-2. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. The effects of race and sex on plasma eltrombopag CL/F estimates were consistent between pediatric and adult patients. East Asian paediatric ITP patients had approximately 43% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients. Female paediatric ITP patients had approximately 25% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to male patients.

The pharmacokinetic parameters of eltrombopag in paediatric subjects with ITP are shown in Table 10.

Table 10 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in paediatric subjects with ITP (50 mg once daily dosing regimen)

Age	**C_{max} (µg/ml)**	**$AUC_{(0-\tau)}$ (µg.hr/ml)**
12 to 17 years (n=62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n=68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n=38)	11.6 (10.4, 12.9)	162 (139, 187)

Data presented as geometric mean (95%CI). $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates

5.3 Preclinical safety data

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥ 6 times the human clinical exposure in adult ITP patients at 75 mg/day and 3 times the human clinical exposure in adult HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥ 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. At non-tolerated doses in pre-weaning juvenile rats dosed from days 4-32 (approximately equating to a 2-year old human at the end of the dosing period), ocular opacities were observed (histology not performed) at 9 times the maximum human clinical exposure in paediatric ITP patients at 75 mg/day, based on AUC. However, cataracts were not observed in juvenile rats given tolerated doses at 5 times the human clinical exposure in paediatric ITP patients, based on AUC. Cataracts have not been observed in adult dogs after 52 weeks of dosing at 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2 year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterised by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 or 0.8 times the human clinical exposure based on AUC in adult or paediatric ITP patients at 75 mg/day and 0.6 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times the human clinical exposure in adult ITP patients and 3 and 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) and in dogs (52 weeks) at 4 or 2 times the human clinical exposure in adult ITP and 3 or 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

At poorly tolerated doses in rats and dogs (> 10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and> 4 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times human clinical exposure in adult or paediatric ITP patients at 75 mg/day and ≤ 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Endosteal hyperostosis was observed in a 28 week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times or 4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two in vivo assays in rats (micronucleus and unscheduled DNA synthesis, 10 times or 8 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day, based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (< 3-fold increase in mutation frequency). These *in vitro* and *in vivo* findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure in adult or adolescent (12-17 years) ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.3 to 0.5 times the human clinical exposure in ITP patients at 75 mg/day and HCV patients at 100 mg/day, based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see section 4.6). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioral or reproductive function of the offspring (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) or ocular phototoxicity (≥ 4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg. This was measured by delayed phototoxic index. Nevertheless, a potential risk of photoallergy cannot be ruled out since no specific preclinical study could be performed.

There are no findings in juvenile rats to suggest a greater risk of toxicity with eltrombopag treatment in paediatric vs. adult ITP patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sucralose
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Following reconstitution, the medicinal product should be administered immediately but may be stored for a maximum period of 30 minutes.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Heat-sealed foil laminate sachets. The laminate material is comprised of polyester (PET) / orientated polyamide (OPA) / 9 µm aluminium foil (AL) / low density polyethylene heat seal layer (LDPE). The product contact material is the polyethylene heat seal layer. The sachets are co-packaged in a kit with a 40 ml HDPE mixing bottle, and a 20 mL oral dosing syringe (polypropylene/silicon rubber) with 1 mL graduations. In addition, a screw cap (ethylene vinyl acetate / LDPE) with syringe-port capability is provided.

Pack size of 30 sachets.

6.6 Special precautions for disposal

Instructions for use

Avoid direct contact with the medicine. Wash any exposed area immediately with soap and water.

Preparation and administration of the powder for oral suspension:

- Administer the oral suspension immediately after preparation. Discard suspension if not administered within 30 minutes after preparation.
- Prepare the suspension with water only.
- Add 20 ml of water and the contents of the prescribed number of sachets (depending on the recommended dose) to the provided mixing bottle and mix gently.
- Give the entire contents of the bottle to the patient using the accompanying oral syringe.
- IMPORTANT: Because some medicine will remain in the mixing bottle, complete the following steps.
- Add 10 ml of water to the mixing bottle and mix gently.
- Give the entire contents of the bottle to the patient using the accompanying oral syringe.

Cleaning of the mixing equipment:

- Remove the plunger from the syringe.
- Rinse the mixing bottle, lid, the syringe and plunger under running water. (The mixing bottle may become stained from the medicine. This is normal.)
- Let all the equipment dry in the air.
- Wash your hands with soap and water.

For more details on preparation and administration of the suspension, see Instructions for Use in the package leaflet.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 March 2010
Date of latest renewal: 15 January 2015

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. MANUFACTURERS 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Revolade 12.5 mg, 25 mg, 50 mg and 75 mg film-coated tablets:

Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations)
Priory Street
Ware, Hertfordshire SG12 0DJ
United Kingdom

Glaxo Wellcome S.A.
Avenida de Extremadura 3
09400 Aranda de Duero
Burgos
Spain

Novartis Pharmaceuticals UK Limited
Frimley Business Park
Frimley
Camberley, Surrey GU16 7SR
United Kingdom

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

Revolade 25 mg powder for oral suspension:

Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations)
Priory Street
Ware, Hertfordshire SG12 0DJ
United Kingdom

Novartis Pharmaceuticals UK Limited
Frimley Business Park
Frimley
Camberley, Surrey GU16 7SR
United Kingdom

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

- **Additional risk minimisation measures**

The MAH shall agree the details of an educational programme with the National Competent Authorities and must implement such programme nationally to ensure that, prior to prescribing all physicians are provided with a healthcare professional information pack containing the following:
- Educational material
- Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling

<u>Key elements to be included in the educational material</u>

Hepatotoxicity

• Educate patients about the potential for hepatic enzyme elevations and severe hepatotoxicity, which might be life-threatening, importance of monthly laboratory monitoring of ALT and AST, as well as the signs and symptoms associated with liver injury (e.g. jaundice).
• Measure serum ALT, AST and bilirubin prior to initiation of Revolade, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose.
• Discontinue Revolade if ALT levels increase (≥ 3 x the upper limit of normal [ULN] in patients with normal liver function, or ≥ 3 x baseline or > 5 x ULN, whichever is the lower, in patients with pre-treatment elevations in transaminases) and are:
- progressive, or
- persistent for > 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.
• Exercise caution when administering eltrombopag to patients with hepatic disease. Use a lower starting dose of eltrombopag and monitor closely when administering eltrombopag to patients with hepatic impairment.

Thromboembolic events
ITP patients

• Eltrombopag should not be used in patients with hepatic impairment (Child Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. If use of eltrombopag is deemed necessary, the starting dose must be 25 mg once daily.
• Educate patients about the potential for thromboembolic events (TEE) in patients with chronic ITP and those known risk factors for thromboembolic events (e.g. Factor V Leiden, ATIII deficiency, antiphospholipid syndrome).
• Educate patients about chronic liver disease and the risk of thromboembolic events.
• In patients with chronic liver disease treated with eltrombopag there was an association between TEE and platelet counts ≥ 200,000µl.
• A dose reduction is recommended for ITP patients with platelet counts between 150,000-250,000/µl.
• Revolade should be interrupted if platelet counts increase to > 250,000/µl. Once the platelet count is < 100,000/µl, reinitiate therapy at a reduced daily dose.

Posology

• Educate patients on the appropriate administration of Revolade (e.g. titration of Revolade, food-medicinal product interaction, dose recommendations for special populations [e.g. East Asians]).

Food Interactions

• Educate patients about the potential food-medicinal product interaction (i.e. chelation with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc). Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least four hours before or two hours after Revolade dosing to avoid significant reduction in Revolade absorption due to chelation.
• Assist patient in developing a plan to administer Revolade at a time each day that fits into the patient's own daily schedule.

Reoccurrence of Thrombocytopenia

• Educate patients about the potential risk of bleeding after treatment has stopped (include incidence in clinical trials and likelihood of reoccurrence of thrombocytopenia after cessation of treatment).
• Following discontinuation of Revolade, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding.
• Monitor platelet count weekly for 4 weeks following discontinuation of Revolade.

Increased Bone Marrow Reticulin Fibres

• Educate patients about the potential for bone marrow reticulin fibre formation.
• Background information on reticulin in the bone marrow (i.e. background rates of reticulin in bone marrow in ITP patients and the observed incidence and potential mechanism of action of reticulin deposition in response to Revolade).
• Prior to initiation of Revolade, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities.
• Following identification of a stable dose of Revolade, perform full blood count (FBC) with white blood cell count (WBC) differential monthly.
• If immature or dysplastic cells are observed, examine peripheral blood smears for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s).
• If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with Revolade and consider a bone marrow biopsy, including staining for fibrosis.

Haematological malignancies

• The diagnosis of ITP in adults and elderly patients should have been confirmed by excluding other clinical entities with thrombocytopenia. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs.
• Educate patients about the theoretical risk of haematological malignancies with thrombopoietin receptor agonists.
• Importance of not using Revolade outside the context of its license unless in a clinical trial setting.

Potential for Off-label Use

• The risk-benefit for the treatment of thrombocytopenia outside of the registered indication has not been established.
• The risk-benefit of Revolade in paediatric HCV-associated thrombocytopenia and SAA has not been established. The paediatric population is defined as those persons aged between 0 and 18 years.
• Awareness to prescribers of the labelled indication and warnings associated with non-indicated populations (e.g. not recommended for use in children, pregnant or breast-feeding women, other off label uses).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 12.5 mg – 14, 28, 84 (3 PACKS of 28) TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 12.5 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 12.5 mg eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
Multipack containing 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral 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

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/010 (14 film-coated tablets)
EU/1/10/612/011 (28 film-coated tablets)
EU/1/10/612/012 84 film-coated tablets (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 12.5 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 INTERMEDIATE CARTON

Multipacks of 84 (3 packs of 28 film-coated tablets) – without blue box – 12.5 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 12.5 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 12.5 mg eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral 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

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 12.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Revolade 12.5 mg film-coated tablets

eltrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 25 mg – 14, 28, 84 (3 PACKS of 28) TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
Multipack containing 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral 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

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/001 (14 film-coated tablets)
EU/1/10/612/002 (28 film-coated tablets)
EU/1/10/612/003 84 film-coated tablets (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 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 INTERMEDIATE CARTON

Multipacks of 84 (3 packs of 28 film-coated tablets) – without blue box – 25 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral 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

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets

eltrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 50 mg – 14, 28, 84 (3 PACKS of 28) TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 50 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
Multipack containing 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral 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

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/004 (14 film-coated tablets)
EU/1/10/612/005 (28 film-coated tablets)
EU/1/10/612/006 84 film-coated tablets (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 50 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 INTERMEDIATE CARTON

Multipacks of 84 (3 packs of 28 film-coated tablets) – without blue box – 50 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 50 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral 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

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 50 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Revolade 50 mg film-coated tablets

eltrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 75 mg – 14, 28, 84 (3 PACKS of 28) TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 75 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
Multipack containing 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral 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

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/007 (14 film-coated tablets)
EU/1/10/612/008 (28 film-coated tablets)
EU/1/10/612/009 84 film-coated tablets (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 75 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 INTERMEDIATE CARTON

Multipacks of 84 (3 packs of 28 film-coated tablets) – without blue box –75 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 75 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral 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

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 75 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Revolade 75 mg film-coated tablets

eltrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton of 25 mg powder for oral suspension

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg powder for oral suspension

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains eltrombopag olamine equivalent to 25 mg of eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 sachets and 1 mixing bottle + 1 oral syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 30 minutes of reconstitution.

9. SPECIAL STORAGE CONDITIONS

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/013 (30 sachets of powder for oral suspension)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 mg sachets

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 of 25 mg powder for oral suspension – without blue box – 30 sachets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg powder for oral suspension

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains eltrombopag olamine equivalent to 25 mg of eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 sachets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 30 minutes of reconstitution.

9. SPECIAL STORAGE CONDITIONS

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 mg sachets

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Revolade 25 mg powder for oral suspension

eltrombopag

Oral use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

Revolade 12.5 mg film-coated tablets
Revolade 25 mg film-coated tablets
Revolade 50 mg film-coated tablets
Revolade 75 mg film-coated tablets

eltrombopag

Read all of this leaflet carefully before you start taking 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 pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet:
1. What Revolade is and what it is used for
2. What you need to know before you take Revolade
3. How to take Revolade
4. Possible side effects
5. How to store Revolade
6. Contents of the pack and other information

1. What Revolade is and what it is used for

Revolade contains eltrombopag, which belongs to a group of medicines called thrombopoietin receptor agonists. It is used to help increase the number of platelets in your blood. Platelets are blood cells that help to reduce or prevent bleeding.

- Revolade is used to treat a bleeding disorder called immune (idiopathic) thrombocytopenic purpura (ITP) in patients aged 1 year and above who have already taken other medicines (corticosteroids or immunoglobulins), which have not worked.

  ITP is caused by a low blood platelet count (thrombocytopenia). People with ITP have an increased risk of bleeding. Symptoms patients with ITP may notice include petechiae (pinpoint-sized flat round red spots under the skin), bruising, nosebleeds, bleeding gums and not being able to control bleeding if they are cut or injured.

- Revolade can also be used to treat low platelet count (thrombocytopenia) in adults with hepatitis C virus (HCV) infections, if they have had problems with side effects while on interferon treatment. Many people with hepatitis C have low platelet counts, not only as a result of the disease, but also due to some of the antiviral medicines that are used to treat it. Taking Revolade may make it easier for you to complete a full course of antiviral medicine (peginterferon and ribavirin).

- Revolade may also be used to treat adult patients with low blood counts caused by severe aplastic anaemia (SAA).

2. What you need to know before you take Revolade

Do not take Revolade

- **if you are allergic** to eltrombopag or any of the other ingredients of this medicine (listed in section 6 under ***'What Revolade contains'***).
  - ➔ **Check with your doctor** if you think this applies to you.

Warnings and precautions

Talk to your doctor before taking Revolade:

- if you have **liver problems**. People who have low platelet counts as well as advanced chronic (long-term) liver disease are more at risk of side effects, including life-threatening liver damage and blood clots. If your doctor considers that the benefits of taking Revolade outweigh the risks, you will be closely monitored during treatment.
- if you are at risk of **blood clots** in your veins or arteries, or you know that blood clots are common in your family.

  You may be at **higher risk of blood clots**:
  - as you get older
  - if you have had to stay in bed for a long time
  - if you have cancer
  - if you are taking the contraceptive birth control pill or hormone replacement therapy
  - if you have recently had surgery or received a physical injury
  - if you are very overweight (obese)
  - if you are a smoker
  - if you have advanced chronic liver disease

  ➔ If any of these apply to you, **tell your doctor** before starting treatment. You should not take Revolade unless your doctor considers that the expected benefits outweigh the risk of blood clots.
- if you have **cataracts** (the lens of the eye getting cloudy)
- if you have another **blood condition**, such as myelodysplastic syndrome (MDS). Your doctor will carry out tests to check that you do not have this blood condition before you start Revolade. If you have MDS and take Revolade, your MDS may get worse.
  - ➔ Tell your doctor if any of these apply to you.

Eye examinations

Your doctor will recommend that you are checked for cataracts. If you do not have routine eye-tests your doctor should arrange regular testing. You may also be checked for the occurrence of any bleeding in or around your retina (the light-sensitive layer of cells at the back of the eye).

You will need regular tests

Before you start taking Revolade, your doctor will carry out blood tests to check your blood cells, including platelets. These tests will be repeated at intervals while you are taking it.

Blood tests for liver function

Revolade can cause blood test results that may be signs of liver damage - an increase of some liver enzymes, especially bilirubin and alanine / aspartate transaminases. If you are taking interferon-based treatments together with Revolade to treat low platelet count due to hepatitis C, some liver problems can get worse.

You will have blood tests to check your liver function before you start taking Revolade and at intervals while you are taking it. You may need to stop taking Revolade if the amount of these substances increases too much, or if you get other signs of liver damage.

➔ **Read the information '*Liver problems*' in section 4 of this leaflet.**

Blood tests for platelet count
If you stop taking Revolade, your blood platelet count is likely to become low again within several days. The platelet count will be monitored, and your doctor will discuss appropriate precautions with you.

A very high blood platelet count may increase the risk of blood clotting. However blood clots can also form with normal or even low platelet counts. Your doctor will adjust your dose of Revolade to ensure that your platelet count does not become too high.

Get medical help immediately if you have any of these signs of a **blood clot**:
- **swelling**, **pain** or tenderness in **one leg**
- **sudden shortness of breath** especially together with sharp pain in the chest or rapid breathing
- abdominal (stomach) pain, enlarged abdomen, blood in your stools

Tests to check your bone marrow
In people who have problems with their bone marrow, medicines like Revolade could make the problems worse. Signs of bone marrow changes may show up as abnormal results in your blood tests. Your doctor may also carry out tests to directly check your bone marrow during treatment with Revolade.

Checks for digestive bleeding
If you are taking interferon-based treatments together with Revolade you will be monitored for any signs of bleeding in your stomach or intestine after you stop taking Revolade.

Heart monitoring
Your doctor may consider it necessary to monitor your heart during treatment with Revolade and carry out an electrocardiogram (ECG) test.

Children and adolescents
Revolade is not recommended for children aged under 1 year who have ITP. It is also not recommended for people under 18 years with low platelet counts due to hepatitis C or severe aplastic anaemia.

Other medicines and Revolade
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some everyday medicines interact with Revolade – including prescription and non-prescription medicines and minerals. These include:
- antacid medicines to treat **indigestion**, **heartburn** or **stomach ulcers** (see also '***When to take it***' in section 3)
- medicines called statins, to **lower cholesterol**
- some medicines to treat **HIV infection**, such as lopinavir and/or ritonavir
- ciclosporin used in the context of **transplantations** or **immune diseases**
- minerals such as iron, calcium, magnesium, aluminium, selenium and zinc which may be found in **vitamin and mineral supplements** (see also ***'When to take it'*** in section 3)
- medicines such as methotrexate and topotecan, to treat **cancer**

➔ **Talk to your doctor** if you take any of these. Some of them are not to be taken with Revolade, or the dose may need adjusting, or you may need to alter the timing of when you take them. Your doctor will review the medicines you are taking, and suggest suitable replacements if necessary.

If you are also taking medicines to prevent blood clots there is a greater risk of bleeding. Your doctor will discuss this with you.

If you are taking **corticosteroids, danazol,** and/or **azathioprine** you may need to take a lower dose or to stop taking them while you are taking Revolade.

Revolade with food and drink
Do not take Revolade with dairy foods or drinks as the calcium in dairy products affects the absorption of the medicine. For more information, see '***When to take it'*** in section 3.

Pregnancy and breast-feeding
Don't use Revolade if you are pregnant unless your doctor specifically recommends it. The effect of Revolade during pregnancy is not known.

- **Tell your doctor if you are pregnant,** think you may be pregnant, or are planning to have a baby.
- **Use a reliable method of contraception** while you're taking Revolade, to prevent pregnancy
- **If you do become pregnant during treatment** with Revolade, tell your doctor.

Don't breast-feed while you are taking Revolade. It is not known whether Revolade passes into breast-milk.

➔ **If you are breast-feeding** or planning to breast-feed, tell your doctor.

Driving and using machines
Revolade can make you dizzy and have other side effects that make you less alert.

➔ **Don't drive or use machines** unless you are sure you're not affected.

3. How to take Revolade

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Do not change the dose or schedule for taking Revolade unless your doctor or pharmacist advises you to. While you are taking Revolade, you will be under the care of a doctor with specialist experience in treating your condition.

How much to take
For ITP
Adults and **children** (6 to 17 years) – the usual starting dose for ITP is **one 50 mg tablet** of Revolade a day. If you are of East Asian origin (Chinese, Japanese, Taiwanese, Thai or Korean) you may need to start at a **lower dose of 25 mg.**

Children (1 to 5 years) — the usual starting dose for ITP is **one 25 mg tablet** of Revolade a day.

For hepatitis C
Adults - the usual starting dose for hepatitis C is **one 25 mg tablet** of Revolade a day. If you are of East Asian origin (Chinese, Japanese, Taiwanese, Thai or Korean) you will start on the **same 25 mg dose.**

For SAA
Adults - the usual starting dose for SAA is **one 50 mg tablet** of Revolade a day. If you are of East Asian origin (Chinese, Japanese, Taiwanese, Thai or Korean) you may need to start at a **lower dose of 25 mg.**

Revolade may take 1 to 2 weeks to work. Based on your response to Revolade your doctor may recommend that your daily dose is changed.

How to take the tablets
Swallow the tablet whole, with some water.

When to take it

Make sure that –
- in the **4 hours before** you take Revolade
- and the **2 hours after** you take Revolade

you don't consume any of the following:
- **dairy foods** such as cheese, butter, yoghurt or ice cream
- **milk or milk shakes,** drinks containing milk, yoghurt or cream
- **antacids,** a type of medicine for **indigestion and heartburn**
- some **mineral and vitamin supplements** including iron, calcium, magnesium, aluminium, selenium and zinc

If you do, the medicine will not be properly absorbed into your body.

For more advice about suitable foods and drinks, talk to your doctor.

If you take more Revolade than you should
Contact a doctor or pharmacist immediately. If possible show them the pack, or this leaflet. Youwill be monitored for any signs or symptoms of side effects and given appropriate treatment immediately.

If you forget to take Revolade
Take the next dose at the usual time. Do not take more than one dose of Revolade in one day.

If you stop taking Revolade
Don't stop taking Revolade without talking to your doctor. If your doctor advises you to stop treatment, your platelet count will then be checked each week for four weeks. See also '***Bleeding or bruising after you stop treatment***' in section 4.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Symptoms needing attention: see a doctor
People taking Revolade for either ITP or low blood platelet counts due to hepatitis C could develop signs of potentially serious side effects. **It is important to tell a doctor if you develop these symptoms**.

Higher risk of blood clots
Certain people may have a higher risk of blood clots, and medicines like Revolade could make this problem worse. The sudden blocking of a blood vessel by a blood clot is an uncommon side effect and may affect up to 1 in 100 people.

Get medical help immediately if you develop signs and symptoms of a blood clot, such as:
- **swelling, pain, heat, redness,** or tenderness in **one leg**
- **sudden shortness of breath**, especially together with sharp pain in the chest or rapid breathing
- abdominal (stomach) pain, enlarged abdomen, blood in your stools.

Liver problems
Revolade can cause changes that show up in blood tests, and may be signs of liver damage. Liver problems (increased enzymes showing up in blood tests) are common and may affect up to 1 in 10 people. Other liver problems (bile not flowing properly) are uncommon and may affect up to 1 in 100 people.

If you have either of these signs of liver problems:
- **yellowing** of the skin or the whites of the eyes (jaundice)
- unusually **dark-coloured urine**

➔ **tell your doctor immediately**.

Bleeding or bruising after you stop treatment
Within two weeks of stopping Revolade, your blood platelet count will usually drop back down to what it was before starting Revolade. The lower platelet count may increase the risk of bleeding or bruising. Your doctor will check your platelet count for at least 4 weeks after you stop taking Revolade.

➔ **Tell your doctor** if you have any bleeding or bruising after stopping Revolade.

Some people have **bleeding in the digestive system** after they stop taking peginterferon, ribavirin, and Revolade. Symptoms include:
- black tarry stools (discoloured bowel movements are a uncommon side effect that may affect up to 1 in 100 people)
- blood in your stools
- vomiting blood or something that looks like coffee grounds

➔ **Tell your doctor** immediately if you have any of these symptoms.

Other possible side effects in adults with ITP

Common side effects
These may affect **up to 1 in 10** people:
- feeling sick (nausea)
- diarrhoea
- cloudy lens in the eye (cataract)
- dry eyes
- unusual hair loss or thinning
- skin rash
- itching
- muscle pain, muscle spasm
- back pain
- bone pain
- tingling or numbness of the hands or feet
- heavy menstrual period
- mouth ulcers

Common side effects that may show up in blood tests:
- increase of liver enzymes
- increase in bilirubin (a substance produced by the liver)
- increased levels of some proteins

Uncommon side effects
These may affect **up to 1 in 100** people:
- interruption of blood supply to part of the heart
- sudden shortness of breath, especially when accompanied with sharp pain in the chest and /or rapid breathing, which could be signs of a blood clot in the lungs (see ***'Higher risk of blood clots'*** earlier in section 4)
- the loss of function of part of the lung caused by a blockage in the lung artery
- liver problems, including yellowing of the eyes and skin (see '***Liver problems'*** earlier in section 4)
- heart beating faster, irregular heartbeat, bluish discolouration of the skin
- disturbances of heart rhythm (QT prolongation)
- inflammation of a vein
- localised swelling filled with blood from a break in a blood vessel (haematoma)
- sore throat and discomfort when swallowing, inflammation of the lungs, sinuses, tonsils, nose and throat
- flu (influenza)
- pneumonia
- loss of appetite
- painful swollen joints caused by uric acid (gout)
- problems sleeping, depression, lack of interest, mood changes
- feeling drowsy, problems with balance speech and nerve function, migraine, shaking
- eye problems, including blurred and less clear vision
- ear pain, spinning sensation (vertigo)
- problems with the nose, throat and sinuses, breathing problems when sleeping
- digestive system problems including: being sick (vomiting), wind, frequent bowel movements, stomach pain and tenderness, food poisoning
- cancer of the rectum
- mouth problems, including dry or sore mouth sensitive tongue, bleeding gums
- skin changes including, excessive sweating, itching bumpy rash, red spots, changes in appearance

- sunburn
- redness or swelling around a wound
- bleeding around a catheter (if present) into the skin
- sensation of a foreign body
- muscular weakness
- kidney problems including: inflammation of the kidney, excessive urination at night, kidney failure, urinary tract infection, white cells in urine
- generally feeling unwell, high temperature, feeling hot, chest pain
- cold sweat
- inflammation of the gum tissue
- infection of skin

Uncommon side effects that may show up in blood tests:
- decreased number of red blood cells (anaemia), white blood cells and platelets
- increased number of red blood cells
- changes in the make-up of the blood
- changes in levels of uric acid, calcium and potassium

Other possible side effects in children with ITP

Very common side effects
These may affect **more than 1 in 10** children:
- sore throat, runny nose, nasal congestion and sneezing
- infection in the nose, sinuses, throat and upper airways, common cold (upper respiratory tract infection)
- diarrhoea

Common side effects
These may affect **up to 1 in 10** children:
- difficulty in sleeping (insomnia)
- abdominal pain
- toothache
- cough
- pain in the nose and throat
- itchy, runny or blocked nose
- high temperature

Other possible side effects in people with hepatitis C

Very common side effects
These may affect **more than 1 in 10** people:
- headache
- decreased appetite
- difficulty in sleeping (insomnia)
- cough
- feeling sick (nausea), diarrhoea
- muscle pain, itching, lack of energy, high temperature, unusual hair loss, feeling weak, flu-like illness, swelling in the hands or feet, chills

Very common side effects that may show up in blood tests:
- decreased number of red blood cells (anaemia).

Common side effects
These may affect **up to 1 in 10** people:
- infection of the urinary system
- inflammation of the nasal passages, throat and mouth, flu-like symptoms, dry mouth, sore or inflamed mouth, toothache
- weight loss
- sleep disorders, abnormal drowsiness, confusion, depression, anxiety, agitation
- dizziness, problems with attention and memory,
- tingling or numbness of the hands or feet
- inflammation in the brain
- eye problems, including: cloudy lens in the eye (cataract), dry eye, small yellow deposits in the retina, yellowing of the whites of the eye
- bleeding in or around the retina (in the back of the eye)
- spinning sensation, fast or irregular heartbeat (palpitations), shortness of breath
- cough bringing up phlegm
- digestive system problems, including: being sick (vomiting), stomach pain, indigestion, constipation, swollen stomach, taste disturbances, inflammation of the stomach, piles (haemorrhoids*)*, swollen blood vessels and bleeding in the gullet (oesophagus), irritation of the gut
- liver problems, including blood clot, yellowing of the whites of the eye or skin (jaundice), tumour in the liver (see ***'Liver problems'*** earlier in section 4)
- skin changes, including: rash, dry skin, eczema, redness of the skin, itching, excessive sweating, unusual skin growths
- joint pain, back pain, bone pain, pain in the hands or feet, muscle spasms
- irritability, generally feeling unwell, chest pain and discomfort
- injection site reaction
- disturbances of heart rhythm (QT prolongation)

Common side effects that may show up in blood tests:
- increased blood sugar (glucose)
- reduced number of white blood cells
- reduced blood proteins
- breakdown of red blood cells (haemolytic anaemia)
- increased bilirubin (a substance produced by the liver)
- changes in the enzymes that control blood clotting

Uncommon side effects
These may affect **up to 1 in 100** people:
- pain when passing urine

Side effects with frequency not known
Frequency cannot be estimated from the available data
- skin discolouration

The following side effects have been reported to be associated with treatment with Revolade in patients with severe aplastic anaemia (SAA).

Very common side effects
These may affect more than 1 in 10 people.
- cough
- headache
- shortness of breath (dyspnoea)
- pain in the nose and throat
- runny nose (rhinorrhoea)
- abdominal pain
- diarrhoea
- nausea
- bruising (ecchymosis)
- joint pain (arthralgia)
- muscle spasms
- pain in extremities (arms, legs, hands and feet)
- dizziness
- feeling very tired (fatigue)
- fever
- inability to sleep (insomnia)

Very common side effects that may show up in the blood tests
- increase in some liver enzymes (transaminases)

Laboratory tests may show abnormal changes to the cells in your bone marrow.

Common side effects
These may affect up to 1 in 10 people.
- anxiety
- depression
- feeling cold
- feeling unwell
- eye problems including: blurred and less clear vision, cloudy lens in the eye (cataract), spots or deposits in eye (vitreous floaters), dry eye, itchy eye, yellowing of the whites of the eye or skin
- nose bleed (epistaxis)
- bleeding of the gums
- blisters in the mouth
- digestive system problems including: being sick (vomiting), change in appetite (increased or decreased) stomach pain/discomfort, swollen stomach, passing wind, change in stool colour
- fainting
- skin problems including: Small red or purple spot caused by bleeding into the skin (petechiae) rash, itching, skin lesion
- back pain
- muscle pain
- bone pain
- weakness (asthenia)
- swelling of tissues, usually in the lower limbs, due to the accumulation of fluids
- abnormal colored urine
- interruption in blood supply to spleen (splenic infarction)

Common side effects that may show up in the blood tests
- increase in enzymes due to muscle breakdown (creatine phosphokinase)
- accumulation of iron in the body (iron overload)
- decreased number of white blood cells (neutropenia)
- decrease in sugar level (hypoglycaemia)
- increased bilirubin (a substance produced by the liver)

Side effects with frequency not known
Frequency cannot be estimated from the available data
- skin discolouration

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 Revolade

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 carton and the blister.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Revolade contains

The active substance in Revolade is eltrombopag.

12.5 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 12.5 mg eltrombopag.

25 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

50 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.

75 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag.

The other ingredients are: hypromellose, macrogol 400, magnesium stearate, mannitol (E421), microcrystalline cellulose, povidone, sodium starch glycolate, titanium dioxide (E171).

Revolade 50 mg film-coated tablets also contain iron oxide red (E172) and iron oxide yellow (E172).

Revolade 75 mg film-coated tablets also contain iron oxide red (E172) and iron oxide black (E172).

What Revolade looks like and contents of the pack

Revolade 12.5 mg film-coated tablets are round, biconvex, white, debossed with 'GS MZ1' and '12.5' on one side.

Revolade 25 mg film-coated tablets are round, biconvex, white, debossed with 'GS NX3' and '25' on one side.

Revolade 50 mg film-coated tablets are round, biconvex, brown, debossed with 'GS UFU' and '50' on one side.

Revolade 75 mg film-coated tablets are round, biconvex, pink, debossed with 'GS FFS' and '75' on one side.

They are supplied in aluminum blisters in a carton containing 14 or 28 film-coated tablets and multipacks containg 84 (3 packs of 28) film-coated tablets).

Not all pack sizes may be available in your country.

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This leaflet was last revised in
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu./

Package Leaflet: Information for the patient

Revolade 25 mg powder for oral suspension

eltrombopag

Read all of this leaflet carefully before you start taking 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 pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet:
1. What Revolade is and what it is used for
2. What you need to know before you take Revolade
3. How to take Revolade
4. Possible side effects
5. How to store Revolade
6. Contents of the pack and other information
Instructions for use

1. What Revolade is and what it is used for

Revolade contains eltrombopag, which belongs to a group of medicines called thrombopoietin receptor agonists. It is used to help increase the number of platelets in your blood. Platelets are blood cells that help to reduce or prevent bleeding.

- Revolade is used to treat a bleeding disorder called immune (idiopathic) thrombocytopenic purpura (ITP) in patients aged 1 year and above who have already taken other medicines (corticosteroids or immunoglobulins), which have not worked.

  ITP is caused by a low blood platelet count (thrombocytopenia). People with ITP have an increased risk of bleeding. Symptoms patients with ITP may notice include petechiae (pinpoint-sized flat round red spots under the skin), bruising, nosebleeds, bleeding gums and not being able to control bleeding if they are cut or injured.

- Revolade can also be used to treat low platelet count (thrombocytopenia) in adults with hepatitis C virus (HCV) infections, if they have had problems with side effects while on interferon treatment. Many people with hepatitis C have low platelet counts, not only as a result of the disease, but also due to some of the antiviral medicines that are used to treat it. Taking Revolade may make it easier for you to complete a full course of antiviral medicine (peginterferon and ribavirin).

- Revolade may also be used to treat adult patients with low blood counts caused by severe aplastic anaemia (SAA).

2. What you need to know before you take Revolade

Do not take Revolade

- if you are **allergic** to eltrombopag or any of the other ingredients of this medicine (listed in section 6 under ***'What Revolade contains'***).
  - ➔ **Check with your doctor** if you think this applies to you.

Warnings and precautions

Talk to your doctor before taking Revolade:

- if you have **liver problems**. People who have low platelet counts as well as advanced chronic (long-term) liver disease are more at risk of side effects, including life-threatening liver damage and blood clots. If your doctor considers that the benefits of taking Revolade outweigh the risks, you will be closely monitored during treatment.
- if you are at risk of **blood clots** in your veins or arteries, or you know that blood clots are common in your family.
  You may be at **higher risk of blood clots**:
  - as you get older
  - if you have had to stay in bed for a long time
  - if you have cancer
  - if you are taking the contraceptive birth control pill or hormone replacement therapy
  - if you have recently had surgery or received a physical injury
  - if you are very overweight (obese)
  - if you are a smoker
  - if you have advanced chronic liver disease
  - ➔ If any of these apply to you **tell your doctor** before starting treatment. You should not take Revolade unless your doctor considers that the expected benefits outweigh the risk of blood clots.
- if you have **cataracts** (the lens of the eye getting cloudy)
- if you have another **blood condition**, such as myelodysplastic syndrome (MDS). Your doctor will carry out tests to check that you do not have this blood condition before you start Revolade. If you have MDS and take Revolade, your MDS may get worse.
  - ➔ Tell your doctor if any of these apply to you.

Eye examinations

Your doctor will recommend that you are checked for cataracts. If you do not have routine eye-tests, your doctor should arrange regular testing. You may also be checked for the occurrence of any bleeding in or around your retina (the light-sensitive layer of cells at the back of the eye).

You will need regular tests

Before you start taking Revolade, your doctor will carry out blood tests to check your blood cells, including platelets. These tests will be repeated at intervals while you are taking it.

Blood tests for liver function

Revolade can cause blood test results that may be signs of liver damage - an increase of some liver enzymes, especially bilirubin and alanine / aspartate transaminases. If you are taking interferon-based treatments together with Revolade to treat low platelet count due to hepatitis C, some liver problems can get worse.

You will have blood tests to check your liver function before you start taking Revolade and at intervals while you are taking it. You may need to stop taking Revolade if the amount of these substances increases too much, or if you get other signs of liver damage.

➔ **Read the information '*Liver problems*' in section 4 of this leaflet.**

Blood tests for platelet count
If you stop taking Revolade, your blood platelet count is likely to become low again within several days. The platelet count will be monitored, and your doctor will discuss appropriate precautions with you.

A very high blood platelet count may increase the risk of blood clotting. However blood clots can also form with normal or even low platelet counts. Your doctor will adjust your dose of Revolade to ensure that your platelet count does not become too high.

⚠ **Get medical help immediately** if you have any of these signs of a **blood clot**:
- **swelling, pain** or tenderness in **one leg**
- **sudden shortness of breath** especially together with sharp pain in the chest or rapid breathing
- abdominal (stomach) pain, enlarged abdomen, blood in your stools

Tests to check your bone marrow
In people who have problems with their bone marrow, medicines like Revolade could make the problems worse. Signs of bone marrow changes may show up as abnormal results in your blood tests. Your doctor may also carry out tests to directly check your bone marrow during treatment with Revolade.

Checks for digestive bleeding
If you are taking interferon-based treatments together with Revolade you will be monitored for any signs of bleeding in your stomach or intestine after you stop taking Revolade.

Heart monitoring
Your doctor may consider it necessary to monitor your heart during treatment with Revolade and carry out an electrocardiogram (ECG) test.

Children and adolescents
Revolade is not recommended for children aged under 1 year who have ITP. It is also not recommended for people under 18 years with low platelet counts due to hepatitis C or severe aplastic anaemia.

Other medicines and Revolade
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some everyday medicines interact with Revolade – including prescription and non-prescription medicines and minerals. These include:
- antacid medicines to treat **indigestion, heartburn** or **stomach ulcers** (see also ***'When to take it'*** in section 3)
- medicines called statins, to **lower cholesterol**
- some medicines to treat **HIV infection**, such as lopinavir and/or ritonavir
- ciclosporin used in the context of **transplantations** or **immune diseases**
- minerals such as iron, calcium, magnesium, aluminium, selenium and zinc which may be found in **vitamin and mineral supplements** (see also ***'When to take it'*** in section 3)
- medicines such as methotrexate and topotecan, to treat **cancer**

➔ **Talk to your doctor** if you take any of these. Some of them are not to be taken with Revolade, or the dose may need adjusting, or you may need to alter the timing of when you take them. Your doctor will review the medicines you are taking, and suggest suitable replacements if necessary.

If you are also taking medicines to prevent blood clots, there is a greater risk of bleeding. Your doctor will discuss this with you.

If you are taking **corticosteroids, danazol,** and/or **azathioprine** you may need to take a lower dose or to stop taking them while you are taking Revolade.

Revolade with food and drink
Do not take Revolade with dairy foods or drinks as the calcium in dairy products affects the absorption of the medicine. For more information, see ***'When to take it'*** in section 3.

Pregnancy and breast-feeding
Don't use Revolade if you are pregnant unless your doctor specifically recommends it. The effect of Revolade during pregnancy is not known.

- **Tell your doctor if you are pregnant,** think you may be pregnant, or are planning to have a baby.
- **Use a reliable method of contraception** while you're taking Revolade, to prevent pregnancy
- **If you do become pregnant during treatment** with Revolade, tell your doctor.

Don't breast-feed while you are taking Revolade. It is not known whether Revolade passes into breast-milk.

➔ **If you are breast-feeding** or planning to breast-feed, tell your doctor.

Driving and using machines
Revolade can make you dizzy and have other side effects that make you less alert.

➔ **Don't drive or use machines** unless you are sure you're not affected.

3. How to take Revolade

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Do not change the dose or schedule for taking Revolade unless your doctor or pharmacist advises you to. While you are taking Revolade, you will be under the care of a doctor with specialist experience in treating your condition.

How much to take
For ITP
Adults and **children** (6 to 17 years) **-** the usual starting dose for ITP is **two 25 mg sachets** of Revolade a day. If you are of East Asian origin (Chinese, Japanese, Taiwanese, Thai or Korean) you may need to start at a **lower dose of 25 mg.**

Children (1 to 5 years) — the usual starting dose for ITP is **one 25 mg sachet** of Revolade a day.

For hepatitis C
Adults - the usual starting dose for hepatitis C is **one 25 mg sachet** of Revolade a day. If you are of East Asian origin (Chinese, Japanese, Taiwanese, Thai or Korean) you will start on the **same 25 mg dose.**

For SAA
Adults - the usual starting dose for SAA is **two 25 mg sachets** of Revolade a day. If you are of East Asian origin (Chinese, Japanese, Taiwanese, Thai or Korean) you may need to start at a **lower dose of 25 mg.**

Revolade may take 1 to 2 weeks to work. Based on your response to Revolade your doctor may recommend that your daily dose is changed.

How to give a dose of medicine
The powder for oral suspension is in sachets, the contents of which will need to mixed before you can take the medicine. After section 6 of this leaflet there are **Instructions For Use** on how to mix and administer the medicine. If you have questions or do not understand the Instructions For Use, talk to your doctor, nurse or pharmacist.

IMPORTANT — Use the medicine immediately after you have mixed the powder with water. If you do not use it **within 30 minutes** of mixing it, you will need to mix a new dose.

When to take it

Make sure –
- in the **4 hours before** you take Revolade
- and the **2 hours after** you take Revolade

you don't consume any of the following:
- **dairy foods** such as cheese, butter, yoghurt or ice cream
- **milk or milk shakes,** drinks containing milk, yoghurt or cream
- **antacids,** a type of medicine for **indigestion and heartburn**
- some **mineral and vitamin supplements** including iron, calcium, magnesium, aluminium, selenium and zinc

If you do, the medicine will not be properly absorbed into your body.

For more advice about suitable foods and drinks, talk to your doctor.

If you take more Revolade than you should
Contact a doctor or pharmacist immediately. If possible show them the pack, or this leaflet. You will be monitored for any signs or symptoms of side effects and given appropriate treatment immediately.

If you forget to take Revolade
Take your next dose at the usual time. Do not take more than one dose of Revolade in one day.

If you stop taking Revolade
Don't stop taking Revolade without talking to your doctor. If your doctor advises you to stop treatment, your platelet count will then be checked each week for four weeks. See also ***'Bleeding or bruising after you stop treatment'*** in section 4.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Symptoms needing attention: see a doctor
People taking Revolade for either ITP or low blood platelet counts due to hepatitis C could develop signs of potentially serious side effects. **It is important to tell a doctor if you develop these symptoms**.

Higher risk of blood clots
Certain people may have a higher risk of blood clots, and medicines like Revolade could make this problem worse. The sudden blocking of a blood vessel by a blood clot is an uncommon side effect and may affect up to 1 in 100 people.

Get medical help immediately if you develop signs and symptoms of a blood clot, such as:
- **swelling, pain, heat, redness** or tenderness in **one leg**
- **sudden shortness of breath**, especially together with sharp pain in the chest or rapid breathing
- abdominal (stomach) pain, enlarged abdomen, blood in your stools.

Liver problems
Revolade can cause changes that show up in blood tests, and may be signs of liver damage. Liver problems (increased enzymes showing up in blood tests) are common and may affect up to 1 in 10 people. Other liver problems (bile not flowing properly) are uncommon and may affect up to 1 in 100 people.

If you have either of these signs of liver problems:
- **yellowing** of the skin or the whites of the eyes (jaundice)
- unusually **dark-coloured urine**

➔ **tell your doctor immediately**.

Bleeding or bruising after you stop treatment
Within two weeks of stopping Revolade, your blood platelet count will usually drop back down to what it was before starting Revolade. The lower platelet count may increase the risk of bleeding or bruising. Your doctor will check your platelet count for at least 4 weeks after you stop taking Revolade.

➔ **Tell your doctor** if you have any bleeding or bruising after stopping Revolade.

Some people have **bleeding in the digestive system** after they stop taking peginterferon, ribavirin, and Revolade. Symptoms include:
- black tarry stools (discoloured bowel movements are a uncommon side effect that may affect up to 1 in 100 people)
- blood in your stools
- vomiting blood or something that looks like coffee grounds

➔ **Tell your doctor** immediately if you have any of these symptoms.

Other possible side effects in adults with ITP

Common side effects
These may affect **up to 1 in 10** people:
- feeling sick (nausea)
- diarrhoea
- cloudy lens in the eye (cataract)
- dry eyes
- unusual hair loss or thinning
- skin rash
- itching
- muscle pain, muscle spasm
- back pain
- bone pain
- tingling or numbness of the hands or feet
- heavy menstrual period
- mouth ulcers

Common side effects that may show up in blood tests:
- increase of liver enzymes
- increase in bilirubin (a substance produced by the liver)
- increased levels of some proteins

Uncommon side effects
These may affect **up to 1 in 100** people:
- interruption of blood supply to part of the heart
- sudden shortness of breath, especially when accompanied with sharp pain in the chest and /or rapid breathing, which could be signs of a blood clot in the lungs (see ***'Higher risk of blood clots'*** earlier in section 4)
- the loss of function of part of the lung caused by a blockage in the lung artery
- liver problems, including yellowing of the eyes and skin (see ***'Liver problems'*** earlier in section 4)
- heart beating faster, irregular heartbeat, bluish discolouration of the skin
- disturbances of heart rhythm (QT prolongation)
- inflammation of a vein
- localised swelling filled with blood from a break in a blood vessel (haematoma)
- sore throat and discomfort when swallowing, inflammation of the lungs, sinuses, tonsils, nose and throat
- flu (influenza)
- pneumonia
- loss of appetite
- painful swollen joints caused by uric acid (gout)
- problems sleeping, depression, lack of interest, mood changes
- feeling drowsy, problems with balance speech and nerve function, migraine, shaking
- eye problems, including blurred and less clear vision
- ear pain, spinning sensation (vertigo)
- problems with the nose, throat and sinuses, breathing problems when sleeping
- digestive system problems including: being sick (vomiting), wind, frequent bowel movements, stomach pain and tenderness, food poisoning
- cancer of the rectum
- mouth problems, including dry or sore mouth sensitive tongue, bleeding gums

- skin changes including, excessive sweating, itching bumpy rash, red spots, changes in appearance
- sunburn
- redness or swelling around a wound
- bleeding around a catheter (if present) into the skin
- sensation of a foreign body
- muscular weakness
- kidney problems including: inflammation of the kidney, excessive urination at night, kidney failure, urinary tract infection, white cells in urine
- generally feeling unwell, high temperature, feeling hot, chest pain
- cold sweat
- inflammation of the gum tissue
- infection of skin

Uncommon side effects that may show up in blood tests:
- decreased number of red blood cells (anaemia), white blood cells and platelets
- increased number of red blood cells
- changes in the make-up of the blood
- changes in levels of uric acid, calcium and potassium

Other possible side effects in children with ITP

Very common side effects
These may affect **more than 1 in 10** children:
- sore throat, runny nose, nasal congestion and sneezing
- infection in the nose, sinuses, throat and upper airways, common cold (upper respiratory tract infection)
- diarrhoea

Common side effects
These may affect **up to 1 in 10** children:
- difficulty in sleeping (insomnia)
- abdominal pain
- toothache
- cough
- pain in the nose and throat
- itchy, runny or blocked nose
- high temperature

Other possible side effects in people with hepatitis C

Very common side effects
These may affect **more than 1 in 10** people:
- headache
- decreased appetite
- difficulty in sleeping (insomnia)
- cough
- feeling sick (nausea), diarrhoea
- muscle pain, itching, lack of energy, high temperature, unusual hair loss, feeling weak, flu-like illness, swelling in the hands or feet, chills

Very common side effects that may show up in blood tests:
- decreased number of red blood cells (anaemia).

Common side effects
These may affect **up to 1 in 10** people:
- infection of the urinary system
- inflammation of the nasal passages, throat and mouth, flu-like symptoms, dry mouth, sore or inflamed mouth, toothache
- weight loss
- sleep disorders, abnormal drowsiness, confusion, depression, anxiety, agitation
- dizziness, problems with attention and memory,
- tingling or numbness of the hands or feet
- inflammation in the brain
- eye problems, including: cloudy lens in the eye (cataract), dry eye, small yellow deposits in the retina, yellowing of the whites of the eye
- bleeding in or around the retina (the back of the eye)
- spinning sensation, fast or irregular heartbeat (palpitations), shortness of breath
- cough bringing up phlegm
- digestive system problems, including: being sick (vomiting), stomach pain, indigestion, constipation, swollen stomach, taste disturbances, inflammation of the stomach, piles (haemorrhoids), swollen blood vessels and bleeding in the gullet (oesophagus), irritation of the gut
- liver problems, including blood clot, yellowing of the whites of the eye or skin (jaundice), tumour in the liver (see **'*Liver problems*'** earlier in section 4)
- skin changes, including: rash, dry skin, eczema, redness of the skin, itching, excessive sweating, unusual skin growths
- joint pain, back pain, bone pain, pain in the hands or feet, muscle spasms
- irritability, generally feeling unwell, chest pain and discomfort
- injection site reaction
- disturbances of heart rhythm (QT prolongation)

Common side effects that may show up in blood tests:
- increased blood sugar (glucose)
- reduced number of white blood cells
- reduced blood proteins
- breakdown of red blood cells (haemolytic anaemia)
- increased bilirubin (a substance produced by the liver)
- changes in the enzymes that control blood clotting

Uncommon side effects
These may affect **up to 1 in 100** people:
- pain when passing urine

Side effects with frequency not known
Frequency cannot be estimated from the available data
- skin discolouration

The following side effects have been reported to be associated with treatment with Revolade in patients with severe aplastic anaemia (SAA).

Very common side effects
These may affect more than 1 in 10 people.
- cough
- headache
- shortness of breath (dyspnoea)
- pain in the nose and throat
- runny nose (rhinorrhoea)
- abdominal pain
- diarrhoea
- nausea
- bruising (ecchymosis)
- joint pain (arthralgia)
- muscle spasms
- pain in extremities (arms, legs, hands and feet)
- dizziness
- feeling very tired (fatigue)
- fever
- inability to sleep (insomnia)

Very common side effects that may show up in the blood tests
- increase in some liver enzymes (transaminases)

Laboratory tests may show abnormal changes to the cells in your bone marrow.

Common side effects
These may affect up to 1 in 10 people.
- anxiety
- depression
- feeling cold
- feeling unwell
- eye problems including: blurred and less clear vision, cloudy lens in the eye (cataract), spots or deposits in eye (vitreous floaters), dry eye, itchy eye, yellowing of the whites of the eye or skin
- nose bleed (epistaxis)
- bleeding of the gums
- blisters in the mouth
- digestive system problems including: being sick (vomiting), change in appetite (increased or decreased) stomach pain/discomfort, swollen stomach, passing wind, change in stool colour
- fainting
- skin problems including: Small red or purple spot caused by bleeding into the skin (petechiae) rash, itching, skin lesion
- back pain
- muscle pain
- bone pain
- weakness (asthenia)
- swelling of tissues, usually in the lower limbs, due to the accumulation of fluids
- abnormal colored urine
- interruption in blood supply to spleen (splenic infarction)

Common side effects that may show up in the blood tests

- increase in enzymes due to muscle breakdown (creatine phosphokinase)
- accumulation of iron in the body (iron overload)
- decreased number of white blood cells (neutropenia)
- decrease in sugar level (hypoglycaemia)
- increased bilirubin (a substance produced by the liver)

Side effects with frequency not known

Frequency cannot be estimated from the available data

- skin discolouration

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 Revolade

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 carton and the sachet.

This medicine does not require any special storage conditions.

Do not open the foil sachets until ready for use. After mixing, Revolade oral suspension should be administered immediately, but may be stored for no more than 30 minutes at room temperature.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Revolade contains

25 mg powder for oral suspension

The active substance in Revolade is eltrombopag. Each sachet contains a powder for reconstitution that delivers 32 mg eltrombopag olamine, equivalent to 25 mg of eltrombopag free acid.

The other ingredients are: mannitol, sucralose and xanthan gum.

What Revolade looks like and contents of the pack

Revolade 25 mg powder for oral suspension is available in kits containing 30 sachets; each sachet contains a reddish-brown to yellow powder. Each pack contains 30 sachets, one 40 ml reusable mixing bottle with lid and cap, and one reusable oral dosing syringe.

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This leaflet was last revised in.
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu./

INSTRUCTIONS FOR USE

Revolade 25 mg powder for oral suspension

(eltrombopag)

Read and follow these instructions to prepare a dose of Revolade and give it to the child. If you have any questions, or if you damage or lose any of the supplies in your kit, ask your doctor, nurse or pharmacist for advice

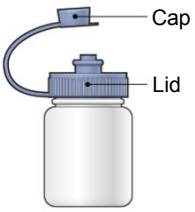
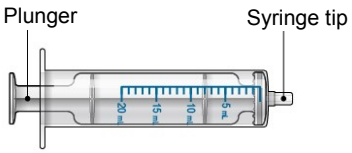
Before you start
Read these messages first

- Revolade powder must be mixed only with **water** at room temperature.

Give the medicine to the child immediately after you have mixed the powder with water. If you don't use the medicine **within 30 minutes** of mixing it, you will need to mix a new dose.
Dispose of the unused mixture in your household waste; **don't pour it down the drain**.

- Try not to let the medicine touch your skin. If this happens, wash the area immediately with soap and water. If you get a skin reaction, or if you have any questions, contact the doctor.
- If you spill any powder or liquid, clean it up with a damp cloth (see step 14 of the instructions).
- **Take care that** the child does not play with the bottle, cap, lid or syringe — there is a risk of choking if the child puts them in their mouth.

What you need
Each Revolade powder for oral suspension kit contains:

30 sachets of powder	
1 reusable mixing bottle with lid and cap (*note — the mixing bottle may become stained*)	
1 reusable oral dosing syringe	

To prepare and give a dose of Revolade, you need:

- The correct number of sachets your doctor has prescribed (supplied in the kit)
- 1 reusable mixing bottle with lid and cap (supplied in the kit)
- 1 reusable oral dosing syringe (supplied in the kit)
- 1 clean glass or cup filled with drinking water (not supplied)
- scissors to cut sachet (not supplied)

Make sure that the bottle, cap, lid and syringe are dry before you use them.

To prepare the dose

1. Make sure the lid is not on the mixing bottle.

2. Fill the syringe with 20 ml drinking water from the glass or cup.

- Start with the plunger pushed all the way into the syringe.
- Put the tip of the syringe all the way into the water
- Pull back on the plunger to the 20 ml mark on the syringe.

3. Empty water into open mixing bottle

- Slowly pushing the plunger all the way into the oral syringe.

4. Take only the prescribed number of sachets for one dose out of the kit.

- **25 mg dose — 1 sachet**
- **50 mg dose — 2 sachets**
- **75 mg dose — 3 sachets**

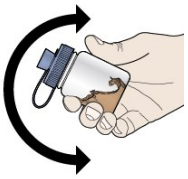
5. Add the powder from the prescribed number of sachets to the bottle.

- Tap the top of each sachet to make sure the contents fall to the bottom
- Cut off the top of each sachet with scissors
- Empty all contents of each sahet into the mixing bottle
- Make sure not to spill the powder outside the mixing bottle.

6. Screw the lid onto the mixing bottle. Make sure the cap is firmly pushed onto the lid, so it is closed.

7. Gently and slowly shake the mixing bottle backwards and forwards for **at least 20 seconds** to mix the water with the powder.

- **Don't shake** the bottle **hard** — that could make the medicine foam.



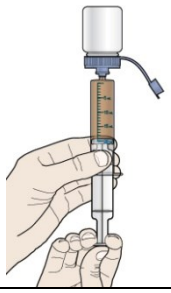
To give a dose to a child

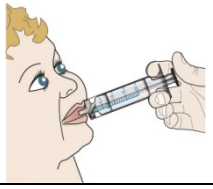
8. Make sure the plunger is pushed all the way into the syringe.

- **Pull cap off** the lid of the mixing bottle
- **Insert the syringe tip** into the hole in the bottle lid.

9. Fill the syringe with the medicine.

- Turn the mixing bottle upside-down together with the syringe.
- Pull back the plunger until all the medicine is in the syringe.
- The medicine is a dark brown liquid.
- Remove the syringe from the bottle.



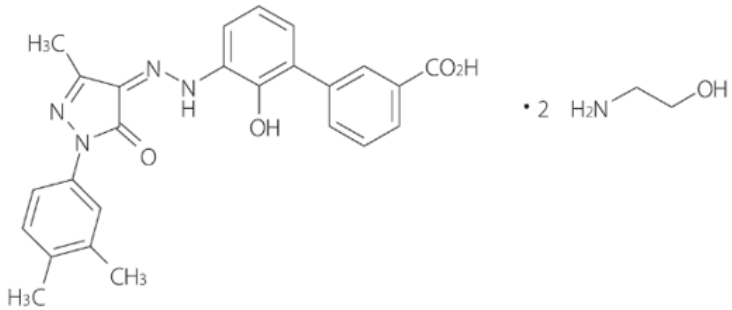
10. Give the medicine to the child. Do this straight away when you have mixed the dose. • Place the tip of the syringe into the inside of the child's cheek. • **Slowly push the plunger all the way down** so the medicine goes into the child's mouth. Make sure the child has time to swallow.	
IMPORTANT: You have now given the child nearly all of their dose of medicine. But there will still be some left in the bottle, even though you may not be able to see it. Now **you need to complete steps 11 to 13** to make sure the child receives all of the medicine.	
11. Again **fill the syringe,** this time with 10 ml of drinking water. • Start with the plunger pushed all the way down into the syringe. • Put the tip of the syringe all the way into the water • Pull back on the plunger to the 10 ml mark on the syringe.	
12. Empty the water into the mixing bottle. • Insert the tip of the syringe into the hole in the lid of the mixing bottle. • Slowly push the plunger all the way into the syringe. • Push the cap firmly back on to the lid of the mixing bottle.	
13. Repeat steps 7 to 10 – gently shake the bottle to mix the rest of the medicine, then give all the rest of the liquid to the child.	
To clean up	
14. If you have spilt any powder or mixed medicine, **clean it up with a damp disposable cloth**. You may choose to wear disposable gloves so your skin doesn't get stained. • Dispose of the cloth and gloves used to clean up the spillage in your household waste.	
15. Clean the mixing equipment. • **Remove the plunger** from the syringe. • **Rinse** the mixing bottle, lid, the syringe, and plunger under running water. (The mixing bottle may become stained from the medicine. This is normal.) • Let all the equipment **dry** in the air. • **Wash your hands** with soap and water.	
After you have used all 30 sachets in the kit, **dispose of the bottle and syringe.** Always start with a complete new kit for each 30 sachets.	

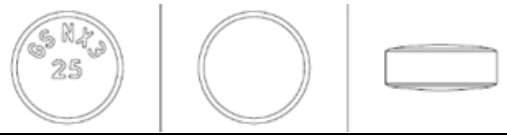
Keep Revolade powder for oral suspension, including the dosing kit, and all medicines out of the reach of children.

1.7 同種同効品一覧表

最新の添付文書を参照する

1 エルトロンボパグ　オラミン / ロミプロスチム

販売名	レボレード錠 12.5 mg，25 mg	ロミプレート皮下注 250 μg 調製用
一般名	エルトロンボパグ　オラミン（Eltrombopag Olamine）	ロミプロスチム（遺伝子組換え）
会社名	ノバルティスファーマ株式会社	協和発酵キリン株式会社
販売開始	2010 年 12 月	2011 年 4 月
再評価年月日 再審査年月日	－	－
規 制 区 分	劇薬、処方箋医薬品	処方箋医薬品
有効成分に関する理化学的知見	構造式：  一般名：エルトロンボパグ　オラミン Eltrombopag Olamine 化学名：3'-｛（2Z）-2-［1-（3,4-Dimethylphenyl）-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene］hydrazino｝-2'-hydroxybiphenyl-3-carboxylic acid bi（s 2-aminoethanol） 分子式：$C_{25}H_{22}N_4O_4$・2（C_2H_7NO） 分子量：564.63	一般名：ロミプロスチム（遺伝子組換え） Romiplostim（Genetical Recombination） 分子量：59,085
剤型・含量	レボレード錠 12.5 mg	ロミプレート皮下注 250 μg 調製用 成分・含量　1 バイアル中ロミプロスチム（遺伝子組換え）　375 μg 注)

<table>
<tr><td>販売名</td><td>レボレード錠 12.5 mg，25 mg</td><td>ロミプレート皮下注 250 µg 調製用</td></tr>
<tr><td></td><td>
<table>
<tr><td>成分・含量</td><td>1 錠中エルトロンボパグオラミン 15.9 mg（エルトロンボパグとして 12.5 mg）を含有</td></tr>
<tr><td>添加物</td><td>結晶セルロース、D-マンニトール、デンプングリコール酸ナトリウム、ステアリン酸マグネシウム、ポビドン、ヒプロメロース、酸化チタン、マクロゴール 400、ポリソルベート 80</td></tr>
<tr><td>性状</td><td>白色円形のフィルムコーティング錠</td></tr>
<tr><td>外形</td><td> </td></tr>
<tr><td>識別コード</td><td>GSMZ1 12.5</td></tr>
<tr><td>大きさ（約）</td><td>直径：7.9mm　厚さ：3.5mm　質量：184mg</td></tr>
</table>
レボレード錠 25 mg
<table>
<tr><td>成分・含量</td><td>1 錠中エルトロンボパグオラミン 31.9 mg（エルトロンボパグとして 25 mg）を含有</td></tr>
<tr><td>添加物</td><td>結晶セルロース、D-マンニトール、デンプングリコール酸ナトリウム、ステアリン酸マグネシウム、ポビドン、ヒプロメロース、酸化チタン、マクロゴール 400、ポリソルベート 80</td></tr>
<tr><td>性状</td><td>白色円形のフィルムコーティング錠</td></tr>
<tr><td>外形</td><td>  </td></tr>
<tr><td>識別コード</td><td>GSNX3 25</td></tr>
<tr><td>大きさ（約）</td><td>直径：10.3mm　厚さ：4.2mm　質量：364mg</td></tr>
</table>
</td><td>
<table>
<tr><td></td><td>ただし、本剤の調製方法に基づき、1 バイアルあたり 0.72 mL の注射用水に溶解した溶液 0.5 mL 中に含まれるロミプロスチム（遺伝子組換え）は 250 µg である。</td></tr>
<tr><td>色・性状</td><td>白色の塊（凍結乾燥製剤）</td></tr>
<tr><td>添加物</td><td>D-マンニトール、精製白糖、L-ヒスチジン、ポリソルベート 20、希塩酸</td></tr>
<tr><td>pH</td><td>5.0</td></tr>
<tr><td>浸透圧</td><td>約 1（500 µg/mL）</td></tr>
</table>
注）本剤は、注射器への吸引時及び投与時の損失を考慮し、1 バイアルから 250 µg を注射可能な量を確保するために過量充填されている。
</td></tr>
<tr><td>効能・効果</td><td>1．慢性特発性血小板減少性紫斑病</td><td>慢性特発性血小板減少性紫斑病</td></tr>
</table>

<table>
<tr><td>販売名</td><td>レボレード錠 12.5 mg，25 mg</td><td>ロミプレート皮下注 250 μg 調製用</td></tr>
<tr><td></td><td>2. 再生不良性貧血
〈効能・効果に関連する使用上の注意〉
1. 慢性特発性血小板減少性紫斑病の場合
(1) 他の治療にて十分な効果が得られない場合、又は忍容性に問題があると考えられる場合に使用すること。
(2) 血小板数、臨床症状からみて出血リスクが高いと考えられる場合に使用すること。
2. 再生不良性貧血の場合
診療ガイドライン等の最新の情報を参考に、本剤の投与が適切と判断される患者に投与すること。（【臨床成績】の項参照）</td><td>〈効能・効果に関連する使用上の注意〉
1. 他の治療にて十分な効果が得られない場合、又は忍容性に問題があると考えられる場合に使用すること。
2. 血小板数、臨床症状からみて出血リスクが高いと考えられる場合に使用すること。</td></tr>
<tr><td>用法・用量</td><td>1. 慢性特発性血小板減少性紫斑病の場合
通常、成人には、エルトロンボパグとして初回投与量 12.5 mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、血小板数、症状に応じて適宜増減する。また、1 日最大投与量は 50mg とする。
2. 再生不良性貧血の場合
抗胸腺細胞免疫グロブリンで未治療の場合
抗胸腺細胞免疫グロブリンとの併用において、通常、成人には、エルトロンボパグとして 75mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、血小板数患者の状態に応じて適宜減量する。
既存治療で効果不十分な場合
通常、成人には、エルトロンボパグとして初回投与量 25mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、血小板数患者の状態に応じて適宜増減する。また、1 日最大投与量は 100mg とする。
〈用法及び用量に関連する使用上の注意〉
1. 本剤は食事とともに服用すると血中濃度が低下することがあるので、食事の前後 2 時間を避けて空腹時に服用すること。（【薬物動態】の項参照）
2. 制酸剤、乳製品、多価陽イオン（鉄、カルシウム、アルミニウム、マグネシウム、セレン、亜鉛等）含有製剤等とともに服用</td><td>通常、成人には、ロミプロスチム（遺伝子組換え）として初回投与量 1 μg/kg を皮下投与する。投与開始後は血小板数、症状に応じて投与量を適宜増減し、週 1 回皮下投与する。
また、最高投与量は週 1 回 10 μg/kg とする。
〈用法及び用量に関連する使用上の注意〉
(1) 本剤は下表を参照の上、治療上必要最小限の用量で使用すること。
<table><tr><th>血小板数</th><th>調節方法</th></tr><tr><td>50,000/μL 未満</td><td>1 μg/kg 増量する。</td></tr><tr><td>50,000/μL ～ 200,000/μL</td><td>出血のリスクを低下できる治療上必要最小限の用量となるよう、適宜減量も考慮する。</td></tr><tr><td>200,000/μL ～ 400,000/μL</td><td>1 μg/kg 減量する。</td></tr><tr><td>400,000/μL 超</td><td>休薬する。休薬後、血小板数が 200,000/μL まで減少した場合には原則として休薬前の投与量より 1 μg/kg 減量し、投与を再開する。</td></tr></table>(1) 本剤投与中は、血小板数が安定するまで（少なくとも 4 週間にわたり用量調整せずに血小板数が 50,000/μL 以上）、血小板数を毎週測定すること。血小板数が安定した場合でも 4 週に 1 回を目安に血小板数を測定すること。
(2) 本剤は出血のリスクが高い場合に使用し、血小板数を正常化する目的で使用しないこと。</td></tr>
</table>

販売名	レボレード錠 12.5 mg，25 mg	ロミプレート皮下注 250 μg 調製用
	すると本剤の血中濃度が低下するので、本剤服用の前4時間及び後 2 時間はこれらの摂取を避けること。（「3. 相互作用」及び【薬物動態】の項参照） 3. 慢性特発性血小板減少性紫斑病の場合 (1) 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記 1）～7）を参照の上、調節すること。本剤の投与開始時及び用量調節時には血小板数及び末梢血塗抹標本検査を含む全血球計算を、血小板数が安定する（血小板数 50,000/μL 以上が少なくとも 4 週間）までは毎週、安定した後は毎月検査することが望ましい。 1) 本剤は治療上必要最小限の用量で使用すること。 2) 本剤の効果は、通常 1～2 週間であらわれるので、効果の確認のためには少なくとも 2 週間は同一用量を維持すること。ただし、肝障害のある患者では、血小板数が定常状態に達するまでの期間が長くなるため、効果の確認のためには少なくとも 3 週間は同一用量を維持すること。 3) 血小板数 50,000/μL を目安とし、血小板数がそれを下回る場合には増量を考慮すること。 4) 血小板数が 50,000/μL～200,000/μL の場合には、出血のリスクを低下できる治療上必要最小限の用量となるよう、適宜減量も考慮すること。 5) 血小板数が 200,000/μL～400,000/μL の場合には本剤を減量すること。 6) 血小板数が 400,000/μL を超えた場合には本剤を休薬すること。この場合血小板数の測定は週に 2 回実施することが望ましい。休薬後、血小板数が 150,000/μL まで減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で投与を再開すること。 7) 本剤の投与量を調節する場合には、通常、12.5 mg/日ずつとする。 (2) 本剤を 1 日 50 mg、4 週間投与しても血小板数が増加せず、臨床的に問題となる出血傾向の改善が認められない場合には、本剤の投与中止を考慮すること。 4. 再生不良性貧血の場合	(3) 最高投与量として週 1 回 10 μg/kg を 4 週間連続投与しても、臨床上重大な出血リスクを回避できるレベルに血小板数が増加しなかった場合は、本剤の投与を中止するなど、適切な処置を行うこと。 (4) 1 バイアルあたり 0.72 mL の注射用水を加え溶解すると、濃度が 500 μg/mL となり、溶液 0.5 mL がロミプロスチムの投与量 250 μg に相当する。本剤は投与液量が少ないため、0.01 mL 目盛り注射器等を用いて投与すること（「適用上の注意」の項参照）。

販売名	レボレード錠 12.5 mg，25 mg	ロミプレート皮下注 250 μg 調製用
	(1) 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記を参照の上、調節すること。本剤の投与量を調節する場合には、通常、25mg/日ずつとする。用量調節時には少なくとも 2 週間は同一用量を維持すること。 抗胸腺細胞免疫グロブリンで未治療の患者に投与する場合 1) 抗胸腺細胞免疫グロブリンの投与により肝機能障害があらわれることがあるので、抗胸腺細胞免疫グロブリン投与後、一定期間経過後に本剤の投与を開始すること。（【臨床成績】の項参照） 2) 抗胸腺細胞免疫グロブリンの投与に際しては、併用薬剤の添付文書を熟読すること。 3) 血小板数が 200,000/μL を超えた場合には本剤の減量を考慮すること。 4) 血小板数が 400,000/μL を超えた場合には本剤を休薬すること。休薬後、血小板数が 200,000/μL 未満に減少した場合には、休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。 5) 本剤を 26 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。 既存治療が効果不十分な患者に投与する場合 1) 血小板数 50,000/μL を目安とし、血小板数がそれを下回る場合には増量を考慮すること。 2) 血小板数が 100,000/μL～200,000/μL の場合には減量を考慮すること。 3) 血小板数が 200,000/μL を超えた場合には少なくとも 1 週間は本剤を休薬すること。休薬後、血小板数が 50,000/μL 未満に減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。 4) 本剤を 16 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。 (2) 3 血球系統の改善（目安として、輸血非依存下で血小板数 50,000/μL を超える、ヘモグロビン値 10 g/dL を超える、好中球数 1,000/μL を超える）が 8 週間以上持続した場合には本剤の投与量を最大で半量まで減量すること。減量後の投与量で血球改善が	

販売名	レボレード錠 12.5 mg，25 mg	ロミプレート皮下注 250 μg 調製用
	更に 8 週間以上持続した場合には、本剤を休薬し、血球数を観察すること。休薬後に血小板数 30,000/μL 未満、ヘモグロビン値 9 g/dL 未満、好中球数 500/μL 未満に低下した場合には休薬前の投与量で投与を再開してもよい。	
使用上の注意	**禁忌（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	**禁忌（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
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) 肝障害のある患者〔肝障害が悪化するおそれがある。また、血中濃度-時間曲線下面積（AUC）が増加する可能性がある。（【薬物動態】の項参照）〕 (2) 腎障害のある患者〔腎障害患者での有効性及び安全性は確立していないため、これらの患者では血小板数の推移に加えて安全性についても慎重に観察すること。（【薬物動態】の項参照）〕 (3) アンチトロンビン III 欠損、抗リン脂質抗体症候群等の血栓塞栓症の素因のある患者〔血栓塞栓症があらわれるおそれがある。〕	**1.慎重投与（次の患者には慎重に投与すること）** (1) 脳梗塞、心筋梗塞、肺塞栓等の患者又はそれらの既往歴を有する患者［血栓症又は血栓塞栓症を起こすおそれがある］（「重要な基本的注意」の項参照） (2) 腎機能障害又は肝機能障害のある患者［使用経験が少ない］
使用上の注意	**2.重要な基本的注意** (1) 本剤は、血液疾患の治療に十分な経験を持つ医師のもとで使用すること。 (2) 本剤の投与により肝機能障害があらわれることがあるので、本剤の投与開始前及び用量調節時は 2 週間毎、用量の変更がなければ 1ヵ月毎に肝機能検査（AST（GOT）、ALT（GPT）、ビリルビン等）を実施すること。（「4．副作用(1)重大な副作用」の項参照） (3) 血小板数が正常範囲以下であっても血栓塞栓症が認められているため、血小板数にかかわらず血栓塞栓症の発現に注意すること（「4．副作用(1)重大な副作用」の項参照）。また、血小板数が正常範囲を超えると、血栓塞栓症のリスクが増加する可能性があるので、観察を十分に行い、血小板数が治療の目標とするレベルを超えた場合には、本剤の減量又は休薬を考慮する等注意すること。 (4) 本剤の投与中止後 2 週間以内に血小板数が投与開始前の値まで低下し、出血を生じることがあるので、本剤の投与中止後 4 週間程	**2.重要な基本的注意** (1) 本剤は、血液疾患の治療に十分な経験を持つ医師のもとで使用すること。 (2) 本剤の投与中止により血小板減少を認めることがあるため、本剤の中止後 4 週間程度は頻回に全血算（赤血球、白血球及び血小板）の検査を実施すること（「重大な副作用」の項参照）。 (3) 特に抗凝固剤又は抗血小板剤を使用中の患者が本剤の投与を中止した場合、血小板減少症の増悪により患者の出血リスクが上昇するおそれがある（「重大な副作用」の項参照）。 (4) 本剤を含むトロンボポエチン受容体作動薬には、骨髄のレチクリン線維の形成及び線維化を進行させる可能性があるので、本剤の投与開始前には、末梢血液像（末梢血塗抹標本）、全血算（赤血球、白血球及び血小板）及び網状赤血球数の検査を行い、全ての血球系の形態異常の有無を十分観察すること。また、本剤投与中は、末梢血液像（末梢血塗抹標本）、全血算（赤血球、白血球及び血小板）及び網状赤血球数の検査を 4 週に 1 回を目安に実施し、全ての血球系の形態異常及び血球減少の存否を観察すること。血球系の形態異常又は血球減少を認めた場合は、本剤の投与を中止し、線維化状態の

<table>
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<tr><td></td><td>度は頻回に血小板数を測定すること。（「4. 副作用(1)重大な副作用」の項参照）
(5) 本剤を含むトロンボポエチン受容体作動薬には、骨髄のレチクリン線維の形成及び線維化を進行させる可能性があるので、本剤の投与開始前には末梢血塗抹標本検査を行い、細胞の形態学的異常を確認すること。また、本剤の投与中は、毎月白血球分画を含む全血球計算を検査し、未熟細胞又は異型細胞が観察された場合には、末梢血塗抹標本検査を行い、形態学的異常（涙滴赤血球、有核赤血球、未熟白血球等）の発現を確認し、血球減少の有無も確認すること。これらの異常が認められた場合には、本剤の投与を中止し、骨髄生検（染色による骨髄線維化の評価等）の実施を考慮すること。（「4. 副作用(1)重大な副作用」の項参照）
(6) トロンボポエチン受容体作動薬には、既存の骨髄異形成症候群等の血液悪性腫瘍を進行させる可能性がある。
(7) 重症再生不良性貧血患者を対象とした海外臨床試験において、本剤投与後に染色体異常が認められた例や骨髄異形成症候群及び急性骨髄性白血病への移行例が報告されている。再生不良性貧血患者への本剤の投与中は、定期的に白血球分画を含む全血球計算及び末梢血塗抹標本検査を行い、幼若細胞や形態学的異常の発現を確認し、血球減少の有無も確認すること。これらの異常が認められた場合には、骨髄検査（染色体異常の評価を含む）の実施を考慮し、本剤の投与継続の可否を判断すること。
(8) げっ歯類を用いた毒性試験において、白内障がみられた。また、臨床試験において白内障が報告されているので、白内障に対する眼科的な検査を定期的に行うことが望ましい。</td><td>確認のため骨髄生検・特殊染色等の実施を考慮すること（「重大な副作用」の項参照）。
(5) 血小板数が正常範囲を超えると、血栓症又は血栓塞栓症のリスクが増加する可能性がある。また、血小板数が正常範囲以下であっても血栓塞栓症が認められているため、血小板数にかかわらず血栓症又は血栓塞栓症の発現に注意すること（「重大な副作用」の項参照）。
観察を十分に行い、血小板数が治療の目標とするレベルを超えた場合には、本剤の減量又は休薬を考慮するなど注意すること。
(6) 本剤に対する反応性の低下が認められた場合、又は血小板数の維持が困難になった場合は、原因（本剤に対する中和抗体の産生、又は骨髄線維症等の可能性）の究明に努めること。
(7) トロンボポエチン受容体作動薬には、既存の骨髄異形成症候群等の血液悪性腫瘍を進行させる可能性がある。</td></tr>
<tr><td>使用上の注意</td><td>3.相互作用
併用注意（併用に注意すること）
<table>
<tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr>
<tr><td>ロスバスタチン</td><td>本剤とロスバスタチンとの併用により、ロスバスタチンの血中濃度が上昇したとの報告がある。
ロスバスタチンの減量を考慮し、患者の状態を慎重に観察すること。</td><td>本剤が OATP1B1 及び BCRP を阻害する可能性がある。（【薬物動態】の項参照）</td></tr>
</table></td><td>－</td></tr>
</table>

<table>
<tr><td>販売名</td><td colspan="3">レボレード錠 12.5 mg，25 mg</td><td>ロミプレート皮下注 250 μg 調製用</td></tr>
<tr><td></td><td>制酸剤
乳製品
多価陽イオン（鉄、カルシウム、アルミニウム、マグネシウム、セレン、亜鉛等）含有製剤等</td><td>同時に服用すると本剤の吸収が著しく妨げられることがあるので、本剤投与の前 4 時間及び後 2 時間はこれらの摂取を避けること。（【薬物動態】の項参照）</td><td>本剤はこれら多価陽イオンと錯体を形成する。</td><td></td></tr>
<tr><td></td><td>ロピナビル／リトナビル配合剤</td><td>本剤とロピナビル／リトナビル配合剤との併用により、本剤の AUC が減少したとの報告があるので、ロピナビル／リトナビル配合剤と併用する場合には、注意すること。</td><td>機序は不明であるが、ロピナビル／リトナビル配合剤が本剤の代謝酵素を誘導する可能性がある。</td><td></td></tr>
<tr><td></td><td>シクロスポリン</td><td>本剤とシクロスポリンとの併用により、本剤の AUC 及び Cmax が減少したとの報告がある。また、本剤の血中濃度が高値を示したとの報告がある。シクロスポリンと併用する場合には、注意すること。</td><td>機序は不明である。</td><td></td></tr>
<tr><td>使用上の注意</td><td colspan="3">4.副作用
慢性特発性血小板減少性紫斑病患者を対象とした国内臨床試験において、23 例中 11 例（48%）に臨床検査値異常を含む副作用が報告された。その主なものは、疲労、ALT（GPT）増加、血小板数増加、低カリウム血症各 2 例（9%）であった（承認時）。また、これら 23 例中 19 例がその後国内長期継続投与試験に移行した。移行した 19 例中 5 例（26%）に副作用が報告された。その主なものは、白内障、胸痛各 2 例（11%）であった。（最終報告時）
慢性特発性血小板減少性紫斑病患者を対象とした海外臨床試験において、135 例中 50 例（37%）に臨床検査値異常を含む副作用が報告された。その主なものは、頭痛 15 例（11%）、ALT（GPT）増加 6 例（4%）、悪心 6 例（4%）、白内障 5 例（4%）、下痢 4 例（3%）であった。（承認時）</td><td>3.副作用
○国内臨床試験成績
国内の臨床試験において、安全性評価対象 46 例中 29 例（63.0%）に副作用（臨床検査値異常を含む）が認められた。主な副作用は、頭痛 17 例（37.0%）、倦怠感 6 例（13.0%）、背部痛 5 例（10.9%）、関節痛 4 例（8.7%）、回転性めまい 3 例（6.5%）、悪心 3 例（6.5%）、疲労 3 例（6.5%）、筋骨格硬直 2 例（4.3%）、四肢痛 2 例（4.3%）等であった。
○海外臨床試験成績</td></tr>
</table>

販売名	レボレード錠 12.5 mg，25 mg	ロミプレート皮下注 250 μg 調製用
	抗胸腺細胞免疫グロブリンで未治療の再生不良性貧血患者を対象とした国内臨床試験において、10 例中 5 例（50%）に臨床検査値異常を含む副作用が報告された。その主なものは、筋肉痛 3 例（30%）、血中ビリルビン増加、悪心各 2 例（20%）であった。（承認時） 既存治療で効果不十分な再生不良性貧血患者を対象とした国内臨床試験において、21 例中 12 例（57%）に臨床検査値異常を含む副作用が報告された。その主なものは、血中 ALP 増加、肝機能異常、高ビリルビン血症、発疹が各 2 例（10%）であった。（承認時） 重大な副作用及びその他の副作用の発現頻度については、上記の国内臨床試験を併合した集計結果に基づき記載した。また、これらの国内臨床試験であらわれてない副作用については頻度不明とした。	海外の臨床試験において、安全性評価対象 607 例中 296 例（48.8%）に副作用（臨床検査値異常を含む）が認められた。主な副作用は、頭痛 95 例（15.7%）、疲労 48 例（7.9%）、注射部位反応（疼痛、血腫、刺激感、腫脹、紅斑、出血、発疹を含む）37 例（6.1%）、関節痛 37 例（6.1%）、筋肉痛 27 例（4.4%）、悪心 25 例（4.1%）、浮腫（末梢性浮腫、全身性浮腫、顔面浮腫を含む）16 例（2.6%）、そう痒症 16 例（2.6%）、発疹 16 例（2.6%）、四肢痛 15 例（2.5%）、浮動性めまい 15 例（2.5%）、錯感覚 14 例（2.3%）、発熱 13 例（2.1%）、筋痙縮 13 例（2.1%）、下痢 12 例（2.0%）、疼痛 12 例（2.0%）、腹痛 11 例（1.8%）、食欲不振 11 例（1.8%）、筋骨格痛 11 例（1.8%）、骨髄レチクリン増生 11 例（1.8%）、感冒様症状 10 例（1.6%）、不眠症 10 例（1.6%）等であった。［承認時］
使用上の注意	(1)**重大な副作用** 1) 肝機能障害：AST（GOT、2%）、ALT（GPT、7%）、ALP（6%）、ビリルビン（13%）の増加等の肝機能障害があらわれることがあるので、本剤投与開始前及び投与中は定期的に肝機能検査を行う等、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等適切な処置を行うこと。（「2．重要な基本的注意」の項参照） 2) 血栓塞栓症：肺塞栓症（頻度不明）、深部静脈血栓症（頻度不明）、一過性脳虚血発作（2%）、心筋梗塞（頻度不明）、虚血性脳卒中（頻度不明）等の血栓塞栓症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等適切な処置を行うこと。（「2．重要な基本的注意」の項参照） 3) 出血：本剤の投与中止後に出血（頻度不明）を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、適切な処置を行うこと。（「2．重要な基本的注意」の項参照） 4) 骨髄線維化：骨髄線維化（頻度不明）があらわれる可能性があるので、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等適切な処置を行うこと。（「2．重要な基本的注意」の項参照）	(1)**重大な副作用** 1) 血栓症・血栓塞栓症　肺塞栓症（0.8%）、深部静脈血栓症（0.8%）、心筋梗塞（0.6%）、血栓性静脈炎（0.5%）等があらわれることがあるため、本剤投与後は、定期的に血小板数を測定すること。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 2) 骨髄レチクリン増生（1.7%）　骨髄レチクリン増生が認められることがあり、骨髄線維化があらわれる可能性がある。血球系の形態異常又は血球減少を認めた場合は、本剤の投与を中止すること。また、線維化状態の確認のため骨髄生検・特殊染色等の実施を考慮すること。 3) 出血（頻度不明）　本剤の投与中止後に出血を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、適切な処置を行うこと。

販売名	レボレード錠 12.5 mg，25 mg	ロミプレート皮下注 250 μg 調製用
使用上の注意	(2)その他の副作用	(2)その他の副作用 次のような症状があらわれた場合には、減量・休薬等の適切な処置を行うこと。

(2)その他の副作用

	5%以上	5%未満	頻度不明
消化器	悪心	－	嘔吐、下痢、口内乾燥
皮膚	－	発疹	脱毛症
筋骨格	筋痛	－	背部痛、筋骨格系胸痛、筋骨格痛
その他	頭痛	疲労、血小板数増加、低カリウム血症、白内障	咽頭炎、尿路感染

〈国内外の臨床試験で認められた副作用〉

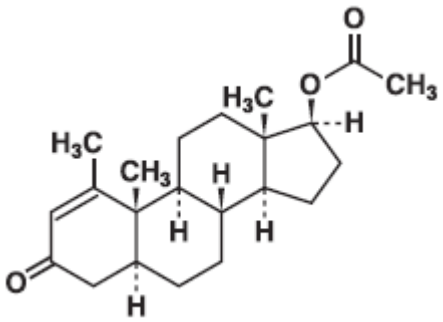
	副作用頻度（%）		
	10%以上	1～10%未満	1%未満
血液およびリンパ系障害		血小板血症、血小板減少症	貧血
精神障害		不眠症	うつ病
神経系障害	頭痛	浮動性めまい、錯感覚（ピリピリ感等）	感覚鈍麻、嗜眠、片頭痛、味覚異常、末梢性ニューロパチー
血管障害			ほてり、潮紅、高血圧
呼吸器、胸郭および縦隔障害			呼吸困難、咳嗽、鼻出血
胃腸障害		悪心、下痢、腹痛	嘔吐、腹部不快感、上腹部痛、消化不良、便秘
皮膚および皮下組織障害		発疹、そう痒症	脱毛症、斑状出血、点状出血、そう痒性皮疹、多汗症
筋骨格系および結合組織障害		四肢痛、関節痛、筋肉痛、筋痙縮、背部痛、筋骨格痛	骨痛、筋力低下、筋骨格系胸痛、筋骨格硬直
全身障害および投与局所様態		疲労、注射部位反応（疼痛、血腫、刺激感、腫脹、紅斑、出血、発疹を含む）、浮腫（末梢性浮腫、全身性浮腫、顔面浮腫を含む）、発熱、疼痛、倦怠感、感冒様症状、無力症、悪寒	胸痛
その他		食欲不振、挫傷、回転性めまい	鼻咽頭炎、動悸、インフルエンザ、血小板数増加、体重減少、膣出血

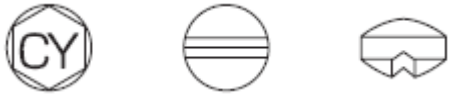
販売名	レボレード錠 12.5 mg，25 mg	ロミプレート皮下注 250 μg 調製用
使用上の注意	**5.高齢者への投与** 高齢者では一般に生理機能が低下しているので、患者の状態を観察しながら注意して投与すること。	**4.高齢者への投与** 高齢者では一般に生理機能（肝機能、腎機能、心機能等）が低下していることが多く、また、合併症を併発又は他の薬剤を使用している可能性が高いことから、患者の状態を観察しながら、慎重に投与を行うこと。
使用上の注意	**6.妊婦、産婦、授乳婦等への投与** (1) 妊婦又は妊娠している可能性のある婦人には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。〔妊婦への投与に関する安全性は確立しておらず、胎児の血小板への影響についても不明である。動物試験（ラット）において母体毒性用量で胚致死、胎児体重の低値及び低頻度の頸肋（変異）の増加が報告されている。〕 (2) 授乳中の婦人には、投与を避けることが望ましい。やむを得ず投与する場合には、授乳を避けさせること。〔動物試験（ラット）で乳汁中への移行が示唆されている。〕	**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［動物実験（ラット）で胎児における血小板数増加及び新生児死亡率の増加並びに動物実験（マウス）で胎児における着床後胚損失率の増加及び母動物における体重増加抑制が報告されている］。 (2) 授乳中の婦人には投与を避けることが望ましい。やむを得ず投与する場合には授乳を避けさせること［授乳中の投与に関する安全性は確立していない］。
使用上の注意	**7.小児等への投与** 小児等に対する安全性及び有効性は確立していない（使用経験がない）。	**6.小児等への投与** 低出生体重児、新生児、乳児、幼児又は小児（18 歳未満）に対する安全性又は有効性は確立していない［国内における使用経験がない］。
使用上の注意	**8.過量投与** 徴候、症状：本剤 5,000 mg を過量投与した症例では、軽度の発疹、一過性の徐脈、疲労、AST（GOT）及び ALT（GPT）上昇が報告され、血小板数は 929,000/μL まで増加した。 処置：吸収を抑えるために、カルシウム、アルミニウム、マグネシウム等の多価陽イオンを含有する製剤の経口投与を考慮すること。また、血小板数の検査を頻回に行い、患者の状態を十分に観察すること。本剤の腎排泄の寄与は小さく、血漿蛋白結合率が高いため、血液透析は有効な除去法ではないと考えられる。	**7.過量投与** 本剤は、過量投与により、血小板数が過剰に増加し、血栓症又は血栓塞栓症の合併症を生じるおそれがある。過量投与の場合は本剤の投与を中止し、血小板数をモニターすること。血小板数が回復した後は、「用法・用量に関連する使用上の注意」に従い、本剤の治療を再開すること。
使用上の注意	**9.適用上の注意** (1) 薬剤交付時：PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。〔PTP シートの誤飲により、硬い鋭角部が	**8.適用上の注意** (1)投与経路： 本剤は皮下投与でのみ使用すること。 (2)調整方法：

<table>
<tr><td>販売名</td><td>レボレード錠 12.5 mg，25 mg</td><td>ロミプレート皮下注 250 μg 調製用</td></tr>
<tr><td></td><td>食道粘膜へ刺入し、更には穿孔を起こして縦隔洞炎等の重篤な合併症を併発することが報告されている。〕
(2) PTP シートからの取り出しは、裏のシールを剥がした後、指の腹で押し出すこと。</td><td>1) 本剤は、1 回使い切りのバイアルであり、注射用水 0.72 mL により溶解し、0.01 mL 目盛り注射器等を用いて投与する。注射用水以外のもので溶解しないこと。本剤の含有量は以下のとおりとなるが、1 バイアルあたり投与できる最大液量は 0.5 mL である。
本剤の含有量
<table>
<tr><td>1 バイアル中の含量</td><td>注射用水 0.72 mL で溶解した溶液 0.5 mL 中に含まれる量</td><td>最終濃度</td></tr>
<tr><td>375 μg</td><td>250 μg/0.5 mL</td><td>500 μg/mL</td></tr>
</table>
2) バイアルは静かに混和し、過度又は急激な攪拌は避けること。振とうしないこと。通常、本剤は 2 分以内に溶解する。溶解後溶液は無色澄明である。変色の有無、及びバイアル内に微粒子が含まれていないか溶解後溶液を目視検査すること。微粒子、又は変色が認められた溶液は使用しないこと。
3) 溶解後溶液は、室温（25°C）又は冷蔵保存（2～8°C）し、24 時間以内に投与を開始すること。溶解後溶液は遮光下で保存すること。
4) 使用後の残液は、保存せずに廃棄すること。1 バイアルから 2 回以上の薬液採取は行わないこと。
(3)投与時：
1) 本剤の投与に際して必要量（mL）を計算するために、まず個々の患者の 1 回投与量（μg）を【用法・用量】に従い算出する。例えば、体重 55 kg の患者が初回投与量 1 μg/kg で投与を開始する場合、必要な患者の 1 回投与量は 55 μg である。これを溶解後溶液の最終濃度（500 μg/mL）で割ると、患者に投与すべき必要量（mL）が算出される。この場合は、必要量は 55（μg）/500（μg/mL）=0.11 mL となる。
2) 1 回当たり 0.5 mL を超える場合には、複数のバイアルから必要量（mL）を確保すること。
3) 投与液量が少ないため、0.01 mL 目盛り注射器等を用いて投与すること。</td></tr>
<tr><td>使用上の注意</td><td>10.その他の注意</td><td>9.その他の注意</td></tr>
</table>

販売名	レボレード錠 12.5 mg，25 mg	ロミプレート皮下注 250 μg 調製用
	本剤はヒト及びチンパンジー以外のトロンボポエチン受容体に対し親和性をもたず、ヒト及びチンパンジー以外の動物に対して薬理活性を示さない。このため毒性試験において、薬理活性に付随する影響は評価されていない。	慢性特発性血小板減少性紫斑病患者を対象とした海外臨床試験において、造血器腫瘍の発現が認められた。 骨髄異形成症候群患者（承認外）では、疾患の進行に伴い急性骨髄性白血病へ移行することが知られている。骨髄異形成症候群患者を対象とした海外臨床試験（海外未承認）において、一過性の芽球の増加と、急性骨髄性白血病への移行が認められたとの報告がある。
添付文書の作成年月日	―	2014 年 9 月改訂〈第 2 版〉
備考		

2 抗ヒト胸腺細胞ウサギ免疫グロブリン / メテノロン酢酸エステル

販売名	サイモグロブリン点滴静注用 25 mg	プリモボラン錠 5 mg
一般名	抗ヒト胸腺細胞ウサギ免疫グロブリン	メテノロン酢酸エステル
会社名	サノフィ株式会社	バイエル薬品株式会社
販売開始	2008 年 11 月	1962 年 11 月
再評価年月日 再審査年月日	ー	1976 年 7 月（再評価結果）
規 制 区 分	生物由来製品、劇薬、処方箋医薬品	処方箋医薬品
有効成分に関する理化学的知見	一般名：抗ヒト胸腺細胞ウサギ免疫グロブリン （Anti-human Thymocyte Immunoglobulin, Rabbit） 本　質： ヒトの胸腺細胞を抗原とし、ウサギを免疫して得られた抗血清から分離精製されたポリクローナル抗体で、免疫グロブリン G に属するたん白質 分子量：約 160,000	構造式：  一般名：メテノロン酢酸エステル Metenolone Acetate 化学名：1-Methyl-3-oxo-5α-androst-1-en-17β-yl acetate 分子式：$C_{22}H_{32}O_3$ 分子量：344.49
剤型・含量	サイモグロブリン点滴静注用 25 mg 成分・含量：1 バイアル中抗ヒト胸腺細胞ウサギ免疫グロブリン 25 mg 添加物：グリシン、D-マンニトール、ポリソルベート 80、塩化ナトリウム、pH 調節剤 2 成分	プリモボラン錠 5 mg 成分・含量：1 錠中、日局メテノロン酢酸エステル 5 mg 含有 添加物：乳糖水和物、トウモロコシデンプン、タルク、ステアリン酸マグネシウム、ゼラチン 色・剤形：白色の素錠

<table>
<tr><th>販売名</th><th>サイモグロブリン点滴静注用 25 mg</th><th>プリモボラン錠 5 mg</th></tr>
<tr><td></td><td>
<table>
<tr><td>性状</td><td>白色ないし乳白色の凍結乾燥製剤である。本剤を日局注射用水で溶解したとき、無色ないし淡黄色の澄明又はわずかに混濁した液となる。</td></tr>
<tr><td>pH 注)</td><td>6.5～7.2</td></tr>
<tr><td>浸透圧比注)</td><td>約 0.9（生理食塩液に対する比）</td></tr>
</table>
注）日局注射用水 5 mL で溶解後
本剤は製造工程でヒトの胸腺細胞及び赤血球を使用している。</td><td>
<table>
<tr><td>外形
（識別コード）</td><td> 
</td></tr>
<tr><td>直径（mm）</td><td>7.0</td></tr>
<tr><td>厚さ（mm）</td><td>2.7</td></tr>
<tr><td>重さ（g）</td><td>0.12</td></tr>
</table>
</td></tr>
<tr><td>効能・効果</td><td>○中等症以上の再生不良性貧血
○造血幹細胞移植の前治療
○造血幹細胞移植後の急性移植片対宿主病
○下記の臓器移植後の急性拒絶反応の治療
腎移植、肝移植、心移植、肺移植、膵移植、小腸移植
〈効能又は効果に関連する使用上の注意〉
○中等症以上の再生不良性貧血の場合
本剤は下記の重症度基準による中等症以上の再生不良性貧血患者に使用すること。
再生不良性貧血の重症度基準
（厚生労働省特定疾患特発性造血障害調査研究班基準
（平成 16 年度修正））
<table>
<tr><td>最重症</td><td>好中球 200/μL 未満に加えて、以下の 1 項目以上を満たす
網赤血球 20,000/μL 未満
血小板 20,000/μL 未満</td></tr>
<tr><td>重症</td><td>以下の 2 項目以上を満たす
網赤血球 20,000/μL 未満
好中球 500/μL 未満
血小板 20,000/μL 未満</td></tr>
<tr><td>やや重症</td><td>以下の 2 項目以上を満たし、定期的な赤血球輸血を必要とする</td></tr>
</table>
</td><td>骨粗鬆症
下記疾患による著しい消耗状態
慢性腎疾患、悪性腫瘍、外傷、熱傷
下記疾患による骨髄の消耗状態
再生不良性貧血</td></tr>
</table>

<table>
<tr><th>販売名</th><th>サイモグロブリン点滴静注用 25 mg</th><th>プリモボラン錠 5 mg</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>網赤血球 60,000/μL 未満
好中球 1,000/μL 未満
血小板 50,000/μL 未満</td></tr>
<tr><td>中等症</td><td>以下の 2 項目以上を満たす
網赤血球 60,000/μL 未満
好中球 1,000/μL 未満
血小板 50,000/μL 未満</td></tr>
<tr><td>軽症</td><td>それ以外のもの</td></tr>
</table>
注）定期的な赤血球輸血とは毎月 2 単位以上の輸血が必要なときを指す。
○造血幹細胞移植後の急性移植片対宿主病の場合
ステロイド療法によっても十分な効果が得られない場合にのみ適用を考慮すること。
○臓器移植後の急性拒絶反応の治療の場合
本剤は、原則としてステロイド療法で十分な治療効果が得られない場合に使用すること。</td><td></td></tr>
<tr><td>用法・用量</td><td>○中等症以上の再生不良性貧血
通常、1 日 1 回体重 1 kg あたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして 2.5～3.75 mg を、生理食塩液又は 5%ブドウ糖注射液 500 mL で希釈して、6 時間以上かけ緩徐に点滴静注する。投与期間は 5 日間とする。
○造血幹細胞移植の前治療
通常、1 日 1 回体重 1 kg あたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして 2.5 mg を、生理食塩液又は 5%ブドウ糖注射液 500 mL で希釈して、6 時間以上かけ緩徐に点滴静注する。投与期間は造血幹細胞移植 5 日前より 4 日間とする。
○造血幹細胞移植後の急性移植片対宿主病</td><td>メテノロン酢酸エステルとして、通常、成人 1 日 10～20 mg を 2～3 回に分割経口投与する。なお、年齢、症状により適宜増減する。</td></tr>
</table>

販売名	サイモグロブリン点滴静注用 25 mg	プリモボラン錠 5 mg
	通常、1 日 1 回体重 1 kg あたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして 2.5～3.75 mg を、生理食塩液又は 5%ブドウ糖注射液 500 mL で希釈して、6 時間以上かけ緩徐に点滴静注する。投与期間は 5 日間とする。 ○臓器移植後の急性拒絶反応の治療 腎移植の場合 通常、1 日 1 回体重 1 kg あたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして 1.5 mg を、1 バイアル（抗ヒト胸腺細胞ウサギ免疫グロブリンとして 25 mg）あたり、生理食塩液又は 5%ブドウ糖注射液 50 mL で希釈して、6 時間以上かけ緩徐に点滴静注する。投与期間は 7～14 日間とする。 肝移植、肺移植、膵移植及び小腸移植の場合 通常、1 日 1 回体重 1 kg あたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして 1.5 mg を、1 バイアル（抗ヒト胸腺細胞ウサギ免疫グロブリンとして 25 mg）あたり、生理食塩液又は 5%ブドウ糖注射液 50 mL で希釈して、6 時間以上かけ緩徐に点滴静注する。投与期間は最大 14 日間とする。 心移植の場合 通常、1 日 1 回体重 1 kg あたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして 1.5 ～ 2.5 mg を、1 バイアル（抗ヒト胸腺細胞ウサギ免疫グロブリンとして 25 mg）あたり、生理食塩液又は 5%ブドウ糖注射液 50 mL で希釈して、6 時間以上かけ緩徐に点滴静注する。投与期間は最大 14 日間とする。 **〈用法及び用量に関連する使用上の注意〉** (1) アナフィラキシー等の過敏症状を起こすことがあるので、使用に際しては、十分な問診を行うとともに、あらかじめ本剤の試験投与を行うこと。 試験投与は通常、本剤 1 バイアルを日局注射用水 5 mL にて溶解後、その 0.5 mL（抗ヒト胸腺細胞ウサギ免疫グロブリンとして 2.5 mg）を 100 mL の生理食塩液で希釈して、1 時間以上かけて点滴静注する。試験投与中は医師が患者の状態を十分に観察し、安全性を確認すること。	

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	(2) 本剤又は他のウサギ血清製剤の投与歴のある患者に本剤をやむを得ず再投与する際には、投与に先立って、本剤に対する抗体の有無を確認する等、必要な処置を講じた上で、医師の十分な観察のもと投与すること。 (3) 臓器移植後の急性拒絶反応の治療に本剤を投与する際には、血小板を含む全血算値に十分注意し、以下に示す減量基準等を参考に、適切な処置を行うこと。 1. 血小板数が 50,000～75,000/mm^3 又は白血球数が 2,000～3,000/mm^3 の場合、本剤の減量を考慮すること。 2. 持続的で重度の血小板減少症（< 50,000/mm^3）又は白血球減少症（< 2,000/mm^3）が認められた場合、本剤の投与中止を考慮すること。 (4) 心移植後の急性拒絶反応の治療において、1.5 mg/kg よりも高用量を投与する期間は、過度の免疫抑制状態の持続を避けるため、5 日間までを目安にすること。	
使用上の注意	**警告** 本剤は、緊急時に十分対応できる医療施設において、再生不良性貧血、造血幹細胞移植又は臓器移植に関する十分な知識・経験を持つ医師のもとで、本剤が適切と判断される症例についてのみ投与すること。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。	―
使用上の注意	**禁忌（次の患者には投与しないこと）** 1．本剤の試験投与でショック状態等の過敏症が認められた患者［〈用法及び用量に関連する使用上の注意〉の項参照］ 2．重症感染症（肺炎、敗血症等）を合併している患者［感染症が増悪し致命的となることがある。］ 3．妊婦［「6．妊婦、産婦、授乳婦等への投与」の項参照］ 4．弱毒生ワクチンを投与中の患者［「3．相互作用（1）」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）**	**禁忌（次の患者には投与しないこと）** (1)アンドロゲン依存性悪性腫瘍（例えば、前立腺癌）及びその疑いのある患者［症状を悪化させるおそれがある。］ (2)妊婦又は妊娠している可能性のある女性［「妊婦、産婦、授乳婦等への投与」の項参照］

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	1. 本剤又は他のウサギ血清製剤の投与歴のある患者［ショックを起こすおそれがある。］ 2. ウイルス感染症の患者 3. 細菌感染症の患者 4. 真菌感染症の患者 ［2. ～ 4. 本剤の免疫抑制作用により病態を悪化させるおそれがある。］	
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) 薬物過敏症の既往歴のある患者 (2) アレルギー素因のある患者 (3) 肝障害のある患者［肝機能を悪化させるおそれがある。］ (4) 腎障害のある患者［腎機能を悪化させるおそれがある。］ (5) 心疾患のある患者［心機能を悪化させるおそれがある。］	**1.慎重投与（次の患者には慎重に投与すること）** (1) 前立腺肥大のある患者［症状を悪化させるおそれがある。］ (2) 心疾患・腎疾患のある患者［ナトリウム又は体液の貯留があらわれることがある。］ (3) 肝疾患のある患者［症状を悪化させることがある。］ (4) 癌の骨転移のある患者［高カルシウム血症があらわれるおそれがある。］ (5) 高齢者［「高齢者への投与」の項参照］ (6) 糖尿病の患者［耐糖能の低下がみられることがある。］
使用上の注意	**2.重要な基本的注意** (1) ショック等重篤な副作用を起こすことがあるので、投与前にショック症状発現時の救急処置対策を考慮しておくこと。投与中は注意して使用し、医師が経過を十分に観察すること。ショック症状があらわれた場合には、速やかに投与を中止し、適切な救急処置を行うこと。［「（1）重大な副作用 1）」の項参照］ (2) 本剤の投与前に感染症が認められた場合、感染症の治療を優先し、患者の状態が安定した後、本剤を投与すること。また、投与中並びに投与後に重篤な感染症（ウイルス感染症、細菌感染症、真菌感染症等）が発症する場合があるので、患者の状態を十分に観察し、異常が認められた場合には、適切な治療を行うこと。［「（1）重大な副作用 3）～6）」の項参照］	**2.重要な基本的注意** (1) 男性に投与する場合は、定期的に前立腺の検査を行うこと。 (2) 女性に投与する場合は、変声の可能性のあることを告げておくこと。 (3) 肝機能障害、黄疸があらわれることがあるので、特に長期投与する場合には、定期的に臨床検査（肝機能検査等）を行うこと。

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	(3) 間質性肺炎を起こすことがあるので、咳嗽、呼吸困難、低酸素症等の呼吸器症状に注意すること。［「（1）重大な副作用 7）」の項参照］ (4) 本剤投与の初期に発熱、悪寒、呼吸困難、悪心、嘔吐、下痢、頻脈、低血圧、高血圧、倦怠感、発疹、頭痛等があらわれることがあるので、その旨を患者にあらかじめ説明しておくこと。また、重度の infusion associated reaction（サイトカイン放出症候群を含む）があらわれ、重篤な心障害や肺障害（心筋梗塞、急性呼吸窮迫症候群、肺水腫）に至ることがあるので、投与中は患者を厳密に観察すること。これらの症状を軽減させるため、あらかじめ副腎皮質ホルモン剤等を投与することが望ましい。また、解熱剤、抗ヒスタミン剤の併用も本剤の投与初期に頻発するこれらの症状を軽減する。［「（1）重大な副作用 2）」の項参照］ (5) 本剤投与時に交差反応性抗体に起因する血小板減少があらわれ、出血傾向が増悪するおそれがあるので、定期的に血小板数を測定し、患者の状態を十分に観察すること。［「（1）重大な副作用 8）,9）」の項参照］ (6) 本剤投与に先立って、本剤又は他のウサギ血清製剤の治療歴の有無を必ず確認すること。また、本剤の投与後には、患者にウサギ血清製剤を投与した旨を十分認識させるために、本剤の医薬品名を記載した用紙に、使用量、使用期間、病院名、担当医師名を記入し、治療終了後に治療歴として保管するとともに同様の記録を患者に渡すこと。 (7) 免疫抑制剤を投与された B 型肝炎ウイルスキャリアの患者において、B 型肝炎ウイルスの再活性化による肝炎があらわれることがある。また、HBs 抗原陰性の患者において、免疫抑制剤の投与開始後に B 型肝炎ウイルスの再活性化による肝炎を発症した症例が報告されている。また、C 型肝炎ウイルスキャリアの患者において、免疫抑制剤の投与開始後に C 型肝炎の悪化がみられることがある。肝炎ウイルスキャリアの患者に本剤を投与する場合は、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や C 型肝炎の悪化の徴候や症状の発現に注意すること。［「（1）重大な副作用 3）」の項参照］	

<table>
<tr><td>販売名</td><td>サイモグロブリン点滴静注用 25 mg</td><td>プリモボラン錠 5 mg</td></tr>
<tr><td></td><td>(8) 臓器移植後の急性拒絶反応の治療の場合、原則として、急性拒絶反応の確定診断後に本剤を投与すること。</td><td></td></tr>
<tr><td>使用上の注意</td><td>3.相互作用
(1)併用禁忌（併用しないこと）
<table>
<tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr>
<tr><td>弱毒生ワクチン
おたふくかぜ、麻疹、風疹及びこれらの混合ワクチン等</td><td>本剤投与後、弱毒生ワクチンを接種する場合には、発病するおそれがある。</td><td>本剤の免疫抑制作用による。</td></tr>
</table>
(2)併用注意（併用に注意すること）
<table>
<tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr>
<tr><td>他の免疫抑制剤
シクロスポリン等</td><td>過度の免疫抑制による感染症あるいはリンパ増殖性疾患を惹起する危険性があるので、併用する場合には慎重に投与すること。</td><td>相加的に免疫抑制作用が増強される可能性がある。</td></tr>
</table></td><td>3.相互作用
併用注意（併用に注意すること）
<table>
<tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr>
<tr><td>副腎皮質ホルモン剤</td><td>耐糖能の低下がみられることがある。観察を十分に行い慎重に投与すること。</td><td>機序は不明</td></tr>
<tr><td>クマリン系抗凝血剤
ワルファリンカリウム等</td><td>これらの作用を増強することがある。観察を十分に行い慎重に投与すること。</td><td>機序は不明</td></tr>
</table></td></tr>
<tr><td>使用上の注意</td><td>4.副作用
国内における再生不良性貧血、造血幹細胞移植の前治療及び造血幹細胞移植後の急性移植片対宿主病に対する臨床試験での安全性評価対象症例 160 例中 159 例（99.4%）に 3,443 件の副作用（臨床検査値異常を含む）が認められた。主な副作用は、発熱 145 例（90.6%）、熱感 120 例（75.0%）、白血球減少 120 例（75.0%）、CRP 増加 113 例（70.6%）、好中球減少 87 例（54.4%）等であった。（承認時）
外国における腎移植後の急性拒絶反応の治療を目的とした二重盲検比較試験において、安全性評価対象症例のうち本剤が投与された 82 例中 82 例（100%）に 940 件の副作用（関連性が unlikely のものを含む）が認められた。主な副作用は、悪寒 40 例（48.8%）、疼痛 38 例（46.3%）、白血球減少 32 例（39.0%）、腹痛 31 例（37.8%）、高血圧 30 例（36.6%）、末梢性浮腫 28 例（34.1%）、無力症、血小板減少症、高カリウム血症各 22 例（26.8%）、発熱 20 例（24.4%）、貧血 19 例（23.2%）等であった。（腎移植適応追加時）</td><td>4.副作用
本剤は使用成績調査等の副作用発現頻度が明確となる調査を実施していない。</td></tr>
</table>

販売名	サイモグロブリン点滴静注用 25 mg	プリモボラン錠 5 mg
	肝移植、心移植、肺移植、膵移植、小腸移植後の急性拒絶反応の治療における副作用発現頻度が明確となる臨床試験は実施していない。	
使用上の注意	**(1)重大な副作用** 1) ショック（頻度不明注）、アナフィラキシー（0.4%）…ショック、アナフィラキシーを起こすことがあるので観察を十分に行い、呼吸困難、血圧低下、頻脈等の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。 2) 重度の infusion associated reaction（サイトカイン放出症候群を含む）（頻度不明注）…重度の infusion associated reaction（サイトカイン放出症候群を含む）があらわれ、重篤な心障害や肺障害（心筋梗塞、急性呼吸窮迫症候群、肺水腫）に至ることがあるので、発熱、悪寒、呼吸困難、悪心、嘔吐、下痢、頻脈、低血圧、高血圧、倦怠感、発疹、頭痛等の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。 3) 感染症（肺炎、敗血症等）（11.2%）…ウイルス（アデノウイルス、サイトメガロウイルス、ヘルペス等）、細菌、真菌（アスペルギルス等）等による重篤な感染症があらわれることがある。また、免疫抑制剤を投与された B 型又は C 型肝炎ウイルスキャリアの患者において、B 型肝炎ウイルスの再活性化による肝炎や C 型肝炎の悪化があらわれることがある。本剤を投与する場合は観察を十分に行い、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。 4) 発熱性好中球減少症（頻度不明注）…発熱性好中球減少症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。 5) 進行性多巣性白質脳症（PML）（頻度不明注）…進行性多巣性白質脳症（PML）があらわれることがあるので、本剤の治療期間中及び治療終了後は患者の状態を十分に観察し、意識障害、認知障害、麻痺症状（片麻痺、四肢麻痺）、言語障害等の症状があらわれた場合は、MRI による画像診断及び脳脊髄液検査を行うとともに、投与を中止し、適切な処置を行うこと。	**(1)重大な副作用** 肝機能障害、黄疸（頻度不明）：AST（GOT）、ALT（GPT）、γ-GTP 等の著しい上昇を伴う肝機能障害や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し、適切な処置を行うこと。

販売名	サイモグロブリン点滴静注用 25 mg	プリモボラン錠 5 mg
	6) BK ウイルス腎症（頻度不明[注)]）…BK ウイルス腎症があらわれることがあるので、このような場合には減量又は投与を中止し、適切な処置を行うこと。 7) 間質性肺炎（2.1%）…間質性肺炎があらわれることがあるので、観察を十分に行い、発熱、咳嗽、呼吸困難、胸部 X 線検査異常等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。 8) 血小板減少（31.0%）、白血球減少（頻度不明[注)]）…血小板減少、白血球減少があらわれることがあるので、定期的に血液検査を行い、異常が認められた場合には投与を中止する等、適切な処置を行うこと。 9) 出血傾向…脳出血（1.7%）、下血、胃腸出血（いずれも 1.2%）、くも膜下出血、肺出血、肺胞出血（いずれも 0.4%）等の出血があらわれることがあるので、臨床症状を十分に観察し、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。 10) 重篤な肝障害（6.2%）…AST（GOT）、ALT（GPT）の上昇等を伴う重篤な肝障害があらわれることがあるので、定期的に血液検査を行う等、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。 11) リンパ増殖性疾患（1.2%）…リンパ増殖性疾患があらわれることがあるので、発熱、リンパ節腫大等が認められた場合には、適切な処置を行うこと。 注）国内における承認時までの臨床試験及び外国における腎移植後の急性拒絶反応の治療を目的とした二重盲検比較試験で認められなかった副作用は頻度不明とした。 (2)重大な副作用（類薬） 急性腎不全…静注用人免疫グロブリンの投与により、急性腎不全があらわれることが報告されているので、投与に先立って患者が脱水状態にないことを確認するとともに、観察を十分に行い、腎機能検査値（BUN、血清クレアチニン等）の悪化、尿量減少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。なお、急性腎不全の危険性の高い患者においては、投与量及び投与速度を出来るだけ低くすることが望ましい。	
使用上の注意	(3)その他の副作用	(2)その他の副作用

<table>
<tr><td>販売名</td><td>サイモグロブリン点滴静注用 25 mg</td><td>プリモボラン錠 5 mg</td></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>40%以上</td><td>10～40%未満</td><td>10%未満</td></tr>
<tr><td>過敏症注1)</td><td></td><td>発疹、そう痒症</td><td>筋痛、紅斑、血清病注3)</td></tr>
<tr><td>発熱及びインフルエンザ様症状注2)</td><td>発熱、熱感</td><td>頭痛、関節痛、悪寒</td><td>胸痛</td></tr>
<tr><td>血液</td><td></td><td>好中球減少、リンパ球減少、血清総蛋白減少、赤血球減少、ヘマトクリット減少、ヘモグロビン減少、高カリウム血症</td><td></td></tr>
<tr><td>精神神経系</td><td></td><td></td><td>感覚減退、筋硬直、めまい</td></tr>
<tr><td>消火器</td><td></td><td>悪心、嘔吐、下痢、腹痛</td><td></td></tr>
<tr><td>肝臓</td><td></td><td>AST（GOT） 増加、ALT（GPT）増加、LDH 増加</td><td>Al-P 増加、ビリルビン増加</td></tr>
<tr><td>循環器</td><td></td><td>動悸、血圧上昇</td><td>血圧低下、頻脈</td></tr>
<tr><td>血管</td><td></td><td></td><td>静脈炎</td></tr>
<tr><td>その他</td><td>CRP 増加</td><td>脱力、疼痛、末梢性浮腫</td><td>耳鳴、呼吸困難、無力症、倦怠感、投与部位反応（疼痛、腫脹、紅斑）</td></tr>
</table>
注 1）副腎皮質ホルモン剤等の併用で軽減される。
注 2）副腎皮質ホルモン剤、解熱剤及び抗ヒスタミン剤等の併用で軽減される。
注 3）発熱、発疹、関節痛、筋肉痛などの症状を伴う。なお、これらの症状は自然に消退する場合があるが、副腎皮質ホルモン剤の投与で速やかに軽減される。
発現頻度は、国内における承認時までの臨床試験及び外国における腎移植後の急性拒絶反応の治療を目的とした二重盲検比較試験の結果をあわせて算出した。
</td><td>下記の副作用があらわれることがあるので、このような場合には適切な処置を行うこと。
<table>
<tr><td colspan="2"></td><td>頻度不明</td></tr>
<tr><td colspan="2">過敏症注)</td><td>過敏症状</td></tr>
<tr><td colspan="2">肝臓</td><td>AST（GOT）上昇、ALT（GPT）上昇</td></tr>
<tr><td colspan="2">胃腸</td><td>悪心、嘔吐</td></tr>
<tr><td rowspan="2">その他注)</td><td>女性</td><td>嗄声（進行すると回復困難な場合がある。通常、月経異常が先発する例が多いとの報告がある。）、多毛、痤瘡、色素沈着、月経異常、陰核肥大、性欲亢進</td></tr>
<tr><td>男性</td><td>痤瘡、陰茎肥大、陰萎、持続性勃起、大量継続投与による精子減少・精液減少等の睾丸機能抑制</td></tr>
</table>
注）投与を中止すること。</td></tr>
<tr><td>使用上の注意</td><td>5.高齢者への投与</td><td>5.高齢者への投与</td></tr>
</table>

販売名	サイモグロブリン点滴静注用 25 mg	プリモボラン錠 5 mg
	高齢者では一般に生理機能（腎機能、肝機能、免疫機能等）が低下しているので、患者の状態を観察しながら慎重に投与すること。	高齢者ではアンドロゲン依存性腫瘍が潜在している可能性があること、及び一般に生理機能が低下しているので慎重に投与すること。
使用上の注意	**6.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、投与しないこと。［妊娠中の投与に関する安全性は確立していない。］ (2) 授乳中の婦人には、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.妊婦、産婦、授乳婦等への投与** 女性胎児の男性化を起こすおそれがあるので、妊婦又は妊娠している可能性のある女性には投与しないこと。
使用上の注意	**7.小児等への投与** (1) 小児に投与する場合は、慎重に投与すること。 (2) 中等症以上の再生不良性貧血、造血幹細胞移植の前治療、造血幹細胞移植後の急性移植片対宿主病：低出生体重児、新生児、乳児、幼児又は小児に対する有効性・安全性は確立していない。［使用経験が少ない。］ (3) 臓器移植後の急性拒絶反応の治療：低出生体重児、新生児、乳児、幼児又は小児に対する有効性・安全性は確立していない。［肺及び膵移植に対する使用経験がなく、腎、肝、心及び小腸移植に対する使用経験が少ない。］	**7.小児等への投与** 骨端の早期閉鎖、性的早熟を来すことがあるので、観察を十分に行い慎重に投与すること。
使用上の注意	**8.臨床検査結果に及ぼす影響** 本剤はウサギ抗体を用いたイムノアッセイなどの検査結果に影響を及ぼす可能性がある。	－
使用上の注意	**9.過量投与** 本剤の過量投与により、白血球減少、血小板減少が発現することがあるので、用法及び用量に定められている投与量を超えて投与しないこと。本剤の過量投与が疑われた場合は、輸血、血液造血因子、抗感染症薬の投与等の支持療法を行うこと。また、必要に応じ無菌管理を考慮し、血液学的検査を頻回に行い、患者の状態を十分に観察すること。	－
使用上の注意	**10.適用上の注意** (1) 調整時： 1) 溶解	**8.適用上の注意** 薬剤交付時：PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。［PTP シートの誤飲により、硬い鋭角部が食道粘膜

販売名	サイモグロブリン点滴静注用 25 mg	プリモボラン錠 5 mg
	①本剤に日局注射用水 5 mL を加える。粉末が完全に溶解するまで、できるだけ泡を立てないよう静かに円を描くように回して溶解する。急激な振盪溶解を避けること。 ②本剤は蛋白製剤であるため、その溶液はわずかに混濁することがあるが、本剤の薬効には影響を及ぼさない。なお、これ以外の外観上の異常を認めた場合には使用しないこと。 ③本剤には防腐剤が含まれていないので、溶解後は速やかに使用すること。 2) 希釈 ①中等症以上の再生不良性貧血、造血幹細胞移植の前治療、造血幹細胞移植後の急性移植片対宿主病に本剤を投与するにあたっては、生理食塩液又は 5%ブドウ糖注射液 500 mL で希釈すること。 ②臓器移植後の急性拒絶反応の治療に本剤を投与するにあたっては、1 バイアル（抗ヒト胸腺細胞ウサギ免疫グロブリンとして 25 mg）あたり、生理食塩液又は 5%ブドウ糖注射液 50 mL で希釈すること。 ③生理食塩液又は 5%ブドウ糖注射液以外の製剤との配合は避けること。 (2) 投与時 1）1 回の投与は 6 時間以上かけて注入するよう流速を設定すること。 2）点滴静注する際には、点滴セットにインラインフィルター（ポアサイズ 0.2 ミクロン）を使用すること。 3）注入後に残った残液は廃棄すること。	へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することが報告されている。]
使用上の注意	**11.その他の注意** (1) 2 週間反復静脈内投与試験（サル）において赤血球パラメータ（赤血球数、ヘマトクリット、ヘモグロビン）の減少がみられた。 (2) 海外市販後の自発報告において本剤投与後の核酸増幅検査で B 型肝炎ウイルスが陽性であった症例が 1 例報告されている。	**9.その他の注意** 蛋白同化ステロイド剤を長期大量に投与された再生不良性貧血の患者等に肝腫瘍の発生が観察されたとの報告がある。
添付文書の作成年月日	2014 年 9 月改訂（第 8 版）	2012 年 3 月改訂〈第 9 版〉

販売名	サイモグロブリン点滴静注用 25 mg	プリモボラン錠 5 mg
備考		

1.8 添付文書（案）

最新の添付文書を参照する

2017 年 X 月改訂（第 7 版）
2017 年 6 月改訂

日本標準商品分類番号	873999

貯法：
室温保存
使用期限：
包装に表示の使用期限内に使用すること

経口~~血小板増加~~造血刺激薬/トロンボポエチン受容体作動薬
劇薬、処方箋医薬品
（注意－医師等の処方箋により使用すること）

レボレード錠®12.5mg
レボレード錠®25mg
REVOLADE® Tablets
エルトロンボパグオラミン錠

承認番号	12.5mg : 22200AMX00960000 25mg : 22200AMX00961000
薬価収載	2010 年 12 月
販売開始	2010 年 12 月
国際誕生	2008 年 11 月
効能追加	2017 年 X 月

【禁忌（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

【組成・性状】

レボレード錠 12.5mg	成分・含量	1 錠中エルトロンボパグ オラミン 15.9mg（エルトロンボパグとして 12.5mg）を含有
	添加物	結晶セルロース、D-マンニトール、デンプングリコール酸ナトリウム、ステアリン酸マグネシウム、ポビドン、ヒプロメロース、酸化チタン、マクロゴール 400、ポリソルベート 80
	性状	白色円形のフィルムコーティング錠
	外形	
	識別コード	GSMZ1 12.5
	大きさ（約）	直径：7.9mm　厚さ：3.5mm　質量：184mg
レボレード錠 25mg	成分・含量	1 錠中エルトロンボパグ オラミン 31.9mg（エルトロンボパグとして 25mg）を含有
	添加物	結晶セルロース、D-マンニトール、デンプングリコール酸ナトリウム、ステアリン酸マグネシウム、ポビドン、ヒプロメロース、酸化チタン、マクロゴール 400、ポリソルベート 80
	性状	白色円形のフィルムコーティング錠
	外形	
	識別コード	GSNX3 25
	大きさ（約）	直径：10.3mm　厚さ：4.2mm　質量：364mg

【効能又は効果】

1. 慢性特発性血小板減少性紫斑病
2. 再生不良性貧血

<効能又は効果に関連する使用上の注意>
1. 慢性特発性血小板減少性紫斑病の場合
(1) 他の治療にて十分な効果が得られない場合、又は忍容性に問題があると考えられる場合に使用すること。
(2) 血小板数、臨床症状からみて出血リスクが高いと考えられる場合に使用すること。
2. 再生不良性貧血の場合
診療ガイドライン等の最新の情報を参考に、本剤の投与が適切と判断される患者に投与すること。（【臨床成績】の項参照）

【用法及び用量】

1. 慢性特発性血小板減少性紫斑病の場合
通常、成人には、エルトロンボパグとして初回投与量 12.5mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、血小板数、症状に応じて適宜増減する。また、1 日最大投与量は 50mg とする。

2. 再生不良性貧血の場合
抗胸腺細胞免疫グロブリンで未治療の場合
抗胸腺細胞免疫グロブリンとの併用において、通常、成人には、エルトロンボパグとして 75mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜減量する。
既存治療で効果不十分な場合
通常、成人には、エルトロンボパグとして初回投与量 25mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜増減する。また、1 日最大投与量は 100mg とする。

<用法及び用量に関連する使用上の注意>
1. 本剤は食事とともに服用すると血中濃度が低下することがあるので、食事の前後 2 時間を避けて空腹時に服用すること。（【薬物動態】の項参照）
2. 制酸剤、乳製品、多価陽イオン（鉄、カルシウム、アルミニウム、マグネシウム、セレン、亜鉛等）含有製剤等とともに服用すると本剤の血中濃度が低下するので、本剤服用の前 4 時間及び後 2 時間はこれらの摂取を避けること。（「3.相互作用」及び【薬物動態】の項参照）
3. 慢性特発性血小板減少性紫斑病の場合
(1) 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記 1）～7）を参照の上、調節すること。本剤の投与開始時及び用量調節時には血小板数及び末梢血塗抹標本検査を含む全血球計算を、血小板数が安定する（血小板数 50,000/μL 以上が少なくとも 4 週間）までは毎週、安定した後は毎月検査することが望ましい。
1) 本剤は治療上必要最小限の用量で使用すること。
2) 本剤の効果は、通常 1～2 週間であらわれるので、効果の確認のためには少なくとも 2 週間は同一用量を維持すること。ただし、肝障害のある患者では、血小板数が定常状態に達するまでの期間が長くなるため、効果の確認のためには少なくとも 3 週間は同一用量を維持すること。
3) 血小板数 50,000/μL を目安とし、血小板数がそれを下回る場合には増量を考慮すること。

4) 血小板数が 50,000/μL～200,000/μL の場合には、出血のリスクを低下できる治療上必要最小限の用量となるよう、適宜減量も考慮すること。
5) 血小板数が 200,000/μL～400,000/μL の場合には本剤を減量すること。
6) 血小板数が 400,000/μL を超えた場合には本剤を休薬すること。この場合血小板数の測定は週に 2 回実施することが望ましい。休薬後、血小板数が 150,000/μL まで減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で投与を再開すること。
7) 本剤の投与量を調節する場合には、通常、12.5mg/日ずつとする。

(2) 本剤を 1 日 50mg、4 週間投与しても血小板数が増加せず、臨床的に問題となる出血傾向の改善が認められない場合には、本剤の投与中止を考慮すること。

4. 再生不良性貧血の場合

(1) 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記を参照の上、調節すること。本剤の投与量を調節する場合には、通常、25mg/日ずつとする。用量調節時には少なくとも 2 週間は同一用量を維持すること。

抗胸腺細胞免疫グロブリンで未治療の患者に投与する場合

1) 抗胸腺細胞免疫グロブリンの投与により肝機能障害があらわれることがあるので、抗胸腺細胞免疫グロブリン投与後、一定期間経過後に本剤の投与を開始すること。（【臨床成績】の項参照）
2) 抗胸腺細胞免疫グロブリンの投与に際しては、併用薬剤の添付文書を熟読すること。
3) 血小板数が 200,000/μL を超えた場合には本剤の減量を考慮すること。
4) 血小板数が 400,000/μL を超えた場合には本剤を休薬すること。休薬後、血小板数が 200,000/μL 未満に減少した場合には、休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。
5) 本剤を 26 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

既存治療で効果不十分な患者に投与する場合

1) 血小板数 50,000/μL を目安とし、血小板数がそれを下回る場合には増量を考慮すること。
2) 血小板数が 100,000/μL～200,000/μL の場合には減量を考慮すること。
3) 血小板数が 200,000/μL を超えた場合には少なくとも 1 週間は本剤を休薬すること。休薬後、血小板数が 50,000/μL 未満に減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。
4) 本剤を 16 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

(2) 3 血球系統の改善（目安として、輸血非依存下で血小板数 50,000/μL を超える、輸血非依存下でヘモグロビン値 10 g/dL を超える、好中球数 1,000/μL を超える）が 8 週間以上持続した場合には本剤の投与量を最大で半量まで減量すること。減量後の投与量で血球改善が更に 8 週間以上持続した場合には、本剤を休薬し、血球数を観察すること。休薬後に血小板数 30,000/μL 未満、ヘモグロビン値 9 g/dL 未満、好中球数 500/μL 未満に低下した場合には休薬前の投与量で投与を再開してもよい。

【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) 肝障害のある患者〔肝障害が悪化するおそれがある。また、血中濃度-時間曲線下面積（AUC）が増加する可能性がある。(【薬物動態】の項参照)〕
(2) 腎障害のある患者〔腎障害患者での有効性及び安全性は確立していないため、これらの患者では血小板数の推移に加えて安全性についても慎重に観察すること。(【薬物動態】の項参照)〕
(3) アンチトロンビンⅢ欠損、抗リン脂質抗体症候群等の血栓塞栓症の素因のある患者〔血栓塞栓症があらわれるおそれがある。〕

2. 重要な基本的注意

(1) 本剤は、血液疾患の治療に十分な経験を持つ医師のもとで使用すること。
(2) 本剤の投与により肝機能障害があらわれることがあるので、本剤の投与開始前及び用量調節時は 2 週間毎、用量の変更がなければ 1 ヵ月毎に肝機能検査（AST（GOT）、ALT（GPT）、ビリルビン等）を実施すること。（「4. 副作用(1)重大な副作用」の項参照）
(3) 血小板数が正常範囲以下であっても血栓塞栓症が認められているため、血小板数にかかわらず血栓塞栓症の発現に注意すること（「4. 副作用(1)重大な副作用」の項参照）。また、血小板数が正常範囲を超えると、血栓塞栓症のリスクが増加する可能性があるので、観察を十分に行い、血小板数が治療の目標とするレベルを超えた場合には、本剤の減量又は休薬を考慮する等注意すること。
(4) 本剤の投与中止後 2 週間以内に血小板数が投与開始前の値まで低下し、出血を生じることがあるので、本剤の投与中止後 4 週間程度は頻回に血小板数を測定すること。（「4. 副作用(1)重大な副作用」の項参照）
(5) 本剤を含むトロンボポエチン受容体作動薬には、骨髄のレチクリン線維の形成及び線維化を進行させる可能性があるので、本剤の投与開始前には末梢血塗抹標本検査を行い、細胞の形態学的異常を確認すること。また、本剤の投与中は、毎月白血球分画を含む全血球計算を検査し、未熟細胞又は異型細胞が観察された場合には、末梢血塗抹標本検査を行い、形態学的異常（涙滴赤血球、有核赤血球、未熟白血球等）の発現を確認し、血球減少の有無も確認すること。これらの異常が認められた場合には、本剤の投与を中止し、骨髄生検（染色による骨髄線維化の評価等）の実施を考慮すること。（「4. 副作用(1)重大な副作用」の項参照）
(6) トロンボポエチン受容体作動薬には、既存の骨髄異形成症候群等の血液悪性腫瘍を進行させる可能性がある。
(7) 重症再生不良性貧血患者を対象とした海外臨床試験において、本剤投与後に染色体異常が認められた例や骨髄異形成症候群及び急性骨髄性白血病への移行例が報告されている。再生不良性貧血患者への本剤の投与中は、定期的に白血球分画を含む全血球計算及び末梢血

塗抹標本検査を行い、幼若細胞や形態学的異常の発現を確認し、血球減少の有無も確認すること。これらの異常が認められた場合には、骨髄検査（染色体異常の評価を含む）の実施を考慮し、本剤の投与継続の可否を判断すること。

(8) げっ歯類を用いた毒性試験において、白内障がみられた。また、臨床試験において白内障が報告されているので、白内障に対する眼科的な検査を定期的に行うことが望ましい。

3. 相互作用

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
ロスバスタチン	本剤とロスバスタチンとの併用により、ロスバスタチンの血中濃度が上昇したとの報告がある。[1] ロスバスタチンの減量を考慮し、患者の状態を慎重に観察すること。（【薬物動態】の項参照）	本剤が OATP1B1 及び BCRP を阻害する可能性がある。（【薬物動態】の項参照）
制酸剤 乳製品 多価陽イオン（鉄、カルシウム、アルミニウム、マグネシウム、セレン、亜鉛等）含有製剤等	同時に服用すると本剤の吸収が著しく妨げられることがあるので、本剤投与の前 4 時間及び後 2 時間はこれらの摂取を避けること。[2-3]（【薬物動態】の項参照）	本剤はこれら多価陽イオンと錯体を形成する。
ロピナビル／リトナビル配合剤	本剤とロピナビル／リトナビル配合剤との併用により、本剤の AUC が減少したとの報告があるので[4]、ロピナビル／リトナビル配合剤と併用する場合には、注意すること。（【薬物動態】の項参照）	機序は不明であるが、ロピナビル／リトナビル配合剤が本剤の代謝酵素を誘導する可能性がある。
シクロスポリン	本剤とシクロスポリンとの併用により、本剤の AUC 及び Cmax が減少したとの報告がある。[5] また、本剤の血中濃度が高値を示したとの報告がある。[6] シクロスポリンと併用する場合には、注意すること。（【薬物動態】の項参照）	機序は不明である。

4. 副作用

慢性特発性血小板減少性紫斑病患者を対象とした国内臨床試験において、23 例中 11 例（48%）に臨床検査値異常を含む副作用が報告された。その主なものは、疲労、ALT（GPT）増加、血小板数増加、低カリウム血症各 2 例（9%）であった（承認時）。また、これら 23 例中 19 例がその後国内長期継続投与試験に移行した。移行した 19 例中 5 例（26%）に副作用が報告された。その主なものは、白内障、胸痛各 2 例（11%）であった。（最終報告時）

慢性特発性血小板減少性紫斑病患者を対象とした海外臨床試験において、135 例中 50 例（37%）に臨床検査値異常を含む副作用が報告された。その主なものは、頭痛 15 例（11%）、ALT（GPT）増加 6 例（4%）、悪心 6 例（4%）、白内障 5 例（4%）、下痢 4 例（3%）であった。（承認時）

抗胸腺細胞免疫グロブリンで未治療の再生不良性貧血患者を対象とした国内臨床試験において、10 例中 5 例（50%）に臨床検査値異常を含む副作用が報告された。その主なものは、筋肉痛 3 例（30%）、血中ビリルビン増加、悪心各 2 例（20%）であった。（承認時）

既存治療で効果不十分な再生不良性貧血患者を対象とした国内臨床試験において、21 例中 12 例（57%）に臨床検査値異常を含む副作用が報告された。その主なものは、血中 ALP 増加、血中ビリルビン増加、肝機能異常、高ビリルビン血症、発疹が各 2 例（10%）であった。（承認時）

重大な副作用及びその他の副作用の発現頻度については、上記の国内臨床試験を併合した集計結果に基づき記載した。また、これらの国内臨床試験であらわれていない副作用については頻度不明とした。

(1) **重大な副作用**

1) **肝機能障害**：AST（GOT、~~4~~2%）、ALT（GPT、~~9~~7%）、ALP（6%）、ビリルビン（~~4~~13%）の増加等の肝機能障害があらわれることがあるので、本剤投与開始前及び投与中は定期的に肝機能検査を行う等、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等適切な処置を行うこと。（「2. 重要な基本的注意」の項参照）

2) **血栓塞栓症**：肺塞栓症（頻度不明~~注1)~~）、深部静脈血栓症（頻度不明~~注1)~~）、一過性脳虚血発作（~~4~~2%）、心筋梗塞（頻度不明~~注1)~~）、虚血性脳卒中（頻度不明~~注1)~~）等の血栓塞栓症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等適切な処置を行うこと。（「2. 重要な基本的注意」の項参照）

3) **出血**：本剤の投与中止後に出血（頻度不明~~注1)~~）を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、適切な処置を行うこと。（「2. 重要な基本的注意」の項参照）

4) **骨髄線維化**：骨髄線維化（頻度不明~~注1)~~）があらわれる可能性があるので、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等適切な処置を行うこと。（「2. 重要な基本的注意」の項参照）

(2) **その他の副作用**

	5%以上	5%未満	頻度不明~~注1)~~
消化器	悪心	~~悪心~~	嘔吐、下痢、口内乾燥
皮膚	—	発疹	脱毛症~~、発疹~~
筋骨格	筋痛	—	背部痛、筋骨格系胸痛、筋骨格痛~~、筋痛~~
その他	~~疲労、血小板数増加、低カリウム血症、白内障、~~頭痛	疲労、血小板数増加、低カリウム血症、白内障	咽頭炎、尿路感染

~~注）海外のみで認められている副作用については頻度不明とした。~~

5. 高齢者への投与

高齢者では一般に生理機能が低下しているので、患者の状態を観察しながら注意して投与すること。

6. 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。〔妊婦への投与に関する安全性は確立しておらず、胎児の血小板への影響についても不明である。動物試験（ラット）において母体毒性用量で胚致死、胎児体重の低値及び低頻度の頸肋（変異）の増加が報告されている。〕

(2) 授乳中の婦人には、投与を避けることが望ましい。やむを得ず投与する場合には、授乳を避けさせること。〔動物試験（ラット）で乳汁中への移行が示唆されている。〕

7. 小児等への投与

小児等に対する安全性及び有効性は確立していない（使用経験がない）。

8. 過量投与

徴候、症状：本剤 5,000mg を過量投与した症例では、軽度の発疹、一過性の徐脈、疲労、AST（GOT）及び ALT（GPT）上昇が報告され、血小板数は 929,000/μL まで増加した。

処置：吸収を抑えるために、カルシウム、アルミニウム、マグネシウム等の多価陽イオンを含有する製剤の経口投与を考慮すること。また、血小板数の検査を頻回に行い、患者の状態を十分に観察すること。本剤の腎排泄の寄与は小さく、血漿蛋白結合率が高いため、血液透析は有効な除去法ではないと考えられる。

9. 適用上の注意

(1) **薬剤交付時：**PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。〔PTP シートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔を起こして縦隔洞炎等の重篤な合併症を併発することが報告されている。〕

(2) PTP シートからの取り出しは、裏のシールを剥がした後、指の腹で押し出すこと。

10. その他の注意

本剤はヒト及びチンパンジー以外のトロンボポエチン受容体に対し親和性をもたず、ヒト及びチンパンジー以外の動物に対して薬理活性を示さない。このため毒性試験において、薬理活性に付随する影響は評価されていない。

【薬物動態】

1. 血中濃度

日本人健康成人男性を対象に、本剤 25、50 あるいは 75mg を空腹時単回及び反復経口投与した時、本剤は速やかに吸収され、投与後 3～4 時間（中央値）で最高血漿中濃度（Cmax）に達した。単回及び反復投与時の曝露量（Cmax 及び AUC）は、投与量の増加に対し、ほぼ線形的に増加した。また、本剤は反復投与開始後約 7 日で定常状態に達すると考えられた。表-1 に薬物動態パラメータを示した。[7, 8)]

表-1 健康成人に単回及び 10 日間反復経口投与した時の薬物動態パラメータ

投与量 (mg)	例数	Cmax (μg/mL)	AUC[a)] (μg·hr/mL)	tmax (hr)	$t_{1/2}$ (hr)	CL/F (L/hr)
単回投与						
25	10	3.56±1.13	55.4±23.2	3.0(2.0-5.0)	29.6±5.0	0.534±0.256
50	10	6.44±2.14	106.6±32.4	3.0(1.5-5.0)	31.0±5.9	0.525±0.218
75	10	8.39±2.84	134.9±37.4	3.0(2.0-6.0)	32.4±7.6	0.604±0.201
反復投与						
25	10	4.83±1.17	58.9±18.4	3.0(1.5-5.0)	39.7±3.2	0.478±0.196
50	9	10.6±2.38	133.8±33.6	4.0(2.0-5.0)	51.3±12.2	0.396±0.102
75	10	12.78±2.84	164.2±35.5	4.0(2.0-5.0)	47.8±11.5	0.476±0.102

算術平均値±標準偏差、tmax は中央値（範囲）

a）単回投与：$AUC_{0-\infty}$、反復投与：$AUC_{0-\tau}$

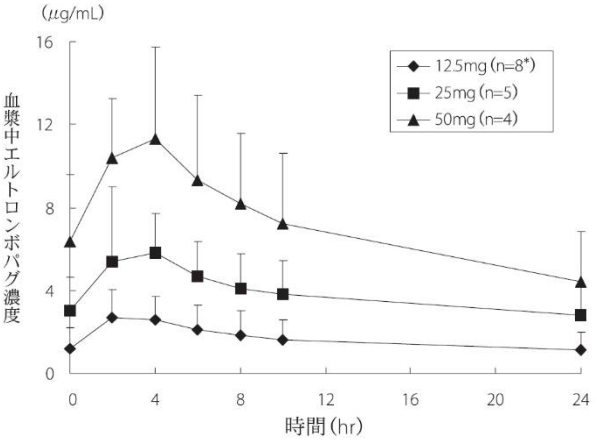
日本人特発性血小板減少性紫斑病患者に本剤 12.5、25 あるいは 50mg を投与した時の定常状態における薬物動態パラメータを表-2 に、血漿中エルトロンボパグ濃度推移を図-1 に示した。[9, 10)]

表-2 日本人特発性血小板減少性紫斑病患者の定常状態における薬物動態パラメータ

投与量 (mg)	例数	Cmax (μg/mL)	tmax (hr)	$AUC_{0-\tau}$ (μg·hr/mL)	$t_{1/2}$[b)] (hr)
12.5	8	2.99±1.25	3.19 (2.00-4.17)	41.64±24.36[a)]	19.5±7.16[a)]
25	5	6.78±2.62	4.00 (2.00-4.00)	92.53±41.12	27.0±7.66
50	4	11.88±3.93	2.97 (1.92-4.17)	171.6±75.24	18.2±4.94

算術平均値±標準偏差、tmax は中央値（範囲）

a）n=7　b）24 時間までのポイントから算出のため、参考値



*：24時間のポイントのみ　n＝7

図-1 日本人特発性血小板減少性紫斑病患者の定常状態における血漿中エルトロンボパグ濃度推移（平均値±標準偏差）

なお、日本人及び外国人の成績を用いた母集団薬物動態解析の結果、エルトロンボパグの $AUC_{0-\tau}$ は、非東アジア系特発性血小板減少性紫斑病患者（主に白人）と比較して、東アジア系特発性血小板減少性紫斑病患者で約 87%高値を示した。また、日本人特発性血小板減少性紫斑病患者の $AUC_{0-\tau}$ は、非東アジア系特発性血小板減少性紫斑病患者の $AUC_{0-\tau}$（母集団薬物動態解析推定値）に比べ、約 85%高値を示した。[11, 12)]

抗胸腺細胞免疫グロブリンに治療抵抗性若しくは再発又は抗胸腺細胞免疫グロブリン治療が受けられない中等症以上の日本人再生不良性貧血患者に本剤 25mg を投与した時の定常状態における薬物動態パラメータを表-3 に示した。[6)]

表-3 日本人再生不良性貧血患者の定常状態における薬物動態パラメータ

投与量 (mg)	例数	Cmax (μg/mL)	tmax (hr)	$AUC_{0-\tau}$[a)] (μg·hr/mL)
25	5	6.41 ± 4.20	2.00 (1.90-7.58)	99.20 ± 119.0

算術平均値±標準偏差、tmax は中央値（範囲）

a）n=3

2. 分布

本剤は *in vitro* 試験の結果、2～100μg/mL の濃度範囲で99.9%以上がヒト血漿蛋白質と結合し、主な結合蛋白質はアルブミンであった。

本剤は BCRP の基質であったが、P-糖蛋白質（Pgp）及び OATP1B1 の基質ではないことが確認された。また、本剤は *in vitro* 試験で OATP1B1 及び BCRP を阻害（IC_{50} 値：いずれも約 2.7μM）した。

3. 代謝

本剤は *in vitro* 試験の結果、最大 100μM の濃度で CYP1A2、CYP2A6、CYP2C19、CYP2D6、CYP2E1、CYP3A4/5 及び CYP4A9/11 の活性を阻害しなかったが、CYP2C8（パクリタキセル）及び CYP2C9（ジクロフェナク）の活性を阻害し、IC_{50} 値はそれぞれ 24.8μM（11μg/mL）及び 20.2μM（8.9μg/mL）であった。[13)]

健康成人男性に本剤 75mg を反復経口投与した時、本剤は CYP1A2、CYP2C19、CYP2C9 及び CYP3A4 の活性を阻害及び誘導しなかった（外国人データ）。[14)]

本剤は *in vitro* 試験の結果、UGT1A1、UGT1A3、UGT1A4、UGT1A6、UGT1A9、UGT2B7 及び UGT2B15 の活性を阻害（IC_{50} 値：3.0～33μM）した。[13)]

健康成人男性に本剤の ^{14}C-標識体 75mg を経口投与した時、酸化体、グルクロン酸抱合体、グルタチオン抱合体又はシステイン抱合体に代謝された（外国人データ）。また、*in vitro* 試験の結果、本剤の酸化的代謝には CYP1A2 及び CYP2C8 が、グルクロン酸抱合には UGT1A1 及び UGT1A3 が関与していると考えられた。[13)]

4. 排泄（外国人データ）[15)]

本剤の主な排泄経路は糞中であり、本剤の ^{14}C-標識体 75mg を単回経口投与後 168 時間までに、平均で投与量の 30.7%が尿中に、投与量の 58.9%が糞中に排泄された。尿中に未変化体（エルトロンボパグ）は認められず、糞中には投与量の約 20%が未変化体として排泄された。

5. 食事の影響（外国人データ）

健康成人に本剤 50mg を、乳製品を含む高カロリー、高脂肪の食事（カルシウム 427mg 含有）とともに単回経口投与した時、空腹時に比べて $AUC_{0-\infty}$は 59%、Cmax は 65%低下した。また、本剤 75mg を高脂肪又は低脂肪のカルシウム含有量の低い（50mg 未満）食事とともに投与した時、いずれもエルトロンボパグの $AUC_{0-\infty}$及び Cmax に影響を与えなかった。[2)]

（参考）

健康成人にエルトロンボパグの経口懸濁液用粉末（以下、PfOS）製剤 25mg（国内未承認）を高カルシウム食（カルシウム約 448mg）摂取 2 時間前に単回投与した時のエルトロンボパグの $AUC_{0-\infty}$及び Cmax は、空腹時投与と比べてそれぞれ 20%及び 14%低下した。一方、高カルシウム食摂取 2 時間後に PfOS 製剤 25mg を単回投与した時、エルトロンボパグの $AUC_{0-\infty}$及び Cmax は、空腹時投与と比べてそれぞれ 47%及び 48%低下した。[3)]

6. 性別・年齢[11)]

母集団薬物動態解析の結果、女性特発性血小板減少性紫斑病患者における $AUC_{0-\tau}$は、男性に比べて約 50%高かった。また、年齢は本剤の薬物動態に影響を及ぼさなかった。

7. 腎障害患者における薬物動態（外国人データ）[16, 17)]

腎障害患者に本剤 50mg を単回経口投与した時のエルトロンボパグの $AUC_{0-\infty}$の幾何平均値は健康成人と比べて軽度の腎障害患者（CLcr：50～80mL/min）で 32%、中等度の腎障害患者（CLcr：30～49mL/min）で 36%、重度の腎障害患者（CLcr：30mL/min 未満）で 60%低かった。しかしながら、健康成人及び軽度～重度の腎障害患者の $AUC_{0-\infty}$の範囲（最小値～最大値）は、順に 32.65～99.32、22.54～83.51、21.10～109.95、3.44～117.54μg･hr/mL とばらつきが大きかった。

8. 肝障害患者における薬物動態（外国人データ）[16, 17)]

肝障害患者に本剤 50mg を単回経口投与した時のエルトロンボパグの $AUC_{0-\infty}$の幾何平均値は健康成人と比べて軽度の肝障害患者（Child-Pugh スコア：5～6）で 41%、中等度の肝障害患者（Child-Pugh スコア：7～9）で 93%、重度の肝障害患者（Child-Pugh スコア：10 以上）で 80%高かった。しかしながら、健康成人及び軽度～重度の肝障害患者の $AUC_{0-\infty}$の範囲（最小値～最大値）は、順に 34.46～174.99、35.86～127.74、57.64～263.22、32.26～263.51μg･hr/mL とばらつきが大きかった。

9. 相互作用~~（外国人データ）~~

(1) **制酸剤（外国人データ）**[2)]

健康成人に、本剤 75mg と多価陽イオン（水酸化アルミニウム及び炭酸マグネシウム）を含む制酸剤を単回併用投与した時、エルトロンボパグの $AUC_{0-\infty}$及び Cmax はともに約 70%低下した。

(2) **ロスバスタチン（外国人データ）**[1)]

健康成人に本剤 75mg 投与の定常状態時に、OATP1B1 及び BCRP の基質であるロスバスタチン 10mg を単回併用投与した時、単独投与時に比べてロスバスタチンの $AUC_{0-\infty}$は 55%、Cmax は 103%増加した（n=39）。層別解析の結果、アジア人では、$AUC_{0-\infty}$は 32%、Cmax は 61%増加した（n=21）。なお、ロスバスタチンは、本剤の薬物動態に影響を及ぼさなかった。

(3) **ロピナビル/リトナビル配合剤（外国人データ）**[4)]

健康成人にロピナビル 400mg/リトナビル 100mg 配合剤 1 日 2 回反復投与時に、本剤 100mg を単回併用投与した時、単独投与時に比べてエルトロンボパグの $AUC_{0-\infty}$は 17%低下した（n＝40）。

(4) **シクロスポリン**

健康成人に本剤 50mg 単回投与時に、シクロスポリン 200mg を単回併用投与した時、単独投与時に比べてエルトロンボパグの $AUC_{0-\infty}$及び Cmax はそれぞれ 18%及び 25%低下した（n=37 及び n=39）。また、シクロスポリン 600mg を単回併用投与した時、単独投与時に比べてエルトロンボパグの $AUC_{0-\infty}$及び Cmax はそれぞれ 24%及び 39%低下した（n=33 及び n=37）。（外国人データ）[5)]

既存治療で効果不十分な再生不良性貧血患者に本剤 50 mg を 1 日 1 回反復投与した時のエルトロンボパグのトラフ値（平均値）は、シクロスポリン非併用患者（n=12）と比べてシクロスポリン 25～250 mg を 1 日 2 回反復併用投与した患者で 73%高値を示した（n=8）。（日本人データ）[6)]

~~（本剤の国内承認用量は 12.5～50mg を 1 日 1 回投与である。）~~

【臨床成績】

1. 慢性特発性血小板減少性紫斑病患者を対象とした臨床試験

(1) 国内二重盲検比較試験[8, 9)]

既治療の慢性特発性血小板減少性紫斑病患者（血小板数が30,000/μL 未満）23 例を対象として、二重盲検下で本剤 12.5 又は 25mg を 1 日 1 回空腹時に、7 週間投与した。投与は 12.5mg から開始し、投与 3 週目の血小板数に応じて 25mg に用量調節した。その結果、投与 6 週目における本剤の有効率（血小板数が 50,000/μL 以上、400,000/μL 以下に増加した患者の割合［95%信頼区間］）は 60%［32.29,83.66］であり、プラセボ（0%［0.00,36.94］）に比べて明らかな血小板数増加効果が認められた。

二重盲検期終了後は、本剤の投与期間が 26 週間になるように本剤を継続投与した。用量は血小板数に応じて 12.5、25 又は 50mg に調節した。その結果、投与 5 週目から 26 週目までの血小板数（中央値）は 50,000/μL を超えて推移し、血小板数の増加に伴い出血症状が改善した（図-2、3）。

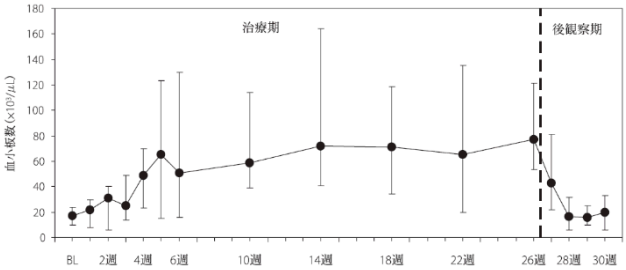


図-2 血小板数（中央値）の推移：TRA108109 試験

Bars represent the 25th and 75th percentiles

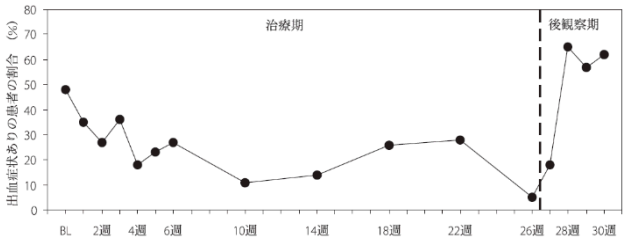


図-3 出血症状がみられた患者の割合の推移：TRA108109 試験

(2) 国内長期継続投与試験[18, 19)]

上記 23 例中 19 例が国内長期継続投与試験に移行した。用量は血小板数に応じて 12.5～50mg に調節し、19 例中 10 例では異なる用量の組み合わせや投与間隔の調節も行った。その結果、長期継続投与試験でも血小板数の増加と出血症状の改善が示された。投与期間の中央値は 833.0 日（範囲：301～981 日）であった。（最終報告時）

(3) 海外二重盲検比較試験[20, 21)]

既治療の慢性特発性血小板減少性紫斑病患者（血小板数が30,000/μL 未満）197 例を対象として、本剤 25、50 又は 75mg を 1 日 1 回空腹時に、26 週間投与する二重盲検試験を実施した（本剤 135 例、プラセボ 62 例）。投与は 50mg から開始し、血小板数に応じて 25、50 又は 75mg に用量調節した。その結果、本剤群のプラセボ群に対する血小板数増加効果のオッズ比［99%信頼区間］は 8.2［3.59,18.73］であり、有意に高かった（p＜0.001）。また、本剤群の血小板数（中央値）は、投与 1 週目より増加し、投与 2～26 週目まで 50,000/μL を超えて推移した（図-4）。本剤投与により出血症状（WHO Bleeding Scale を用いて評価、Grade2～4）が認められた患者の割合について、本剤群のプラセボ群に対するオッズ比［95%信頼区間］は 0.35［0.19,0.64］であり、本剤群の方が有意に低下した（p＜0.001）。

（本剤の国内承認用量は 12.5～50mg を 1 日 1 回投与である。）

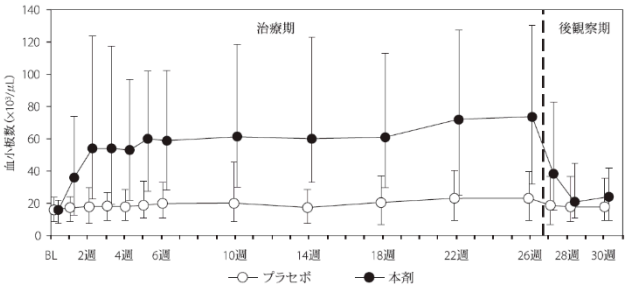


図-4 血小板数（中央値）の推移

2. 再生不良性貧血患者を対象とした臨床試験

(1) 抗胸腺細胞免疫グロブリンで未治療の再生不良性貧血患者を対象とした国内第 II/III 相試験[22)]

抗胸腺細胞免疫グロブリンで未治療の再生不良性貧血患者（中等症以上）10 名を対象として、抗胸腺細胞免疫グロブリン／シクロスポリンに本剤を併用投与した。抗胸腺細胞免疫グロブリン／シクロスポリン開始後、15 日目から初回投与量として本剤 75mg を 1 日 1 回空腹時に経口投与し、血小板数に応じて 2 週間ごとに 25mg ずつ減量した。その結果、投与 26 週時の奏効率［95%信頼区間］は 70.0%［34.8,93.3］であった。なお、奏効率は寛解（輸血非依存かつ血球数の改善）が得られた患者の割合と定義した。

(2) 既存治療で効果不十分な再生不良性貧血患者を対象とした国内第 II/III 相試験[6)]

抗胸腺細胞免疫グロブリンに治療抵抗性若しくは再発又は抗胸腺細胞免疫グロブリン治療が受けられない再生不良性貧血患者（中等症以上）21 名を対象として、初回投与量として本剤 25mg を 1 日 1 回空腹時に経口投与し、血小板数に応じて 2 週間ごとに 25mg ずつ、最大 100mg/日まで用量調節した。その結果、投与 26 週時における血液学的反応率［95%信頼区間］は、47.6%［25.7,70.2］であった。なお、血液学的反応率は 1 系統以上の血球に改善〔血小板数が≥20,000/μL 増加又は血小板輸血非依存、ヘモグロビン値が≥1.5 g/dL 増加（投与前値が 9 g/dL 未満の場合）又は赤血球輸血量の減少、好中球数が≥100%（投与前値が 500/μL 未満の場合）又は≥500/μL 増加のうち、1 つ以上該当〕を認めた患者の割合と定義した。投与継続により血球系統（血小板、赤血球及び好中球）の更なる改善を認め、投与 26 週時点で 2 系統に改善を認めた 4 名では投与 52 週時点には 3 系統が改善した。

【薬効薬理】

1. 作用機序[23)]

ヒトトロンボポエチン受容体との特異的な相互作用を介して、トロンボポエチンのシグナル伝達経路の一部を活性化することにより~~骨髄前駆細胞から巨核球及び~~

~~骨髄前駆に至る過程における~~巨核球及び骨髄前駆細胞の増殖及び分化を促進させ~~、その結果として血小板数を増加させ~~る。

2. 血小板産生促進作用 [23)]

(1) *In vitro* において、ヒト巨核球系細胞株の増殖を促進させ、ヒト骨髄前駆細胞の巨核球への分化を誘導した。

(2) チンパンジーへの 5 日間経口投与により、最終投与の6～10 日後に血小板数は約 2 倍に増加した。

3. 造血促進作用（再生不良性貧血） [24)]

In vitro 及び *in vivo* において、ヒト骨髄幹細胞及び前駆細胞の増殖及び分化を促進させ、多系統の血球が増加した。

4. 正常血小板機能に及ぼす影響 [25)]

ヒト正常血小板においてアデノシン二リン酸誘発の血小板凝集に影響を及ぼさず、P-セレクチンの発現を誘導しなかった。

【有効成分に関する理化学的知見】

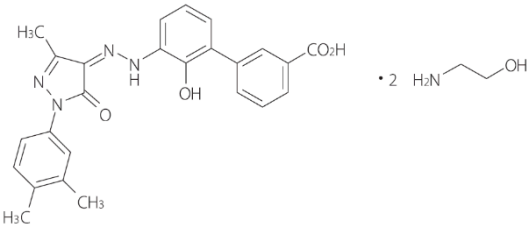
一般名：エルトロンボパグ　オラミン（Eltrombopag Olamine）

化学名：3'-｛(2*Z*)-2-［1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene］hydrazino｝-2'-hydroxybiphenyl-3-carboxylic acid bis(2-aminoethanol)

分子式：$C_{25}H_{22}N_4O_4$・2（C_2H_7NO）

分子量：564.63

構造式：



性　状：赤色～褐色の粉末

分配係数（log P）：4.05

【承認条件】

医薬品リスク管理計画を策定の上、適切に実施すること。

【包装】

レボレード錠 12.5mg70 錠（7 錠×10）両面アルミニウム PTP

レボレード錠 25mg　70 錠（7 錠×10）両面アルミニウム PTP

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【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下さい。

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1.8.2 効能・効果（案），用法・用量（案）及びその設定根拠

目　次

目　次 2
略号一覧 3
1 効能又は効果（案）及びその設定根拠 4
1.1 効能又は効果（案） 4
1.2 効能又は効果（案）の設定根拠 4
1.2.1 薬理学的特性 4
1.2.2 臨床試験成績 4
1.2.3 まとめ 5
1.3 効能又は効果に関連する使用上の注意（案） 6
1.4 効能又は効果に関連する使用上の注意（案）の設定根拠 6
2 用法及び用量（案）及びその設定根拠 6
2.1 用法及び用量（案） 6
2.2 用法及び用量（案）の設定根拠 7
2.3 用法及び用量に関連する使用上の注意（案） 8
2.4 用法及び用量に関連する使用上の注意（案）の設定根拠 10
3 参考文献 11

略号一覧

略号	省略していない表現 (英)	省略していない表現 (日)
AA	aplastic anemia	再生不良性貧血
AML	acute myeloid leukemia	急性骨髄性白血病
ATG	anti-thymocyte globulin	抗ヒト胸腺細胞免疫グロブリン
CsA	ciclosporin	シクロスポリン
ITP	idiopathic thrombocytopenic purpura	特発性血小板減少性紫斑病
MDS	myelodysplastic syndrome	骨髄異形成症候群
NIH	National Institute of Health	米国国立衛生研究所
SAA	severe aplastic anemia	重症再生不良性貧血
TPO-R	thrombopoietin-receptor	トロンボポエチン受容体

1 効能又は効果（案）及びその設定根拠

1.1 効能又は効果（案）

1. 慢性特発性血小板減少性紫斑病
2. 再生不良性貧血

（下線：追記）

1.2 効能又は効果（案）の設定根拠

1.2.1 薬理学的特性

エルトロンボパグ　オラミン（以下，エルトロンボパグ）は，経口投与可能なトロンボポエチン受容体（thrombopoietin-receptor，TPO-R）の低分子アゴニストである。エルトロンボパグは，巨核球，骨髄幹細胞及び前駆細胞に存在する TPO-R の膜貫通ドメインとの相互作用を介して骨髄幹細胞から巨核球に至る過程における細胞の分化を促進させる（Erickson-Miller et al. 2010, Sun et al. 2012）。

TPO-R は血小板・巨核球系細胞のみならず造血幹細胞や他の系統の前駆細胞にも発現しており（Alexander et al. 1996），エルトロンボパグは TPO-R を介して未分化な造血幹細胞に作用し造血を促進させる作用があることが示唆されている。

1.2.2 臨床試験成績

国内で実施した以下の 2 試験より，難治性及び未治療再生不良性貧血（aplastic anemia，AA）患者に対するエルトロンボパグの有効性及び安全性を評価した。結果の概略を以下に示す。

- 抗ヒト胸腺細胞免疫グロブリン（anti-thymocyte globulin，ATG）治療に抵抗性又は再発，もしくは ATG 治療を受けられない中等症以上の AA 患者を対象とした第 II/III 相試験［CETB115E1201 試験（E1201 試験）］
- 中等症以上の未治療 AA 患者を対象にエルトロンボパグとウサギ ATG / シクロスポリン（ciclosporin，CsA）を併用する第 II/III 相試験［CETB115E1202 試験（E1202 試験）］

難治性再生不良性貧血患者に対する有効性（E1201 試験）

- エルトロンボパグ投与により，他に治療選択肢がない難治性 AA 患者の 47.6%に 1 系統以上の血球改善効果を示した（投与 26 週時点）。
- エルトロンボパグの投与継続により血球改善効果はさらに向上し，投与 52 週時点では反応例の 10 名中 4 名に 3 系統の血球改善を認めた。
- エルトロンボパグによる血液学的反応には持続性が認められ，反応例における効果持続期間の中央値は 9.12 ヵ月であった。また，投与 52 週までに明らかな再発は認められていない。

- ベースライン時に血小板輸血依存であった 6 名中 5 名（83.3%）で輸血量が減少し，うち 4 名が輸血非依存となった。また，赤血球輸血依存であった 19 名中 14 名（73.7%）で輸血量が減少し，うち 9 名が輸血非依存となった。

未治療再生不良性貧血患者に対する有効性（E1202 試験）

- エルトロンボパグの併用により 10 名中 7 名の被験者に奏効が得られた。この結果は，ウサギ ATG / CsA の公表論文に基づく奏効率（概ね 50 %）と比べて高い結果であった。また，部分集団解析の結果，PNH 型血球の有無にかかわらず治療効果が示された。
- 治療 26 週までに奏効を認めた被験者については，少なくとも治療 14 週までに好中球数，網赤血球数が増加し，造血の回復傾向が示された。
- 治療 26 週までに奏効を認めた被験者における効果持続期間の中央値は 2.33 ヵ月であった（ただし，データカットオフ時点までの成績）。また，治療 26 週までに再発は認められていない。
- ベースライン時に血小板輸血依存であった 8 名中 6 名（75.0%）で輸血量が減少し，うち 5 名（62.5%）が輸血非依存となった。また，赤血球輸血依存であった 6 名中 4 名（66.7%）が輸血非依存となった。
- 主要解析（26 週解析）に加えて実施した 52 週解析の結果から，中等症以上の未治療 AA 患者に対するウサギ ATG / CsA とエルトロンボパグの併用投与の治療効果の持続性が確認された。
  - 治療 26 週時点で奏効を認めた 7 名中 6 名が治療 52 週時点でも奏効が維持された。
  - 治療 52 週までに奏効を認めた被験者における効果持続期間の中央値は 8.31 ヵ月であった（52 週解析のデータカットオフ時点までの成績）。また，治療 52 週までに再発が認められた被験者は 1 名のみであった。
  - ベースライン時に血小板輸血依存であった 8 名中 5 名（62.5%）が治療 52 週までに少なくとも 1 回輸血非依存となり，うち 4 名は治療 52 週時点でも輸血非依存状態が持続していた。また，ベースライン時に赤血球輸血依存であった 6 名中 4 名（66.7%）が治療 52 週までに少なくとも 1 回輸血非依存となり，うち 3 名は治療 52 週時点でも輸血非依存状態が持続していた。

再生不良性貧血患者に対する安全性（E1201 及び E1202 試験）

- 難治性 AA 患者に対する投与，未治療 AA 患者におけるウサギ ATG / CsA との併用投与において，エルトロンボパグの忍容性は良好であり，新たな懸念となる事象は認められなかった。

1.2.3 まとめ

非臨床データの報告より，エルトロンボパグは TPO-R を介して未分化な造血幹細胞に作用し造血を促進させる作用があることが示唆され，国内 2 試験の結果から，エルトロンボパグは日本人

AA 患者の汎血球減少を改善するとともに，ウサギ ATG / CsA との併用において既存治療の治療効果を上回る結果が示された。以上を踏まえ，エルトロンボパグの効能又は効果（案）は「再生不良性貧血」と設定した。

1.3 効能又は効果に関連する使用上の注意（案）

1. 慢性特発性血小板減少性紫斑病の場合

(1) 他の治療にて十分な効果が得られない場合、又は忍容性に問題があると考えられる場合に使用すること。

(2) 血小板数、臨床症状からみて出血リスクが高いと考えられる場合に使用すること。

2. 再生不良性貧血の場合

診療ガイドライン等の最新の情報を参考に、本剤の投与が適切と判断される患者に投与すること。（【臨床成績】の項参照）

（下線：追記）

1.4 効能又は効果に関連する使用上の注意（案）の設定根拠

2. 再生不良性貧血の場合

診療ガイドライン等の最新の情報を参考に、本剤の投与が適切と判断される患者に投与すること。（【臨床成績】の項参照）

（下線：追記）

本剤の効能又は効果（案）は，E1201 試験，E1202 試験成績に基づき設定した。本剤の適応患者の選択に際し，これらの試験の【臨床成績】の内容を熟知し，本剤の投与対象及び有効性を十分理解する必要があると考え，使用上の注意として注意喚起することとした。また，ATG/CsA の治療対象や CsA 単独投与の効果判定時期などについては診療ガイドライン（再生不良性貧血診療の参照ガイド平成 26 年度改訂版）を参照することで，本剤の適切な投与対象を特定できると考え，診療ガイドライン等の最新の情報を参考とする旨を記載した。

2 用法及び用量（案）及びその設定根拠

2.1 用法及び用量（案）

1. 慢性特発性血小板減少性紫斑病の場合

通常、成人には、エルトロンボパグとして初回投与量 12.5mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、血小板数、症状に応じて適宜増減する。また、1 日最大投与量は 50mg とする。

2. 再生不良性貧血の場合

抗胸腺細胞免疫グロブリンで未治療の場合

抗胸腺細胞免疫グロブリンとの併用において、通常、成人には、エルトロンボパグとして75mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜減量する。
既存治療で効果不十分な場合
通常、成人には、エルトロンボパグとして初回投与量 25mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜増減する。また、1 日最大投与量は 100mg とする。

（下線：追記）

2.2 用法及び用量（案）の設定根拠

抗胸腺細胞免疫グロブリンで未治療の場合の用法及び用量

ATG で未治療の場合のエルトロンボパグの用法・用量は E1202 試験の成績に基づき設定した。

ATG / CsA の治療開始直後には血小板数が著減するため，血小板数を可能な限り早期に改善することを目的としてエルトロンボパグの初回投与量を高用量に設定する必要がある。E1202 試験では，未治療の SAA 患者を対象とした外国 NIH 12-H-0150 試験（150 試験）における東アジア人の用法・用量（75 mg，1 日 1 回投与）に基づき，日本人未治療 AA 患者に対するエルトロンボパグの初回投与量を 75 mg と設定した。また，投与開始後の用量調節は血小板数に応じて 2 週間ごとに 25 mg ずつ減量することとした。なお，E1201 試験では 1 日最大投与量を 100 mg に設定したが，外国 150 試験においてエルトロンボパグ 150 mg とウマ ATG / CsA との併用時のエルトロンボパグの $AUC_{0-\tau}$ の幾何平均値（694 µg.h/mL）が他の疾患における Dose-normalized $AUC_{0-\tau}$（ITP 患者：336 µg.h/mL）に比べ高かったことから，E1202 試験の初回投与量は 75 mg とした。

E1202 試験の結果，ATG / CsA にエルトロンボパグを追加投与した際の有効性及び安全性が確認されたことにより（1.2.2 項），E1202 試験で使用した用法及び用量を ATG 治療と併用する際の用法及び用量と設定した。

既存治療で効果不十分な場合の用法及び用量

既存治療で効果不十分な患者に対するエルトロンボパグの用法及び用量は E1201 試験の成績に基づき設定した。

E1201 試験の用法・用量は，治療抵抗性の SAA 患者を対象とした外国 NIH 09-H-0154 試験（154 試験）における東アジア人の用法・用量に基づき設定した。154 試験では，東アジア人の用量は非東アジア人の半量（25 mg を 1 日 1 回投与）と設定されていたため，E1201 試験では日本人難治性 AA 患者に対するエルトロンボパグの初回投与量を 25 mg/日と設定し，投与開始後の用量調節は血小板数に応じて 2 週間ごとに 25 mg ずつ，最大 100 mg まで増量することとした。

AA 等の造血不全症では，エルトロンボパグは骨髄微小環境の造血前駆細胞や造血幹細胞を刺激する必要がある。一方，既承認効能の慢性特発性血小板減少性紫斑病（idiopathic

thrombocytopenic purpura，ITP）患者では，エルトロンボパグは巨核球の分化後期（主に巨核球系前駆細胞）に作用する。さらに，ITP 患者では造血機能及び骨髄細胞密度は正常であるのに対し，AA 患者の骨髄は低形成である。以上を踏まえ，AA 患者の治療においては，エルトロンボパグを高用量で使用し，かつ長期間の治療が必要となると考えられた。治療抵抗性の SAA 患者を対象とした外国 154 試験では，血液学的反応が認められたほとんどすべての被験者において 1 日最大投与量である 150 mg（東アジア人では 75 mg）まで増量が行われ，当該投与量の忍容性も良好であったことから，治療効果のさらなる向上を期待して日本人患者における 1 日最大投与量を 100 mg（日本人健康成人男性においてエルトロンボパグの忍容性が確認されている最高用量）と設定し，E1201 試験を実施した。

E1201 試験の結果，既存治療が効果不十分又は不適当な AA 患者におけるエルトロンボパグの有効性及び安全性が確認されたことにより（1.2.2 項），E1201 試験で使用した用法及び用量を難治性 AA 患者に対する用法及び用量と設定した。

2.3 用法及び用量に関連する使用上の注意（案）

1. 本剤は食事とともに服用すると血中濃度が低下することがあるので、食事の前後 2 時間を避けて空腹時に服用すること。（【薬物動態】の項参照）
2. 制酸剤、乳製品、多価陽イオン（鉄、カルシウム、アルミニウム、マグネシウム、セレン、亜鉛等）含有製剤等とともに服用すると本剤の血中濃度が低下するので、本剤服用の前 4 時間及び後 2 時間はこれらの摂取を避けること。（「3.相互作用」及び【薬物動態】の項参照）
3. <u>慢性特発性血小板減少性紫斑病の場合</u>

(1) 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記 1）～7）を参照の上、調節すること。本剤の投与開始時及び用量調節時には血小板数及び末梢血塗抹標本検査を含む全血球計算を、血小板数が安定する（血小板数 50,000/μL 以上が少なくとも 4 週間）までは毎週、安定した後は毎月検査することが望ましい。

1) 本剤は治療上必要最小限の用量で使用すること。
2) 本剤の効果は、通常 1～2 週間であらわれるので、効果の確認のためには少なくとも 2 週間は同一用量を維持すること。ただし、肝障害のある患者では、血小板数が定常状態に達するまでの期間が長くなるため、効果の確認のためには少なくとも 3 週間は同一用量を維持すること。
3) 血小板数 50,000/μL を目安とし、血小板数がそれを下回る場合には増量を考慮すること。
4) 血小板数が 50,000/μL～200,000/μL の場合には、出血のリスクを低下できる治療上必要最小限の用量となるよう、適宜減量も考慮すること。
5) 血小板数が 200,000/μL～400,000/μL の場合には本剤を減量すること。

6) 血小板数が 400,000/μL を超えた場合には本剤を休薬すること。この場合血小板数の測定は週に 2 回実施することが望ましい。休薬後、血小板数が 150,000/μL まで減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で投与を再開すること。

7) 本剤の投与量を調節する場合には、通常、12.5mg/日ずつとする。

(2) 本剤を 1 日 50mg、4 週間投与しても血小板数が増加せず、臨床的に問題となる出血傾向の改善が認められない場合には、本剤の投与中止を考慮すること。

4. 再生不良性貧血の場合

(1) 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記を参照の上、調節すること。本剤の投与量を調節する場合には、通常、25mg/日ずつとする。用量調節時には少なくとも 2 週間は同一用量を維持すること。

抗胸腺細胞免疫グロブリンで未治療の患者に投与する場合

1) 抗胸腺細胞免疫グロブリンの投与により肝機能障害があらわれることがあるので、抗胸腺細胞免疫グロブリン投与後、一定期間経過後に本剤の投与を開始すること。（【臨床成績】の項参照）

2) 抗胸腺細胞免疫グロブリンの投与に際しては、併用薬剤の添付文書を熟読すること。

3) 血小板数が 200,000/μL を超えた場合には本剤の減量を考慮すること。

4) 血小板数が 400,000/μL を超えた場合には本剤を休薬すること。休薬後、血小板数が 200,000/μL 未満に減少した場合には、休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。

5) 本剤を 26 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

既存治療が効果不十分又は不適当な患者に投与する場合

1) 血小板数 50,000/μL を目安とし、血小板数がそれを下回る場合には増量を考慮すること。

2) 血小板数が 100,000/μL～200,000/μL の場合には減量を考慮すること。

3) 血小板数が 200,000/μL を超えた場合には少なくとも 1 週間は本剤を休薬すること。休薬後、血小板数が 50,000/μL 未満に減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。

4) 本剤を 16 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

(2) 3 血球系統の改善（目安として、輸血非依存下で血小板数 50,000/μL を超える、ヘモグロビン値 10 g/dL を超える、好中球数 1,000/μL を超える）が 8 週間以上持続した場合には本剤の投与量を最大で半量まで減量すること。減量後の投与量で血球改善が更に 8 週間以上持続した場合には、本剤を休薬し、血球数を観察すること。休薬後に血小板数 30,000/μL

未満、ヘモグロビン値 9 g/dL 未満、好中球数 500/μL 未満に低下した場合には休薬前の投与量で投与を再開してもよい。

（下線：追記）

2.4 用法及び用量に関連する使用上の注意（案）の設定根拠

1. 本剤は食事とともに服用すると血中濃度が低下することがあるので、食事の前後 2 時間を避けて空腹時に服用すること。（【薬物動態】の項参照）
2. 制酸剤、乳製品、多価陽イオン（鉄、カルシウム、アルミニウム、マグネシウム、セレン、亜鉛等）含有製剤等とともに服用すると本剤の血中濃度が低下するので、本剤服用の前 4 時間及び後 2 時間はこれらの摂取を避けること。（「3.相互作用」及び【薬物動態】の項参照）

（現行の記載から変更なし）

ITP の承認時に設定したもので，本申請においても同様の注意喚起が必要であると考え，設定した。

4. 再生不良性貧血の場合

(1) 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記を参照の上、調節すること。本剤の投与量を調節する場合には、通常、25mg/日ずつとする。用量調節時には少なくとも 2 週間は同一用量を維持すること。

（下線：追記）

E1201 試験及び E1202 試験では，血小板数に応じて投与量を 25mg/日ずつ，2 週間間隔で調節していたことから，同様の用量調節を行うことが必要と考え，設定した。また，肝機能検査の実施について，ITP と同様，本申請においても注意喚起が必要であると考え，設定した。

抗胸腺細胞免疫グロブリンで未治療の患者に投与する場合

1) 抗胸腺細胞免疫グロブリンの投与により肝機能障害があらわれることがあるので、抗胸腺細胞免疫グロブリン投与後、一定期間経過後に本剤の投与を開始すること。（【臨床成績】の項参照）
2) 抗胸腺細胞免疫グロブリンの投与に際しては、併用薬剤の添付文書を熟読すること。
3) 血小板数が 200,000/μL を超えた場合には本剤の減量を考慮すること。
4) 血小板数が 400,000/μL を超えた場合には本剤を休薬すること。休薬後、血小板数が 200,000/μL 未満に減少した場合には、休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。
5) 本剤を 26 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

既存治療で効果不十分な患者に投与する場合

1) 血小板数 50,000/μL を目安とし、血小板数がそれを下回る場合には増量を考慮すること。
2) 血小板数が 100,000/μL～200,000/μL の場合には減量を考慮すること。
3) 血小板数が 200,000/μL を超えた場合には少なくとも 1 週間は本剤を休薬すること。休薬後、血小板数が 50,000/μL 未満に減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。
4) 本剤を 16 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

（下線：追記）

E1201 試験及び E1202 試験で設定した，血小板数による投与量の調節基準に基づき設定した。

(2) 3 血球系統の改善（目安として、輸血非依存下で血小板数 50,000/μL を超える、輸血非依存下でヘモグロビン値 10 g/dL を超える、好中球数 1,000/μL を超える）が 8 週間以上持続した場合には本剤の投与量を最大で半量まで減量すること。減量後の投与量で血球改善が更に 8 週間以上持続した場合には、本剤を休薬し、血球数を観察すること。休薬後に血小板数 30,000/μL 未満、ヘモグロビン値 9 g/dL 未満、好中球数 500/μL 未満に低下した場合には休薬前の投与量で投与を再開してもよい。

（下線：追記）

E1201 試験及び E1202 試験で設定した，造血回復が認められた被験者におけるエルトロンボパグの漸減基準に基づき設定した。

3 参考文献

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1.8.3 使用上の注意（案）及びその設定根拠

目　　次

目　　次 2
1　警告欄 4
1.1　警告 4
1.2　警告の設定根拠 4
2　禁忌欄 4
2.1　禁忌 4
2.2　禁忌の設定根拠 4
3　慎重投与欄 4
3.1　慎重投与（次の患者には慎重に投与すること） 4
3.2　慎重投与の設定根拠 4
4　重要な基本的注意欄 5
4.1　重要な基本的注意 5
4.2　重要な基本的注意の設定根拠 6
5　相互作用欄 6
5.1　相互作用 6
5.2　相互作用の設定根拠 7
6　副作用欄 7
6.1　副作用（下線部追加） 7
6.2　副作用の設定根拠 8
7　高齢者への投与欄 9
7.1　高齢者への投与 9
7.2　高齢者への投与の設定根拠 9
8　妊婦，産婦，授乳婦等への投与欄 9
8.1　妊婦，産婦，授乳婦等への投与 9
8.2　妊婦，産婦，授乳婦等への投与の設定根拠 9
9　小児等への投与欄 9
9.1　小児等への投与 9
9.2　小児等への投与の設定根拠 9
10　過量投与欄 9
10.1　過量投与 9
10.2　過量投与の設定根拠 10
11　適用上の注意欄 10
11.1　適用上の注意 10
11.2　適用上の注意の設定根拠 10
12　その他の注意欄 10
12.1　その他の注意 10

12.2　その他の注意の設定根拠 10

1　警告欄

1.1　警告

【警告】
設定なし

（赤字・赤枠）

1.2　警告の設定根拠

設定なし。

2　禁忌欄

2.1　禁忌

【禁忌（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

（赤枠）

2.2　禁忌の設定根拠

現行の添付文書に記載されている内容について，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

3　慎重投与欄

3.1　慎重投与（次の患者には慎重に投与すること）

(1) 肝障害のある患者〔肝障害が悪化するおそれがある。また、血中濃度-時間曲線下面積（AUC）が増加する可能性がある。（【薬物動態】の項参照）〕

(2) 腎障害のある患者〔腎障害患者での有効性及び安全性は確立していないため、これらの患者では血小板数の推移に加えて安全性についても慎重に観察すること。（【薬物動態】の項参照）〕

(3) アンチトロンビン III 欠損、抗リン脂質抗体症候群等の血栓塞栓症の素因のある患者〔血栓塞栓症があらわれるおそれがある。〕

3.2　慎重投与の設定根拠

現行の添付文書に記載されている内容について，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

4 重要な基本的注意欄

4.1 重要な基本的注意

(1) 本剤は、血液疾患の治療に十分な経験を持つ医師のもとで使用すること。

(2) 本剤の投与により肝機能障害があらわれることがあるので、本剤の投与開始前及び用量調節時は 2 週間毎、用量の変更がなければ 1 ヵ月毎に肝機能検査（AST（GOT）、ALT（GPT）、ビリルビン等）を実施すること。（「4. 副作用(1)重大な副作用」の項参照）

(3) 血小板数が正常範囲以下であっても血栓塞栓症が認められているため、血小板数にかかわらず血栓塞栓症の発現に注意すること（「4. 副作用(1)重大な副作用」の項参照）。また、血小板数が正常範囲を超えると、血栓塞栓症のリスクが増加する可能性があるので、観察を十分に行い、血小板数が治療の目標とするレベルを超えた場合には、本剤の減量又は休薬を考慮する等注意すること。

(4) 本剤の投与中止後 2 週間以内に血小板数が投与開始前の値まで低下し、出血を生じることがあるので、本剤の投与中止後 4 週間程度は頻回に血小板数を測定すること。（「4. 副作用(1)重大な副作用」の項参照）

(5) 本剤を含むトロンボポエチン受容体作動薬には、骨髄のレチクリン線維の形成及び線維化を進行させる可能性があるので、本剤の投与開始前には末梢血塗抹標本検査を行い、細胞の形態学的異常を確認すること。また、本剤の投与中は、毎月白血球分画を含む全血球計算を検査し、未熟細胞又は異型細胞が観察された場合には、末梢血塗抹標本検査を行い、形態学的異常（涙滴赤血球、有核赤血球、未熟白血球等）の発現を確認し、血球減少の有無も確認すること。これらの異常が認められた場合には、本剤の投与を中止し、骨髄生検（染色による骨髄線維化の評価等）の実施を考慮すること。（「4. 副作用(1)重大な副作用」の項参照）

(6) トロンボポエチン受容体作動薬には、既存の骨髄異形成症候群等の血液悪性腫瘍を進行させる可能性がある。

(7) <u>重症再生不良性貧血患者を対象とした海外臨床試験において、本剤投与後に染色体異常が認められた例や骨髄異形成症候群及び急性骨髄性白血病への移行例が報告されている。再生不良性貧血患者への本剤の投与中は、定期的に白血球分画を含む全血球計算及び末梢血塗抹標本検査を行い、幼若細胞や形態学的異常の発現を確認し、血球減少の有無も確認すること。これらの異常が認められた場合には、骨髄検査（染色体異常の評価を含む）の実施を考慮し、本剤の投与継続の可否を判断すること。</u>

(8) げっ歯類を用いた毒性試験において、白内障がみられた。また、臨床試験において白内障が報告されているので、白内障に対する眼科的な検査を定期的に行うことが望ましい。

4.2 重要な基本的注意の設定根拠

重症再生不良性貧血患者を対象とした海外臨床試験において，本剤投与後に染色体異常が認められた例や骨髄異形成症候群及び急性骨髄性白血病への移行例が報告されていることから，（7）に，検査を行うこと，及び異常が認められた場合の対応を追記した。

5 相互作用欄

5.1 相互作用

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
ロスバスタチン	本剤とロスバスタチンとの併用により、ロスバスタチンの血中濃度が上昇したとの報告がある。[1] ロスバスタチンの減量を考慮し、患者の状態を慎重に観察すること。（【薬物動態】の項参照）	本剤が OATP1B1 及び BCRP を阻害する可能性がある。（【薬物動態】の項参照）
制酸剤 **乳製品** **多価陽イオン（鉄、カルシウム、アルミニウム、マグネシウム、セレン、亜鉛等）含有製剤等**	同時に服用すると本剤の吸収が著しく妨げられることがあるので、本剤投与の前 4 時間及び後 2 時間はこれらの摂取を避けること。[1)~~-~~2, 3)]（【薬物動態】の項参照）	本剤はこれら多価陽イオンと錯体を形成する。
ロピナビル／リトナビル配合剤	本剤とロピナビル／リトナビル配合剤との併用により、本剤の AUC が減少したとの報告があるので[4]、ロピナビル／リトナビル配合剤と併用する場合には、注意すること。（【薬物動態】の項参照）	機序は不明であるが、ロピナビル／リトナビル配合剤が本剤の代謝酵素を誘導する可能性がある
シクロスポリン	本剤とシクロスポリンとの併用により、本剤の AUC 及び Cmax が減少したとの報告がある。~~ので、~~[5] また、本剤の血中濃度が高値を示したとの報告がある。[6] シクロスポリンと併用する場合には、注意すること。（【薬物動態】の項参照）	機序は不明である。

1) Allred, A. J. et al. ：Br. J. Clin. Pharmacol. 72 (2), 321, 2011〔20152521〕
2) Williams, D. D. et al. ：Clin. Ther. 31 (4), 764, 2009〔20152327〕
3) Wire, M.B. et al. ：Clin. Therap. 34（3）, 699, 2012〔20152675〕
4) Wire, M. B. et al.：Antimicrob. Agents Chemother. 56 (6), 2846, 2012〔20152670〕
5) 社内資料：シクロスポリンとの薬物相互作用〔20160747〕
6) 社内資料：国内第Ⅱ/Ⅲ相試験（ETB115E1201 試験）〔20170501〕

5.2 相互作用の設定根拠

既存治療で効果不十分な再生不良性貧血患者を対象とした CETBE1201 試験において，本剤とシクロスポリンの併用により，本剤の血漿中濃度（トラフ値の平均値）が高値を示したことから，“シクロスポリン”の「臨床症状・措置方法」に，“また，本剤の血中濃度が高値を示したとの報告がある。”を追記し，該当の引用文献を付し，（【薬物動態】の項参照）”を追記した。（【薬物動態】の項には，CETBE1201 試験における本剤及びシクロスポリンの投与量，本剤のトラフ値（平均値）が 73%高値を示した旨等を追記し，引用文献を付した。）
なお，「相互作用」の項内の記載の整合性を図り，“ロスバスタチン”，“制酸剤他”，“ロピナビル/リトナビル配合剤”にも各引用文献及び“（【薬物動態】の項参照）”を追記した。

6 副作用欄

6.1 副作用（下線部追加）

慢性特発性血小板減少性紫斑病患者を対象とした国内臨床試験において、23 例中 11 例（48%）に臨床検査値異常を含む副作用が報告された。その主なものは、疲労、ALT（GPT）増加、血小板数増加、低カリウム血症各 2 例（9%）であった（承認時）。また、これら 23 例中 19 例がその後国内長期継続投与試験に移行した。移行した 19 例中 5 例（26%）に副作用が報告された。その主なものは、白内障、胸痛各 2 例（11%）であった。（最終報告時）
慢性特発性血小板減少性紫斑病患者を対象とした海外臨床試験において、135 例中 50 例（37%）に臨床検査値異常を含む副作用が報告された。その主なものは、頭痛 15 例（11%）、ALT（GPT）増加 6 例（4%）、悪心 6 例（4%）、白内障 5 例（4%）、下痢 4 例（3%）であった。　（承認時）
抗胸腺細胞免疫グロブリンで未治療の再生不良性貧血患者を対象とした国内臨床試験において、10 例中 5 例（50%）に臨床検査値異常を含む副作用が報告された。その主なものは、筋肉痛 3 例（30%）、血中ビリルビン増加、悪心各 2 例（20%）であった。（承認時）
既存治療で効果不十分な再生不良性貧血患者を対象とした国内臨床試験において、21 例中 12 例（57%）に臨床検査値異常を含む副作用が報告された。その主なものは、血中 ALP 増加、肝機能異常、高ビリルビン血症、発疹が各 2 例（10%）であった。（承認時）
重大な副作用及びその他の副作用の発現頻度については、上記の国内臨床試験を併合した集計結果に基づき記載した。また、これらの国内臨床試験であらわれていない副作用については頻度不明とした。

(1) 重大な副作用

1）肝機能障害：AST（GOT、~~4~~2%）、ALT（GPT、~~9~~7%）、ALP（6%）、ビリルビン（~~4~~7%）の増加等の肝機能障害があらわれることがあるので、本剤投与開始前及び投与

中は定期的に肝機能検査を行う等、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等適切な処置を行うこと。（「2.重要な基本的注意」の項参照）

2）**血栓塞栓症**：肺塞栓症（頻度不明~~注）~~）、深部静脈血栓症（頻度不明~~注）~~）、一過性脳虚血発作（~~4~~2%）、心筋梗塞（頻度不明~~注）~~）、虚血性脳卒中（頻度不明~~注）~~）等の血栓塞栓症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等適切な処置を行うこと。（「2.重要な基本的注意」の項参照）

3）**出血**：本剤の投与中止後に出血（頻度不明~~注）~~）を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、適切な処置を行うこと。（「2.重要な基本的注意」の項参照）

4）**骨髄線維化**：骨髄線維化（頻度不明~~注）~~）があらわれる可能性があるので、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等適切な処置を行うこと。（「2.重要な基本的注意」の項参照）

(2) **その他の副作用**

	5%以上	5%未満	頻度不明~~注）~~
消化器	悪心	~~悪心~~	嘔吐、下痢、口内乾燥
皮膚	-	発疹	脱毛症~~、発疹~~
筋骨格	筋痛	-	背部痛、筋骨格系胸痛、筋骨格痛~~、筋痛~~
その他	~~疲労、血小板数増加、低カリウム血症、白内障、~~頭痛	疲労、血小板数増加、低カリウム血症、白内障	咽頭炎、尿路感染

~~注）海外のみで認められている副作用については頻度不明とした。~~

6.2 副作用の設定根拠

再生不良性貧血患者を対象とした国内臨床試験（抗胸腺細胞免疫グロブリンで未治療の再生不良性貧血患者を対象とした CETB115E1202 試験，及び既存治療で効果不十分な再生不良性貧血患者を対象とした CETB115E1201 試験）の副作用発現状況を，発現状況の概要に追記した（2 例以上のもの）。

各副作用の発現頻度については，現行では，現在の適応症である慢性特発性血小板性紫斑病患者を対象とした国内臨床試験の集計に基づき記載しているが，CETB115E1202 試験及び CETB115E1201 試験における副作用と併合した発現頻度に変更した。また，その発現頻度の算出についての説明を発現状況の概要の末尾に追記した。更に，発現頻度不明についての説明も追記したことから，現行の「その他の副作用」の脚注を削除し，各副作用に付していた“注）”も削除した。

7　高齢者への投与欄

7.1　高齢者への投与

高齢者では一般に生理機能が低下しているので、患者の状態を観察しながら注意して投与すること。

7.2　高齢者への投与の設定根拠

現行の添付文書に記載されている内容について，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

8　妊婦，産婦，授乳婦等への投与欄

8.1　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。〔妊婦への投与に関する安全性は確立しておらず、胎児の血小板への影響についても不明である。動物試験（ラット）において母体毒性用量で胚致死、胎児体重の低値及び低頻度の頸肋（変異）の増加が報告されている。〕

(2) 授乳中の婦人には、投与を避けることが望ましい。やむを得ず投与する場合には、授乳を避けさせること。〔動物試験（ラット）で乳汁中への移行が示唆されている。〕

8.2　妊婦，産婦，授乳婦等への投与の設定根拠

現行の添付文書に記載されている内容について，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

9　小児等への投与欄

9.1　小児等への投与

小児等に対する安全性及び有効性は確立していない（使用経験がない）。

9.2　小児等への投与の設定根拠

現行の添付文書に記載されている内容について，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

10　過量投与欄

10.1　過量投与

徴候、症状：本剤 5,000mg を過量投与した症例では、軽度の発疹、一過性の徐脈、疲労、AST（GOT）及び ALT（GPT）上昇が報告され、血小板数は 929,000/μL まで増加した。

処置：吸収を抑えるために、カルシウム、アルミニウム、マグネシウム等の多価陽イオンを含有する製剤の経口投与を考慮すること。また、血小板数の検査を頻回に行い、患者の状態を十分に観察すること。本剤の腎排泄の寄与は小さく、血漿蛋白結合率が高いため、血液透析は有効な除去法ではないと考えられる。

10.2　過量投与の設定根拠

現行の添付文書に記載されている内容について，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

11　適用上の注意欄

11.1　適用上の注意

(1) **薬剤交付時**：PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。〔PTP シートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔を起こして縦隔洞炎等の重篤な合併症を併発することが報告されている。〕

(2) PTP シートからの取り出しは、裏のシールを剥がした後、指の腹で押し出すこと。

11.2　適用上の注意の設定根拠

現行の添付文書に記載されている内容について，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

12　その他の注意欄

12.1　その他の注意

本剤はヒト及びチンパンジー以外のトロンボポエチン受容体に対し親和性をもたず、ヒト及びチンパンジー以外の動物に対して薬理活性を示さない。このため毒性試験において、薬理活性に付随する影響は評価されていない。

12.2　その他の注意の設定根拠

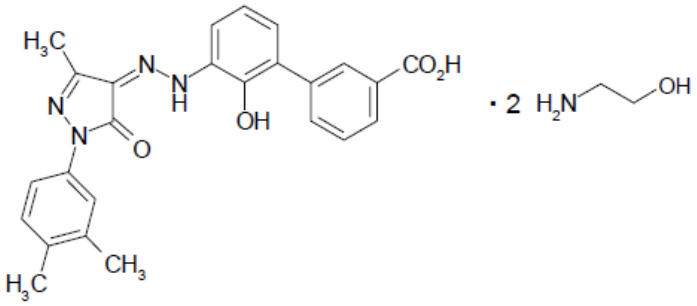
現行の添付文書に記載されている内容について，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

1.9 一般的名称に係る文書

今回の承認申請で追加すべき資料はないため，該当資料なし

1.10 毒薬・劇薬等の指定審査資料のまとめ

＜現行＞

化学名・別名	3'-{(2Z)-2-[1-(3,4-ジメチルフェニル)-3-メチル-5-オキソ-1,5-ジヒドロ-4H-ピラゾール-4-イリデン]ヒドラジノ}-2'-ヒドロキシビフェニル-3-カルボン酸 ビス(2-アミノエタノール)
構造式	
効能・効果	慢性特発性血小板減少性紫斑病
用法・用量	通常、成人には、エルトロンボパグとして初回投与量 12.5 mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、血小板数、症状に応じて適宜増減する。また、1 日最大投与量は 50 mg とする。
劇薬等の指定	劇薬：原体・製剤 処方せん医薬品：製剤
市販名及び有効成分・分量	原体：エルトロンボパグ オラミン 製剤：レボレード錠 12.5 mg、25 mg（1 錠中エルトロンボパグとして 12.5 mg、25mg 含有）
毒性	単回投与 概略の致死量 (mg/kg) 経口 ラット♂♀ 1000 イヌ♂♀ >300 反復投与 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 / 28 週間 / 経口 / 3, 10, 30, 60 / 30 / 60：死亡，自発運動低下，異常呼吸，削痩，体重増加量・摂餌量↓，白内障，肝臓重量↑，肝細胞変性・壊死・空胞化・肥大，副腎皮質束状帯細胞空胞化・壊死，大腿骨・脛骨骨内膜過形成 イヌ / 52 週間 / 経口 / 3, 10, 30 / 30 / なし
副作用	副作用発現率（臨床検査値異常変動を含む） 11/23 ＝48% 副作用の種類 例数 アラニン・アミノトランスフェラーゼ増加 2 血小板数増加 2 低カリウム血症 2 疲労 2 等
会社	グラクソ・スミスクライン株式会社 製剤：輸入

＜削除・追加＞取り消し線，下線部

化学名・別名	
構造式	
効能・効果	1. 慢性特発性血小板減少性紫斑病 2. 再生不良性貧血
用法・用量	1. 慢性特発性血小板減少性紫斑病の場合 通常、成人には、エルトロンボパグとして初回投与量 12.5mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、血小板数、症状に応じて適宜増減する。また、1 日最大投与量は 50mg とする。 2. 再生不良性貧血の場合 抗胸腺細胞免疫グロブリンで未治療の場合 抗胸腺細胞免疫グロブリンとの併用において、通常、成人には、エルトロンボパグとして 75mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜減量する。 既存治療で効果不十分な場合 通常、成人には、エルトロンボパグとして初回投与量 25mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜増減する。また、1 日最大投与量は 100mg とする。
劇薬等の指定	
市販名及び有効成分・分量	
毒性	
副作用	慢性特発性血小板減少性紫斑病患者を対象とした国内臨床試験において、23 例中 11 例（48%）に臨床検査値異常を含む副作用が報告された。その主なものは、疲労、ALT（GPT）増加、血小板数増加、低カリウム血症各 2 例（9%）であった（承認時）。また、これら 23 例中 19 例がその後国内長期継続投与試験に移行した。移行した 19 例中 5 例（26%）に副作用が報告された。その主なものは、白内障、胸痛各 2 例（11%）であった。（最終報告時） 慢性特発性血小板減少性紫斑病患者を対象とした海外臨床試験において、135 例中 50 例（37%）に臨床検査値異常を含む副作用が報告された。その主なものは、頭痛 15 例（11%）、ALT（GPT）増加 6 例（4%）、悪心 6 例（4%）、白内障 5 例（4%）、下痢 4 例（3%）であった。（承認時） 抗胸腺細胞免疫グロブリンで未治療の再生不良性貧血患者を対象とした国内臨床試験において、10 例中 5 例（50%）に臨床検査値異常を含む副作用が報告された。その主なものは、筋肉痛 3 例（30%）、血中ビリルビン増加、悪心各 2 例（20%）であった。（承認時） 既存治療で効果不十分な再生不良性貧血患者を対象とした国内臨床試験において、21 例中 12 例（57%）に臨床検査値異常を含む副作用が報告された。その主なものは、血中 ALP 増加、肝機能異常、高ビリルビン血症、発疹が各 2 例（10%）であった。（承認時）
会社	ノバルティスファーマ株式会社 製剤：輸入

1.12 添付資料一覧

目次

目次 2
第 3 部 3
第 4 部 3
第 5 部 3

第 3 部

該当資料なし

第 4 部

該当資料なし

第 5 部

添付資料番号	表題	著者	試験実施期間	試験実施場所	報種類（国内／海外）	掲載誌	評価／参考
5.2 全臨床試験一覧表							
5.2	全臨床試験一覧表	ノバルティス	–	–	国内	社内報告書	評価
5.3 試験報告書及び関連情報							
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	Method Validation Report Quantitation of SB-497115 in Human Plasma via HPLC with MS/MS Detection	[redacted]	20[redacted]年[redacted]月	米国	海外	社外報告書	評価
5.3.1.4-2	Amendment 1 Method Validation Report Addendum 1 Quantitation of SB-497115 in Human Plasma via HPLC with MS/MS Detection	[redacted]	20[redacted]年[redacted]月[redacted]日	米国	海外	社外報告書	評価
5.3.1.4-3	Method validation report Quantitative determination of SB-497115 in Human Plasma by LC-MS/MS	[redacted]	20[redacted]年[redacted]月[redacted]日	中国	海外	社外報告書	評価

添付資料番号	表題	著者	試験実施期間	試験実施場所	報種類（国内／海外）	掲載誌	評価／参考
5.3.1.4-4	Method validation report Amendment No. 01 Quantitative determination of SB-497115 in Human Plasma by LC-MS/MS	[redacted]	20[redacted]年[redacted]月[redacted]日	中国	海外	社外報告書	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	—	—	—	—	—	—
5.3.3 臨床薬物動態（PK）試験報告書							
5.3.3.1 健康被験者における PK 及び初期忍容性試験報告書							
	該当資料なし	—	—	—	—	—	—
5.3.3.2 患者における PK 及び初期忍容性試験報告書							
	該当資料なし	—	—	—	—	—	—
5.3.3.3 内因性要因を検討した PK 試験報告書							
	該当資料なし	—	—	—	—	—	—
5.3.3.4 外因性要因を検討した PK 試験報告書							
5.3.3.4-1	A Phase I, Open-label, Randomized, Three-period Cross-over Study Evaluating the Effect of Cyclosporine on the Pharmacokinetics of Eltrombopag in Healthy Adult Subjects	GlaxoSmithKline	2014 年 11 月 5 日～2014 年 12 月 24 日	米国，計 1 施設	海外	社外報告書	評価
5.3.3.5 ポピュレーション 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 non-randomized, open-label, phase II study to assess the safety and efficacy of eltrombopag in Japanese subjects with refractory, moderate or more severe aplastic anemia	ノバルティス	2014 年 7 月 23 日～20[redacted]年[redacted]月[redacted]日	日本，計 12 施設	国内	社内報告書	評価

添付資料番号	表題	著者	試験実施期間	試験実施場所	報種類（国内／海外）	掲載誌	評価／参考
5.3.5.2-2	A non-randomized, phase II study of eltrombopag in combination with rabbit anti-thymocyte globulin/cyclosporine A (ATG/CsA) in subjects with moderate or more severe aplastic anemia who have not received prior ATG/anti-lymphocyte globulin (ALG)-based immunosuppressive therapy	ノバルティス	2015 年 5 月 22 日～ 20[redacted]年[redacted]月[redacted]日	日本，計 11 施設	国内	社内報告書	評価
5.3.5.2-3	A Pilot Study of a Thrombopoietin-receptor Agonist (TPO-R agonist), Eltrombopag, in Aplastic Anemia Patients with Immunosuppressive-therapy Refractory Thrombocytopenia	GlaxoSmithKline	2009 年 6 月 23 日～ 20[redacted]年[redacted]月[redacted]日	米国，計 1 施設	海外	社内報告書	参考
5.3.5.2-4	Extended dosing with Eltrombopag in Subjects with refractory severe aplastic anemia (SAA)	GlaxoSmithKline	2013 年 6 月～ 20[redacted]年[redacted]月[redacted]日	米国，計 1 施設	海外	社内報告書	参考
5.3.5.2-5	Eltrombopag added to standard immunosuppression in treatment-naïve severe aplastic anemia	GlaxoSmithKline	2012 年 6 月～ 20[redacted]年[redacted]月[redacted]日	米国，計 1 施設	海外	社内報告書	参考
5.3.5.2-6	CETB115E1201- Neoral subpopulation outputs	ノバルティス	－	－	国内	社内報告書	評価
5.3.5.2-7	CETB115E1202- Neoral subpopulation outputs	ノバルティス	－	－	国内	社内報告書	評価
5.3.5.2-8	A non-randomized, phase II study of eltrombopag in combination with rabbit anti-thymocyte globulin/cyclosporine A (ATG/CsA) in subjects with moderate or more severe aplastic anemia who have not received prior ATG/anti-lymphocyte globulin (ALG)-based immunosuppressive therapy (Week 52 follow-up)	ノバルティス	－	日本，計 11 施設	国内	社内報告書	評価
5.3.5.2-9	CETB115E1202_Neoral subpopulation outputs (Week 52 follow-up)	ノバルティス	－	－	国内	社内報告書	評価
5.3.5.2-10	CETB115E1201_Safety outputs -Week 52 (updated on DBL of 10May2017)	ノバルティス	－	－	国内	社内報告書	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	Integrated Summary of Safety, data analyses	ノバルティス	－	－	国内	社内報告書	評価
5.3.5.3-2	Integrated Summary of Safety, data analyses	ノバルティス	－	－	国内	社内報告書	評価
5.3.5.4 その他の臨床試験報告書							
	該当資料なし	－	－	－	－	－	－

添付資料番号	表題	著者	試験実施期間	試験実施場所	報種類（国内／海外）	掲載誌	評価／参考
5.3.6 市販後の使用経験に関する報告書							
5.3.6-1	PERIODIC BENEFIT RISK EVALUATION REPORT/EU PERIODIC SAFETY UPDATE REPORT(PBRER/EU RMP)	GlaxoSmithKline	Period covered: 2014 年 10 月 1 日～ 2015 年 9 月 30 日	－	海外	社内報告書	評価
5.3.6-2	PERIODIC SAFETY UPDATE REPORT(PSUR)	ノバルティス	Period covered: 2015 年 10 月 01 日 ～ 2016 年 9 月 30 日	－	海外	社内報告書	評価
5.3.7 患者データ一覧表及び症例記録							
5.3.7-1	症例一覧表	ノバルティス	－	－	国内	社内報告書	評価
5.3.7-2	副作用一覧表						
5.3.7-3	重篤な有害事象一覧表						
5.3.7-4	臨床検査値の異常変動一覧表						
5.3.7-5	臨床検査値推移図						

添付資料番号	著者・表題・掲載誌	報種類 （国内／海外）
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