ハーセプチン注射用 60
ハーセプチン注射用 150
に関する資料

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1.5　起原又は発見の経緯及び開発の経緯

1.5.1　起原又は発見の経緯

トラスツズマブ（遺伝子組換え）（製品名「ハーセプチン注射用 60、同 150」）はヒト癌遺伝子 HER2/neu（c-erbB-2）の遺伝子産物 であるヒト上皮増殖因子受容体 2 型（HER2）蛋白に特異的に結合する遺伝子組み換えヒト化モノクローナル抗体製剤である。HER2 蛋白は、細胞表面に存在する約 185 kDa の糖タンパクで、受容体型チロシンキナーゼである。HER2 タンパクは正常細胞において細胞の増殖、分化などの調節に関与しているが、何らかの理由で HER2 遺伝子の増幅や遺伝子変異が起こると、細胞の増殖・分化の制御ができなくなり、細胞は悪性化する。HER2 遺伝子はがん遺伝子でもあり、多くの種類のがんで遺伝子増幅がみられる。従って、既承認の乳癌や胃癌以外の癌種においても HER2 を標的とする薬剤を用いることで疾患の制御が期待できると考えられる。

1.5.2　開発の経緯

1.5.2.1　非臨床開発の経緯

トラスツズマブの薬理作用，薬物動態，安全性については新たに実施した試験はない。

1.5.2.2　臨床試験の経緯

1.5.2.2.1　国内における臨床開発の経緯

HER2 陽性の唾液腺癌患者に対してトラスツズマブとドセタキセルの併用療法の効果が示唆された報告があったことから [1),2),3),4),5),6),7)]、「HER2 陽性再発転移の唾液腺癌に対するトラスツズマブとドセタキセルの併用療法の有効性と安全性を確認する多施設共同非対照オープンラベル試験（HUON-003-01 試験）」が北海道大学により医師主導治験（以下、「本治験」）として企画された。本治験は 20[redacted] 年[redacted] 月に実施した医薬品戦略相談で独立行政法人医薬品医療機器総合機構との合意を経て実施された。本治験は、国立研究開発法人日本医療研究開発機構（AMED）の「臨床研究・治験推進研究事業」、「産学連携に対する薬事承認を目指した医薬品シーズの実用化を推進する研究、カテゴリー2：臨床研究・医師主導治験の完了、企業導出」に採択され、AMED より委託された資金により実施された。

本治験は HER2 陽性再発転移の唾液腺癌に対するトラスツズマブとドセタキセルの併用療法の有効性と安全性を評価することを目的とした多施設共同非対照オープンラベル試験で、治験期間は 2015 年 7 月～2019 年 3 月であった。投与期間は最大 8 コース（24 週間）とし、効果判定は固形がんの治療効果判定のための新ガイドライン（RECIST）v1.1（日本語訳日本臨床腫瘍研究グループ［JCOG］版 ver1.0）に従って奏効率が評価された。中央画像評価委員会判定の最良総合効果に基づく奏効率（95%信頼区間）は 60.0（32.3～83.7）%で、奏効率の 95%信頼区間下限は閾値である 25%を上回った。無増悪生存期間の中央値（95%信頼区間）は、260.0（184.0～386.0）日、全生存期間中央値（95%信頼区間）は、1028.0（515.0～推定不能）日、病勢制御率（95%信頼区間）は、93.3（68.1~99.8）%（15 例中 14 例）であった。本治験おける奏効率 60.0%は、カルボプ

ラチン/パクリタキセル併用の奏効率 39%を大幅に上回った[8)]。また、無増悪生存期間 260 日、全生存期間 1028 日（いずれも中央値）は、カルボプラチン/パクリタキセル併用における無増悪生存期間 6.5 ヵ月、全生存期間 26.5 ヵ月を上回り臨床的に意義がある値であった。 また、本治験で認められた重篤な副作用は既知の副作用であり、トラスツズマブとドセタキセルの併用による新たな安全性のリスクはみとめられなかったことから、トラスツズマブとドセタキセルの併用療法は HER2 陽性再発・転移の唾液腺癌に対して十分なベネフィットがあると考えられた。

1.5.2.2.2　海外における臨床開発の経緯

海外では唾液腺癌に対する開発は行われていない。

1.5.2.3　申請製剤、申請効能以外の開発の概略

トラスツズマブは HER2 タンパク質を標的とする分子標的薬であることから、腫瘍組織パラフィン検体を用いて IHC 及び DISH 法で、それぞれ HER2 の過剰発現及び遺伝子増幅を確認するために中央検査機関で検査を実施した。HER2 の測定には IHC 法では ultraView パスウェー HER2(4B5)、DISH 法ではインフォーム Dual ISH HER2 キット（いずれもベンタナ社の市販品）を用いた。

本剤のコンパニオン診断薬として「ベンタナ ultraView パスウェーHER2(4B5)」承認番号：22300AMX01167000 及び「ベンタナ インフォーム Dual ISH HER2 キット」承認番号：22300AMX00002000 と同等の性能を有する「ベンタナ DISH HER2 キット」を本剤のコンパニオン診断薬としての使用目的追加のための体外診断用医薬品承認事項一部変更承認申請を行う予定である。

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1.6　外国における使用状況等に関する資料

1.6.1　外国における承認申請状況

ハーセプチン注射用 60、同 150（以下、本剤）は 1998 年 9 月に米国で「転移病巣に対する化学療法が 1 レジメン以上施行された HER2 過剰発現が確認された転移性乳癌」を適応症として最初に承認され、欧州連合においては 2000 年 8 月に「転移病巣に対する化学療法が 2 レジメン以上施行された HER2 陽性の転移性乳癌」を適応症として承認された。その後、乳癌については一次治療、術後補助療法等の追加適応が米国及び欧州連合で承認された。

乳癌以外では「転移病巣に対する化学療法が未施行の HER2 陽性の転移性胃癌又は胃食道接合部癌」に対して 2010 年 1 月に欧州連合、「転移病巣に対する治療が未施行の HER2 過剰発現が確認された転移性の胃癌又は胃食道接合部癌」に対して 2010 年 10 月に米国で承認された。

これら乳癌及び胃癌又は胃食道接合部癌に対しては 2020 年 9 月時点で 130 以上の国又は地域で承認されている。なお、2021 年 3 月時点で、申請効能・効果である唾液腺癌に関連する適応症を取得している国又は地域はない。

1.6.2　代表的な外国添付文書の和訳概要

1.6.2.1　米国添付文書の和訳概要

本剤の代表的な外国添付文書として、米国の添付文書（2021 年 2 月版）の和訳概要を以下に示す。

警告：心筋症，Infusion reaction，胚・胎児毒性及び肺毒性

心筋症

ハーセプチン投与により，無症候性及び症候性の心不全が発現することがある。アントラサイクリン系薬剤を含有する化学療法レジメンとハーセプチンを併用している患者で，発現率と重症度が最も高い。

すべての患者においてハーセプチン投与前と投与中は左室機能の評価を行うこと。術後補助療法のためにハーセプチン投与を受けている患者で臨床上重大な左室機能の低下が認められる場合には投与を中止すること。更に転移性の癌の治療のためにハーセプチン投与を受けている患者において，臨床上重大な左室機能の低下が認められる場合は，投与を中止すること *［用法・用量（2.3）及び警告及び使用上の注意（5.1）参照］*。

Infusion reaction；肺毒性

ハーセプチン投与により重篤でかつ致死的な Infusion reaction 及び肺毒性が発現することがある。これらの症状は，通常ハーセプチンの投与中又は投与後 24 時間以内に発現している。呼吸困難，又は臨床上重大な低血圧が発現した場合には，ハーセプチンの投与を中断すること。症状が完全に消失するまで，患者を観察すること。アナフィラキシー，血管浮腫，間質性肺臓炎又は急性呼吸窮迫症候群がみられた場合には，ハーセプチンの投与を中止すること *［警告及び使用上の注意（5.2，5.4）参照］*。

胚・胎児毒性

妊娠中のハーセプチン投与により羊水過少及び，肺形成不全，骨格異常及び新生児死亡を合併する羊水過少が発現することがある。これらのリスクと有効な避妊方法の必要性について患者に助言すること *[警告及び使用上の注意（5.3）並びに特別な集団への投与（8.1，8.3）を参照]*。

1　適応症及び使用方法

1.1　乳癌術後補助療法

ハーセプチンは，HER2 過剰発現が確認されたリンパ節転移陽性又はリンパ節転移陰性（エストロゲン受容体及びプロゲステロン受容体陰性，又はいずれか 1 つのハイリスク要因*［臨床試験（14.1）参照］*を有する）の乳癌患者の以下の術後補助療法に適応される。

- ドキソルビシン，シクロホスファミド及びパクリタキセル又はドセタキセルのいずれかを含む治療レジメンの一環として
- ドセタキセル及びカルボプラチンを併用した治療レジメンの一環として
- アントラサイクリンをベースとした集学的治療後の単剤療法として

ハーセプチンの FDA 承認済みのコンパニオン診断に基づいて治療を行う患者を選択すること*［用法・用量（2.1）参照］*。

1.2　遠隔転移を伴う乳癌

ハーセプチンは以下のように適応される：

- HER2 過剰発現が確認された遠隔転移を伴う乳癌患者の一次治療におけるパクリタキセルとの併用療法
- HER2 過剰発現が確認された乳癌患者のうち，転移病巣に対し 1 レジメン以上の化学療法治療歴がある患者に対するハーセプチン単剤療法

ハーセプチンの FDA 承認済みのコンパニオン診断に基づいて治療を行う患者を選択すること*［用法・用量（2.1）参照］*。

1.3　遠隔転移を伴う胃癌

ハーセプチンはカペシタビン又は 5-FU，及びシスプラチンとの併用で転移病巣に対する治療が未施行の HER2 過剰発現が確認された転移性の胃癌又は胃食道接合部癌患者に対して適応される。

ハーセプチンの FDA 承認済みのコンパニオン診断に基づいて治療を行う患者を選択すること*［用法・用量（2.1）参照］*。

2　用法・用量

2.1　患者選択

腫瘍標本における HER2 蛋白過剰発現又は HER2 遺伝子増幅に基づいて患者を選択すること*[適応症及び使用方法（1）並びに臨床試験（14）を参照]*。HER2 蛋白過剰発現及び HER2 遺伝子増幅の評価は，乳癌や胃癌に特化した FDA 承認済みの検査を用いて，技術的水準が実証された検査室で行う必要がある。HER2 蛋白過剰発現及び HER2 遺伝子増幅を検出するための FDA 承認済みの検査に関する情報は，http://www.fda.gov/CompanionDiagnostics より入手可能である。

遠隔転移を伴う胃癌における HER2 蛋白過剰発現及び HER2 遺伝子増幅の評価は，胃癌では HER2 発現の不均一性が高く，細胞膜の染色が不完全であるなど，胃癌と乳癌での病理組織学的な違いがあるため，胃癌に対して FDA より承認を受けた特定の検査法を用いて実施すること。

適切に固定されていない組織標本の使用，指定試薬の不使用，検査法に関する手順からの逸脱，及びアッセイバリデーションの際に適切な対照を用いない等，不適切な分析の実施は，信頼できない結果につながりかねない。

2.2　推奨用量及び投与スケジュール

- **急速静注又は静脈内大量投与は行ってはならない。他剤と混合してはならない。**
- **ハーセプチン（トラスツズマブ）をトラスツズマブ エムタンシンの代わりに使用したり併用したりしないこと。**

乳癌術後補助療法

以下のいずれかの用法・用量によりハーセプチンを合計 52 週間投与すること。

パクリタキセル，ドセタキセル，又はドセタキセル／カルボプラチンとの併用投与中及び併用終了後：

- 併用投与中の 12 週間（パクリタキセル又はドセタキセル）及び 18 週間（ドセタキセル／カルボプラチン）は，初回用量 4 mg/kg を 90 分かけて点滴静注した後，1 週間間隔で，2 mg/kg を 30 分かけて点滴静注する。
- 1 週間間隔投与の最終投与 1 週間後からは，ハーセプチン 6 mg/kg を 3 週間間隔で，30～90 分かけて点滴静注する。

アントラサイクリンをベースとした集学的治療後 3 週間以内に単剤療法を行う場合：

- 初回用量 8 mg/kg を 90 分かけて点滴静注する。
- その後，3 週間ごとに 6 mg/kg を 30～90 分かけて点滴静注する*［用法・用量（2.3）参照］*。
- 術後補助療法を 1 年以上延長することは推奨されない*［副作用（6.1）参照］*。

転移性乳癌の治療

- ハーセプチンを単剤又はパクリタキセルとの併用により投与する。初回用量 4 mg/kg を 90 分かけて点滴静注し，続いて，2 mg/kg を 1 週間間隔で 30 分かけて点滴静注する。ハーセプチンは病勢進行まで投与すること。

遠隔転移を伴う胃癌

- 初回用量 8 mg/kg を 90 分かけて点滴静注し，続いて，6 mg/kg を 3 週間隔で 30～90 分かけて病勢進行まで点滴静注する。*［用法・用量（2.3）参照］*

2.3　投与に関する重要な考慮事項

ハーセプチンの投与スケジュールから外れた期間が 1 週間以下であれば，できるだけ早く通常の維持用量（1 週間 1 回投与：2 mg/kg；3 週間 1 回投与：6 mg/kg）を投与すること。次に予定されていたサイクルまで待たないこと。その後，1 週間 1 回又は 3 週間 1 回のスケジュールに従って，ハーセプチンの維持用量をそれぞれ 7 日後又は 21 日後に投与する。

ハーセプチンの投与スケジュールから外れた期間が 1 週間を超える場合，できるだけ早くハーセプチンを約 90 分かけて（1 週間 1 回投与：4 mg/kg；3 週間 1 回投与：8 mg/kg）再投与する。その後，ハーセプチンの維持用量（1 週間 1 回投与：2 mg/kg；3 週間 1 回投与：6 mg/kg）を 1 週間 1 回又は 3 週間 1 回のスケジュールに従って，それぞれ 7 日後又は 21 日後に投与する。

Infusion reaction

［枠内の警告，警告及び使用上の注意（5.2）参照］

- 軽度から中等度の Infusion reaction の場合，投与速度を緩めること
- 呼吸困難，又は臨床上重大な低血圧患者においては，投与を中断すること
- 重度及び生命を脅かす Infusion reaction の場合，ハーセプチン投与を中止すること

心筋症

［枠内の警告，警告及び使用上の注意（5.1）参照］

ハーセプチン投与前，及び投与中は定期的に左室駆出率（LVEF）の評価を行うこと。次のいずれかに該当する場合は，少なくとも 4 週間はハーセプチンの投与を中止すること：

- LVEF が治療前値から，絶対値として 16%以上低下した場合
- LVEF が施設基準値を下回り，かつ治療前値から絶対値として 10%以上低下した場合

4～8 週間以内に，LVEF が基準値以内かつ，ベースラインからの低下が絶対値として 15%以下まで回復した場合は，ハーセプチンの投与を再開できる。

持続的な（8 週を超える）LVEF の低下，又は心筋症によるハーセプチンの休薬が 3 回を上回った場合は，ハーセプチン投与を中止すること。

2.4　投与準備

投薬過誤を防ぐには，バイアルのラベルをチェックして，調製及び投与する薬剤がトラスツズマブ エムタンシンではなくハーセプチン（トラスツズマブ）であることを確認することが重要である。

150 mg 単回投与バイアル

溶解

ハーセプチンの各 150 mg バイアルを 7.4 mL の注射用滅菌水（SWFI）（未付属）で溶解し，7.15 mL（トラスツズマブ 150 mg）となるように 21 mg/mL のトラスツズマブを含む単回投与用溶液を調製する。

以下の溶解手順を実施する際には，適切な無菌技術を用いること：

- 滅菌シリンジを用いて，外観がケーキのようなハーセプチンの凍結乾燥粉末の入ったバイアル中に 7.4 mL の SWFI（未付属）をゆっくりと注入する。希釈液を塊に向けて注入すること。溶解後のバイアルからは，21 mg/mL のトラスツズマブを含む単回投与用の溶液が得られる。
- 溶解させるために，バイアルを静かに回す。**振り混ぜてはならない。**
- 溶解時にはわずかに泡立ちが認められる。バイアルを約 5 分間静置する。
- 得られた溶液は，投与前に，粒状物質や変色がないかについて可能な限り目視で調べること。粒状物質や変色について目視で調べること。得られた溶液は目に見える粒子がなく，澄明からわずかに乳白光を有し，無色から微黄色でなければならない。
- ハーセプチン溶液は保存剤を含んでおらず，単回投与のみを目的としているため，SWFI で溶解した後は直ちに使用すること。溶解したハーセプチン溶液は 2～8°C（36～46°F）で保存し，未使用のハーセプチンは溶解から 28 日後には廃すること。**凍結させてはならない。**

希釈

- ハーセプチンの必要量（mg）を求めること*［用法・用量（2.1）参照］*。
- 必要となる 21 mg/mL の溶解後のハーセプチン溶液の量を計算する。
- 滅菌済みの針とシリンジを使用してバイアルからこの量を抜き取り，250 mL の 0.9%塩化ナトリウム注射液（USP）を含む輸液バッグに添加する。**ブドウ糖（5%）溶液は使用してはならない。**
- バッグを静かに転倒させ，溶液を混合する。
- 0.9%塩化ナトリウム注射液（USP）を含むポリ塩化ビニル又はポリエチレンの輸液バッグに入った希釈後の点滴用ハーセプチン溶液は，2～8°C（36～46°F）で保管し，24 時間を超えたものは使用してはならない。24時間後に廃棄すること。この保存時間は，溶解後のバイアルの保管時間に加算される。**凍結させてはならない。**

3　剤型及び力価

- 注射用：単回投与バイアル入り凍結乾燥粉末 150 mg

4　禁忌

なし。

5　警告及び使用上の注意

5.1　心筋症

ハーセプチンは左室機能障害，不整脈，高血圧，障害に至る心不全，心筋症，心臓死を惹き起こすことがある*［枠内の警告：心筋症］*。また，ハーセプチンは無症候性の左室駆出率（LVEF）低下を発現することがある。

ハーセプチンの単剤若しくは併用療法を受けた患者では，ハーセプチンを投与しなかった患者と比較し，症候性の心筋機能障害の発現率は 4～6 倍の増加がみられた。ハーセプチンにアントラサイクリンを併用するとき，症候性の心筋機能障害は最も高頻度に発現する。

LVEF 値が治療前値から絶対値として 16%以上低下した場合，又は LVEF が施設基準値を下回りなおかつ治療前値から絶対値として 10%以上低下した場合はハーセプチンの投薬を控えること*［用法・用量（2.3）参照］*。ハーセプチンに起因する左室機能障害発現後の，ハーセプチンの継続投与や再投与の安全性に関する試験は実施されていない。

ハーセプチン中止後にアントラサイクリン系薬剤の投与を受けている患者でも，心機能障害のリスクが高まる可能性がある*［薬物相互作用（7）及び臨床薬理（12.3）参照］*。

心機能モニタリング

既往歴，身体学的検査，心エコー又は MUGA スキャンによる LVEF 測定を含む，心機能検査を徹底的に実施すること。その場合以下の手順が推奨される：

- ハーセプチン投与開始直前の LVEF ベースラインの測定
- ハーセプチン投与中の 3 カ月ごと，投与終了時の LVEF の測定
- 重大な左室機能障害がみられハーセプチン投与を中断した場合の，4 週ごとの LVEF の測定*［用法・用量（2.3）参照］*
- ハーセプチンを含む術後補助療法終了後少なくとも 2 年間の，6 カ月ごとの LVEF 測定

試験 1 では，AC-TH 群で追跡期間中央値が 8.7 年の後に 15%（1031 例中 158 例）の患者が，ハーセプチン投与による心筋機能障害の臨床的徴候，又は重大な LVEF 低下によりハーセプチン投与を中止している。試験 3（ハーセプチン 1 年投与）では，追跡期間中央値 12.6 カ月時点で心毒性によりハーセプチンを中止した患者数は 2.6%（1678 例中 44 例）であった。試験 4 においては TCH 投与群（化学療法フェイズ 1.5%，単独療法フェイズ 1.4%）の合計 2.9%（1056 例中 31 例），AC-TH 投与群（化学療法フェイズ 1.5%，単独投与フェイズ 4.2%）の合計 5.7%（1068 例中 61 例）の患者で，心毒性によりハーセプチンの投与を中止した。

試験 1 及び 2 で補助化学療法を受けうっ血性心不全を発現した 64 例のうち，1 例が心筋症で死亡，1 例が突然死（病因の記録なし），33 例が最終追跡調査時点で心臓に対する治療を受けていた。生存患者のうち約 24%は，継続的な医学的管理により，最終追跡調査時点で LVEF が正常値（50%以上と定義）に回復し，症状がみられなかった。うっ血性心不全（CHF）の発現率を表 1 に示した。ハーセプチンに起因する左室機能障害発現後の，ハーセプチンの継続投与や再投与の安全性に関する試験は実施されていない。

表 1

乳癌術後補助療法の試験におけるうっ血性心不全の発現率

試験	レジメン	CHF の発現率	
		ハーセプチン群	対照群
1 及び 2[a]	AC[b]→パクリタキセル + ハーセプチン	3.2% (64/2000)[c]	1.3% (21/1655)
3[d]	化学療法→ハーセプチン	2% (30/1678)	0.3% (5/1708)
4	AC[b]→ドセタキセル + ハーセプチン	2% (20/1068)	0.3% (3/1050)
4	ドセタキセル + カルボプラチン + ハーセプチン	0.4% (4/1056)	0.3% (3/1050)

[a] 試験 1 と試験 2 を併合した追跡期間中央値は，AC→TH 群で 8.3 年であった。

[b] アントラサイクリン（ドキソルビシン）及びシクロホスファミド。

[c] 心筋症で死亡した 1 例と病因が記録されていない突然死の 1 例を含む。

[d] ハーセプチン 1 年投与群の追跡期間中央値 12.6 カ月時点の NYHA 分類 II～IV 及び心臓死を含む。

試験3（ハーセプチン1年投与）では，追跡期間中央値が8年の時点で，重度の CHF（NYHA 分類 III 及び IV）の発現率は0.8%であり，軽度の症候性及び無症候性の左室機能不全の発現率は4.6%であった。

表 2

遠隔転移を伴う乳癌を対象とした試験における心機能障害の発現率

		発現率			
		NYHA I～IV		NYHA III～IV	
試験	事象	ハーセプチン群	対照群	ハーセプチン群	対照群
5 (AC)[b]	心機能障害	28%	7%	19%	3%
5（パクリタキセル）	心機能障害	11%	1%	4%	1%
6	心機能障害[c]	7%	N/A	5%	N/A

[a] うっ血性心不全又は，重大な無症候性の LVEF 低下

[b] アントラサイクリン（ドキソルビシン又はエピルビシン）及びシクロホスファミド

[c] 心筋症で死亡した 1 例の患者を含む

試験 4 では，NCI-CTC のグレード 3/4 に分類される虚血性心疾患／梗塞の発現率はハーセプチンを含むレジメンで高かった（AC-TH：0.3%［1068 例中 3 例］及び TCH：0.2%［1056 例中 2 例］）のに対し，AC-T では 0%であった。

5.2 Infusion reaction

Infusion reaction は，発熱及び悪寒を特徴とする複合症状であり，ときに，悪心，嘔吐，疼痛（一部の症例では腫瘍部位における疼痛），頭痛，浮動性めまい，呼吸困難，低血圧，発疹及び無力症を伴う*［副作用（6.1）参照］*。

市販後調査において，重篤かつ致死的な Infusion reaction が報告されている。気管支痙攣，アナフィラキシー，血管浮腫，低酸素症，及び重度の低血圧等の重度の Infusion reaction は，通常，初回の投与中又は投与直後に報告されている。しかし，その発現と臨床経過は多様であり，徐々に悪化する場合，初期に改善した後の臨床的悪化，又は急激な臨床的悪化を伴う遅延反応等がみられた。致死的事象としては，重篤な Infusion reaction が発現した後，数時間から数日以内に死亡に至っている。

呼吸困難及び臨床上重大な血圧低下が認められたすべての患者について，ハーセプチン投与を中断し，エピネフリン，副腎皮質ステロイド，ジフェンヒドラミン，気管支拡張薬及び酸素吸入等による治療を実施すること。徴候及び症状が完全に消失するまで，患者を評価し，慎重に観察すること。重度の Infusion reaction が発現したすべての患者について，投与中止を十分に検討すること。

重度の Infusion reaction 発現後に，ハーセプチンを安全に再投与できる患者を特定する最適な方法についてのデータはない。重度の Infusion reaction を発現した患者の大部分は，ハーセプチンの投与再開前に，抗ヒスタミン薬及び／又は副腎皮質ステロイドによる前投薬を行っていた。ハーセプチン投与に忍容性を示した患者もいたが，前投薬が行われたにも関わらず，重度の Infusion reaction を再び発現した患者もいた。

5.3 胚・胎児毒性

ハーセプチンは，妊娠している女性に投与した場合，胎児へ害を及ぼす可能性がある。市販後調査の報告において，妊娠中のハーセプチンの使用により羊水過少及び，肺形成不全，骨格異常及び新生児死亡を合併する羊水過少を発現した患者がいた。

生殖能を有する女性には，ハーセプチンの投与開始前に妊娠状況を確認すること。妊娠中の女性及び生殖能を有する女性には，妊娠中又は妊娠前7カ月以内にハーセプチンに曝露すると胎児に害が及ぶ可能性があることを伝える。生殖能を有する女性にはハーセプチンの治療期間中及び治療終了後7カ月間は有効な避妊方法を用いるように助言すること*［特別な集団への投与（8.1, 8.3）及び臨床薬理（12.3）参照］*。

5.4　肺毒性

ハーセプチン投与により重篤かつ致死的な肺毒性が発現することがある。肺毒性には，呼吸困難，間質性肺臓炎，肺浸潤，胸水，非心原性肺水腫，肺機能不全及び低酸素，急性呼吸窮迫症候群，肺線維症などがある。これらの事象は，Infusion reaction の続発症として発現することがある*［警告及び使用上の注意（5.2）参照］*。症候性の内因性肺疾患，又は肺の広範囲な腫瘍病変により安静時呼吸困難のある患者は，より重度の毒性が現れる可能性がある。

5.5　化学療法誘発性好中球減少症の悪化

無作為化比較臨床試験において，NCI-CTC グレード 3～4 の好中球減少症及び発熱性好中球減少症を発現した患者の割合は，化学療法を単独投与された患者と比べ，骨髄抑制作用を有する化学療法剤とハーセプチンを併用投与された患者の方が高かった。敗血症による死亡の発現率はハーセプチンを投与した患者と投与しなかった患者で同程度であった*［副作用（6.1）参照］*。

6　副作用

以下の副作用に関しては，他のセクションで，より詳細に検討されている：

- 心筋症*［警告及び使用上の注意（5.1）参照］*
- Infusion reaction*［警告及び使用上の注意（5.2）参照］*
- 胚・胎児毒性*［警告及び使用上の注意（5.3）参照］*
- 肺毒性*［警告及び使用上の注意（5.4）参照］*
- 化学療法誘発性好中球減少症の悪化*［警告及び使用上の注意（5.5）参照］*

乳癌の補助化学療法及び遠隔転移を伴う乳癌において，ハーセプチンを投与された患者で最もよくみられる副作用は，発熱，悪心，嘔吐，Infusion reaction，下痢，感染，咳嗽増加，頭痛，疲労，呼吸困難，発疹，好中球減少症，貧血，筋肉痛である。ハーセプチン治療の中断や中止が必要となる副作用はCHF，左室機能の著しい低下，重度の Infusion reaction，肺毒性等である*［用法・用量（2.3）参照］*。

遠隔転移を伴う胃癌において，化学療法群に比べハーセプチン併用群で高頻度（≥ 5%）に発現した最もよくみられる副作用（≥ 10%）は，好中球減少症，下痢，疲労，貧血，口内炎，体重減少，上気道感染，発熱，血小板減少症，粘膜の炎症，鼻咽頭炎，味覚不全である。ハーセプチン群で疾患の進行がない状態で治療中止に至った副作用で最もよくみられたものは，感染，下痢，発熱性好中球減少症であった。

6.1　臨床試験における使用経験

臨床試験は様々な条件下で実施されているため，ある医薬品の臨床試験で認められた副作用発現率は，他の医薬品の臨床試験における副作用発現率と直接比較することはできないし，実地医療における発現率を反映していないかもしれない。

乳癌術後補助療法による試験

以下のデータは，乳癌補助療法における 3 つの無作為化非盲検試験でのハーセプチンの 1 年投与の曝露結果を示している。試験 1，2 及び 3 はトラスツズマブ投与群（n＝3678）とトラスツズマブ非投与群（n＝3363）からなる。

下記の表 3 では，試験 3 でハーセプチンを投与された 1678 例におけるハーセプチンの曝露結果を要約している。投与期間の中央値は 51 週で，投与回数の中央値は 18 回であった。試験 3 での観察群及びハーセプチン 1 年投与群に登録された 3386 例のうち，ハーセプチン群の追跡期間中央値は 12.6 カ月であり，年齢中央値は 49 歳（範囲：21～80 歳），83%は白人，13%はアジア人であった。

表 3

試験 3 でみられた副作用 [a]，全グレード [b]

副作用	ハーセプチン 1 年投与群 (n = 1678)	観察群 (n = 1708)
心臓障害		
高血圧	64 (4%)	35 (2%)
浮動性めまい	60 (4%)	29 (2%)
駆出率減少	58 (3.5%)	11 (0.6%)
動悸	48 (3%)	12 (0.7%)
心不整脈 [c]	40 (3%)	17 (1%)
うっ血性心不全	30 (2%)	5 (0.3%)
心不全	9 (0.5%)	4 (0.2%)
心障害	5 (0.3%)	0 (0%)
心室機能不全	4 (0.2%)	0 (0%)
呼吸器，胸郭および縦隔障害		
咳嗽	81 (5%)	34 (2%)
インフルエンザ	70 (4%)	9 (0.5%)
呼吸困難	57 (3%)	26 (2%)
上気道感染	46 (3%)	20 (1%)
鼻炎	36 (2%)	6 (0.4%)
咽喉頭疼痛	32 (2%)	8 (0.5%)
副鼻腔炎	26 (2%)	5 (0.3%)
鼻出血	25 (2%)	1 (0.06%)
肺高血圧症	4 (0.2%)	0 (0%)
間質性肺臓炎	4 (0.2%)	0 (0%)
胃腸障害		
下痢	123 (7%)	16 (1%)
悪心	108 (6%)	19 (1%)
嘔吐	58 (3.5%)	10 (0.6%)
便秘	33 (2%)	17 (1%)
消化不良	30 (2%)	9 (0.5%)
上腹部痛	29 (2%)	15 (1%)
筋骨格系および結合組織障害		
関節痛	137 (8%)	98 (6%)
背部痛	91 (5%)	58 (3%)
筋肉痛	63 (4%)	17 (1%)
骨痛	49 (3%)	26 (2%)
筋痙縮	46 (3%)	3 (0.2%)
神経系障害		
頭痛	162 (10%)	49 (3%)
錯感覚	29 (2%)	11 (0.6%)
皮膚および皮下組織障害		
発疹	70 (4%)	10 (0.6%)
爪の障害	43 (2%)	0 (0%)
そう痒症	40 (2%)	10 (0.6%)

表 3（続き）

試験 3 でみられた副作用[a]，全グレード[b]

副作用	ハーセプチン 1 年投与群 (n = 1678)	観察群 (n = 1708)
一般的全身障害		
発熱	100 (6%)	6 (0.4%)
末梢性浮腫	79 (5%)	37 (2%)
悪寒	85 (5%)	0 (0%)
無力症	75 (4.5%)	30 (2%)
インフルエンザ様疾患	40 (2%)	3 (0.2%)
突然死	1 (0.06%)	0 (0%)
感染		
上咽頭炎	135 (8%)	43 (3%)
尿路感染	39 (3%)	13 (0.8%)
免疫系障害		
過敏症	10 (0.6%)	1 (0.06%)
自己免疫性甲状腺炎	4 (0.3%)	0 (0%)

[a] ハーセプチン 1 年投与群で追跡期間中央値 12.6 カ月。

[b] 各事象のグレード 3 以上の副作用発現率は，両群で 1%未満

[c] 高位グループ用語

試験 3 では，3 週間 1 回のハーセプチン治療の 2 年投与と 1 年投与の比較も行った。無症候性心機能障害の発現率は，ハーセプチン 2 年投与群で上昇した（ハーセプチン 1 年投与群の 4.6%に対して 8.1%）。ハーセプチン 2 年投与群では，ハーセプチン 1 年投与群（16.3%）より，グレード 3 以上の副作用が 1 回以上発現した患者が多かった（20.4%）。

試験 1 及び試験 2 の安全性データが 3655 例から得られ，そのうち 2000 例がハーセプチンを投与されていた。投与期間の中央値は 50 週であった。年齢の中央値は 49 歳（範囲：24～80 歳）で，84%が白人，7%が黒人，4%がヒスパニック，3%がアジア人であった。

試験 1 において，グレード 3～5 の重篤な有害事象，治療と関連したグレード 2 の有害事象，及びグレード 2～5 の呼吸困難が，プロトコールで規定された治療期間中及び治療から 3 カ月の期間に発現した。次に挙げるグレード 2～5 の非心臓性の副作用発現率は化学療法単独群と比較してハーセプチン + 化学療法群の方が，少なくとも 2%高かった：疲労（29.5% vs. 22.4%），感染（24.0% vs. 12.8%），ほてり（17.1% vs. 15.0%），貧血（12.3% vs. 6.7%），呼吸困難（11.8% vs. 4.6%），発疹／落屑（10.9% vs. 7.6%），白血球減少症（10.5% vs. 8.4%），好中球減少症（6.4% vs. 4.3%），頭痛（6.2% vs. 3.8%），疼痛（5.5% vs. 3.0%），浮腫（4.7% vs. 2.7%），不眠症（4.3% vs. 1.5%）。これら事象の大半は，重症度がグレード 2 であった。

試験 2 では，次の事象のうち，治験責任医師が治療に関連すると判断した副作用のみが収集された：NCI-CTC グレード 4 及び 5 の血液学的毒性，グレード 3～5 の非血液学的毒性，タキサン系薬剤に関連したグレード 2～5 の毒性（筋肉痛，関節痛，爪の変化，運動ニューロパシー，知覚ニューロパシー），及び化学療法及び／又はハーセプチン治療中に発現したグレード 1～5 の心毒性。次に挙げるグレード 2～5 の非心臓性の副作用発現率は化学療法単独群と比較してハーセプチン + 化学療法群の方が，少なくとも 2%高かった：関節痛（12.2% vs. 9.1%），爪の変化（11.5% vs. 6.8%），呼吸困難（2.4% vs. 0.2%），下痢（2.2% vs. 0%）。これら事象の大半は，重症度がグレード 2 であった。

試験 4 の安全性データは，術後補助療法の一環で少なくとも 1 回ハーセプチンの治療を受けた 2124 例（AC-TH：n = 1068；TCH：n = 1056）におけるハーセプチンへの曝露を反映している。全体の治療期間の中央値は AC-TH 群，TCH 群ともに 54 週であった。投与回数の中央値は AC-TH

群 26 回，TCH 群 30 回であった（化学療法剤投与期間の 1 週間 1 回投与と，単独療法期間の 3 週間 1 回投与を含む）。患者の年齢の中央値は 49 歳（範囲：22～74 歳）であった。試験 4 における毒性のプロファイルは，TCH 群でうっ血性心不全の発現率が低かったことを除けば，試験 1，2 及び 3 と同様であった。

遠隔転移を伴う乳癌を対象とした試験

以下のデータは，遠隔転移を伴う乳癌患者に対する無作為化非盲検試験である試験 5（トラスツズマブ投与群：235 例，トラスツズマブ非投与群：234 例）及び，遠隔転移を伴う乳癌患者に対する単群試験（試験 6：222 例）のハーセプチンの曝露結果を示している。表 4 のデータは試験 5 及び試験 6 に基づく。

試験 5 で治療された患者は 464 例であり，年齢の中央値は 52 歳（範囲：25～77 歳）であった。89%が白人，5%が黒人，1%がアジア人，5%が他の人種／民族集団であった。すべての患者がハーセプチンを初回 4 mg/kg，2 回目以降 2 mg/kg，週 1 回投与された。6 カ月以上，あるいは 12 カ月以上ハーセプチンの治療を受けた患者の割合は，それぞれ 58%，9%であった。

単独投与を受けた 352 例（うち 213 例は，試験 6 の患者）では，年齢の中央値は 50 歳（範囲：28～86 歳）であり，86%が白人，3%が黒人，3%がアジア人，8%が他の人種／民族集団であった。ほとんどの患者がハーセプチンを初回 4 mg/kg，2 回目以降は 2 mg/kg，週 1 回投与された。6 カ月以上，あるいは 12 カ月以上ハーセプチンの治療を受けた患者の割合は，それぞれ 31%，16%であった。

表 4

対照群を設定していない試験において発現率 5%以上，あるいはハーセプチン群で発現率が上昇した副作用の発現率（試験 5 及び試験 6）

	単剤[a] n = 352	ハーセプチン + パクリタキセル n = 91	パクリタキセルのみ n = 95	ハーセプチン + AC[b] n = 143	AC[b] のみ n = 135
一般的全身障害					
疼痛	47%	61%	62%	57%	42%
無力症	42%	62%	57%	54%	55%
発熱	36%	49%	23%	56%	34%
悪寒	32%	41%	4%	35%	11%
頭痛	26%	36%	28%	44%	31%
腹痛	22%	34%	22%	23%	18%
背部痛	22%	34%	30%	27%	15%
感染	20%	47%	27%	47%	31%
インフルエンザ症候群	10%	12%	5%	12%	6%
事故による外傷	6%	13%	3%	9%	4%
アレルギー反応	3%	8%	2%	4%	2%
心・血管障害（一般）					
頻脈	5%	12%	4%	10%	5%
うっ血性心不全	7%	11%	1%	28%	7%
胃腸障害					
悪心	33%	51%	9%	76%	77%
下痢	25%	45%	29%	45%	26%
嘔吐	23%	37%	28%	53%	49%
嘔気および嘔吐	8%	14%	11%	18%	9%
食欲不振	14%	24%	16%	31%	26%
血液およびリンパ系障害					
貧血	4%	14%	9%	36%	26%
白血球減少症	3%	24%	17%	52%	34%
代謝および栄養障害					
末梢性浮腫	10%	22%	20%	20%	17%
浮腫	8%	10%	8%	11%	5%
筋および骨格系障害					
骨痛	7%	24%	18%	7%	7%
関節痛	6%	37%	21%	8%	9%

表 4（続き）

対照群を設定していない試験において発現率 5%以上，あるいはハーセプチン群で発現率が上昇した副作用の発現率（試験 5 及び試験 6）

	単剤[a] n = 352	ハーセプチン + パクリタキセル n = 91	パクリタキセルのみ n = 95	ハーセプチン + AC[b] n = 143	AC[b] のみ n = 135
神経系障害					
不眠症	14%	25%	13%	29%	15%
浮動性めまい	13%	22%	24%	24%	18%
錯感覚	9%	48%	39%	17%	11%
うつ病	6%	12%	13%	20%	12%
末梢神経炎	2%	23%	16%	2%	2%
ニューロパチー	1%	13%	5%	4%	4%
呼吸器系障害					
咳嗽増加	26%	41%	22%	43%	29%
呼吸困難	22%	27%	26%	42%	25%
鼻炎	14%	22%	5%	22%	16%
咽頭炎	12%	22%	14%	30%	18%
副鼻腔炎	9%	21%	7%	13%	6%
皮膚および皮下組織障害					
発疹	18%	38%	18%	27%	17%
単純ヘルペス	2%	12%	3%	7%	9%
ざ瘡	2%	11%	3%	3%	< 1%
泌尿器・生殖器障害					
尿路感染	5%	18%	14%	13%	7%

[a] 試験 4 のハーセプチン単独投与のデータには，試験 6 の 213 例を含む。

[b] アントラサイクリン（ドキソルビシン又はエピルビシン）及びシクロホスファミド

遠隔転移を伴う胃癌

以下のデータは，フッ化ピリミジン系薬剤（カペシタビン又は 5-FU）及びシスプラチンとの併用でハーセプチンの治療を受けた 294 例（試験 7）の曝露結果を示している。化学療法とハーセプチンの併用群では，ハーセプチンを初回 8 mg/kg で Day1（化学療法より前）に投与し，2 回目以降 6 mg/kg，21 日ごとに病勢進行まで投与された。シスプラチンは Day1 に 80mg/m^2 投与され，フッ化ピリミジン系薬剤は，カペシタビン 1000 mg/m^2 を 1 日 2 回，Day1 から Day14 まで経口投与するか又は 5-FU 800 mg/m^2/日を Day1 から 5 日間かけて持続静脈内投与した。化学療法は 21 日を 1 サイクルとして 6 サイクル投与された。ハーセプチンの投与期間の中央値は 21 週間であり，投与回数の中央値は 8 回であった。

表 5

試験 7：ハーセプチン投与群において発現率が高い全グレード（群間の発現率≥ 5%）
又はグレード 3/4（群間の発現率> 1%）の副作用発現率

身体系統／有害事象	ハーセプチン + FC (N = 294) N (%)		FC (N = 290) N (%)	
	全グレード	グレード 3/4	全グレード	グレード 3/4
臨床検査				
好中球減少症	230 (78)	101 (34)	212 (73)	83 (29)
低カリウム血症	83 (28)	28 (10)	69 (24)	16 (6)
貧血	81 (28)	36 (12)	61 (21)	30 (10)
血小板減少症	47 (16)	14 (5)	33 (11)	8 (3)
血液およびリンパ系障害				
発熱性好中球減少症	—	15 (5)	—	8 (3)
胃腸障害				
下痢	109 (37)	27 (9)	80 (28)	11 (4)
口内炎	72 (24)	2 (1)	43 (15)	6 (2)
嚥下障害	19 (6)	7 (2)	10 (3)	1 (≤ 1)
一般的全身障害				
疲労	102 (35)	12 (4)	82 (28)	7 (2)
発熱	54 (18)	3 (1)	36 (12)	0 (0)
粘膜の炎症	37 (13)	6 (2)	18 (6)	2 (1)
悪寒	23 (8)	1 (≤ 1)	0 (0)	0 (0)
代謝および栄養障害				
体重減少	69 (23)	6 (2)	40 (14)	7 (2)
感染症および寄生虫症				
上気道感染	56 (19)	0 (0)	29 (10)	0 (0)
上咽頭炎	37 (13)	0 (0)	17 (6)	0 (0)
腎および尿路障害				
腎不全および腎機能障害	53 (18)	8 (3)	42 (15)	5 (2)
神経系障害				
味覚不全	28 (10)	0 (0)	14 (5)	0 (0)

乳癌補助療法試験，遠隔転移を伴う乳癌試験，遠隔転移を伴う胃癌試験，市販後使用経験で認められた副作用の追加詳細情報を以下のサブセクションに示す。

心筋症

乳癌術後補助療法の臨床試験で心機能（LVEF）の経時的な測定を行っている。試験 3 におけるフォローアップ期間の中央値は 12.6 カ月（観察群：12.4 カ月，ハーセプチン 1 年投与群：12.6 カ月），試験 1 及び 2 については，AC-T 投与群が 7.9 年，AC-TH 投与群が 8.3 年であった。試験 1 及び 2 では，無作為化され，AC 化学療法後に LVEF が上昇したすべての患者の 6%が心機能

障害（LVEF が基準値下限未満，又は，AC 終了時の LVEF がベースラインから 16 ポイント以上低下）のため，AC 化学療法後のハーセプチン投与を開始できなかった。ハーセプチンの治療開始後，用量制限を要する新たな心筋機能障害の発現率は，試験 1 及び 2 ではパクリタキセル単独投与を受けた患者に比べてハーセプチンとパクリタキセルの併用投与を受けた患者で，試験 3 では観察群に比べてハーセプチン単剤の 1 年投与を受けた患者で高かった（表 6，図 1 及び 2 参照）。新たに発現した心機能障害の患者別発現率は LVEF で測定され，AC-TH 群を対象に追跡期間中央値 2.0 年時点で実施した解析と比較しても同程度であった。この解析では，左室機能障害の可逆性のエビデンスも示され，AC-TH 群で症候性 CHF がみられた患者の 64.5%が最新の追跡調査で無症状であり，90.3%で LVEF の完全又は部分的な回復がみられた。

表 6[a]

試験 1，2，3 及び 4 における心筋機能障害（LVEF による）の
投与群ごとの新規発現率

	LVEF < 50% かつベースライン値からの絶対的低下			LVEF の絶対的低下	
	LVEF < 50%	≥ 10% 低下	≥ 16% 低下	< 20%かつ ≥ 10%	≥ 20%
試験 1 及び 2[b,c]					
AC→TH (n = 1856)	23.1% (428)	18.5% (344)	11.2% (208)	37.9% (703)	8.9% (166)
AC→T (n = 1170)	11.7% (137)	7.0% (82)	3.0% (35)	22.1% (259)	3.4% (40)
試験 3[d]					
ハーセプチン群 (n = 1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
観察群 (n = 1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
試験 4[e]					
TCH (n = 1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n = 1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n = 1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

[a] 試験 1，2 及び 3 では，事象はハーセプチン投与開始からカウントした。試験 4 では，事象は無作為化された日からカウントした。

[b] 試験 1 及び 2 のレジメン：ドキソルビシン及びシクロホスファミドの後，パクリタキセル（AC→T）又はパクリタキセル + ハーセプチン（AC→TH）。

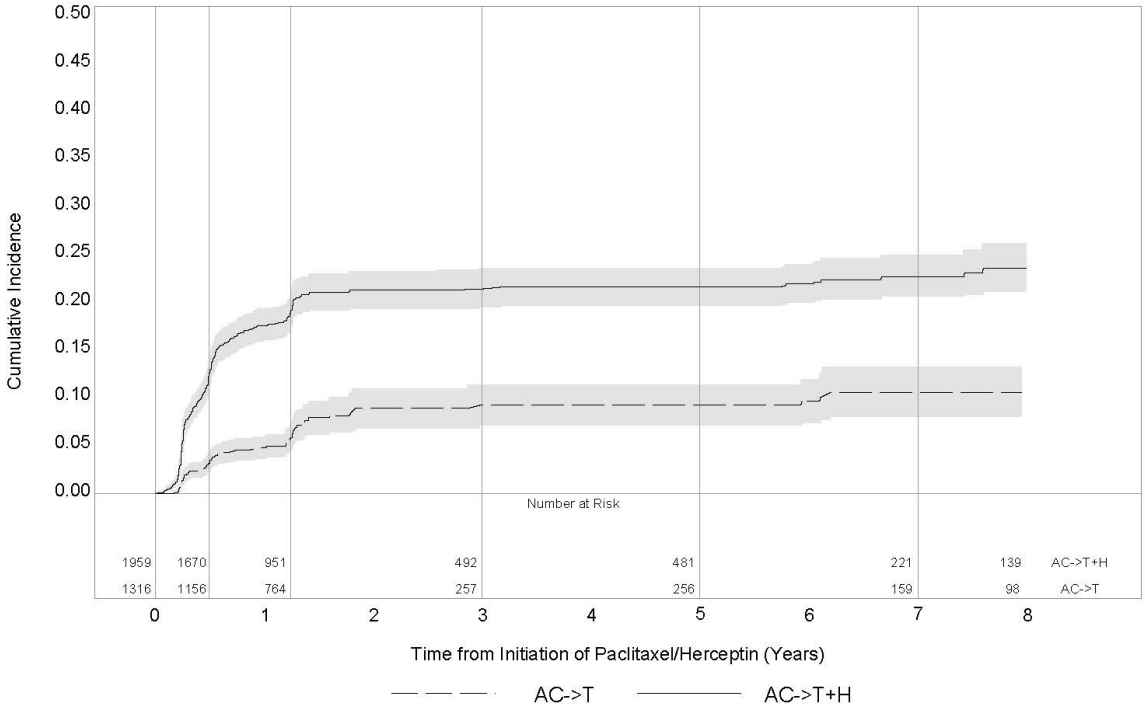
[c] 試験 1 と試験 2 を併合した追跡期間中央値は，AC-TH 群で 8.3 年であった。

[d] ハーセプチン 1 年投与群で追跡期間中央値 12.6 カ月。

[e] 試験 4 のレジメン：ドキソルビシン及びシクロホスファミドの後，ドセタキセル（AC→T）又はドセタキセル + ハーセプチン（AC→TH），ドセタキセル及びカルボプラチン + ハーセプチン（TCH）。

図 1

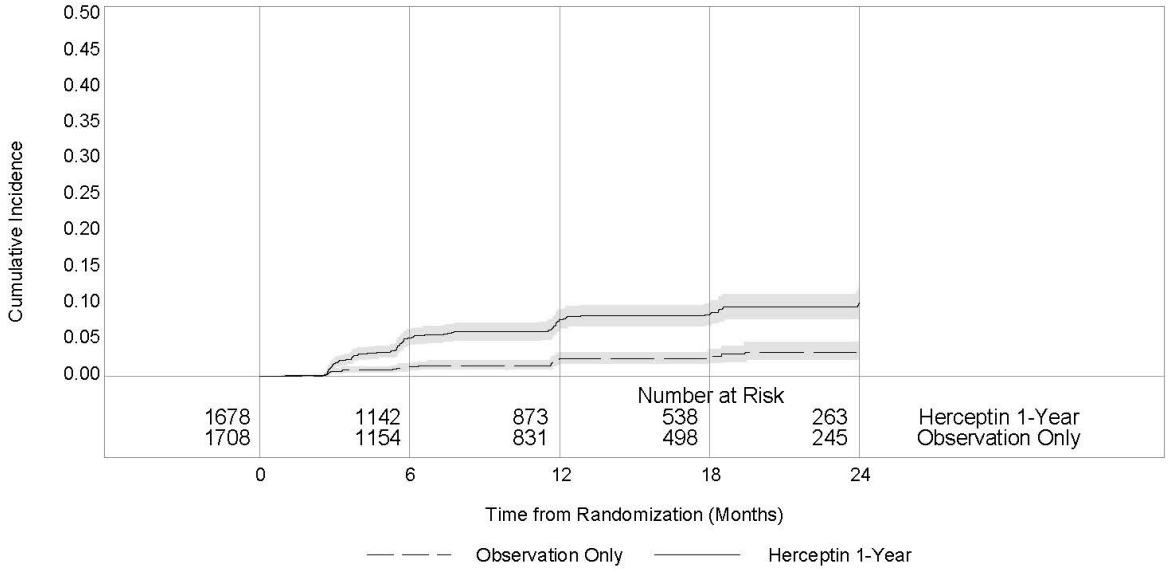
試験 1 及び 2：最初に LVEF がベースライン値から 10 ポイント以上低下
かつ 50%以下になるまでの時間の累積発生率
（死亡を競合リスクイベントとした場合）



Time 0は，パクリタキセル単剤又はハーセプチン ＋ パクリタキセルの治療開始時とした。

表 2

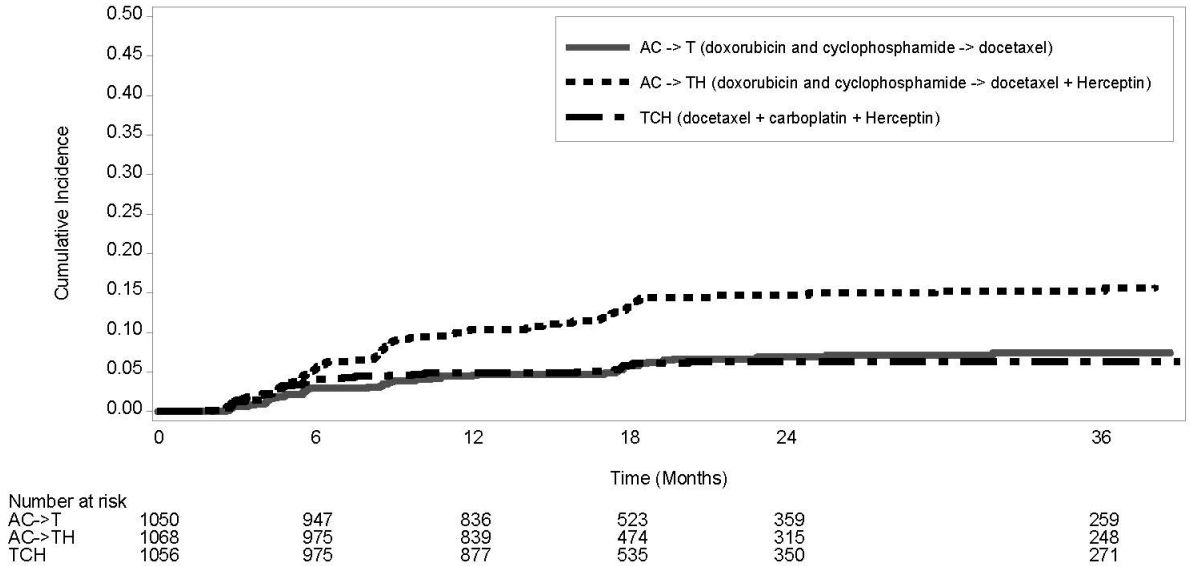
試験 3：最初に LVEF がベースライン値から 10 ポイント以上低下
かつ 50%以下になるまでの時間の累積発生率
（死亡を競合リスクイベントとした場合）



Time 0は無作為化された日とした。

表 3

試験 4：最初に LVEF がベースライン値から 10 ポイント以上低下
かつ 50%以下になるまでの時間の累積発生率
（死亡を競合リスクイベントとした場合）



Time 0は無作為化された日とした。

遠隔転移を伴う乳癌の試験において，治療中に発現したうっ血性心不全の発現率は，ニューヨーク心臓学会分類法（I～IV，ここでは，IV が最も重症度の高い心不全）による重症度で分類された（表 2 参照）。遠隔転移を伴う乳癌の試験では，心機能異常を起こす確率は，アントラサイクリン系薬剤とハーセプチンを併用した患者で最も高かった。

試験 7 において，LVEF 値が 50%未満かつ投与前値から 10%以上低下した患者は，化学療法群で 1.1%であったのに対し，ハーセプチン併用群では 5.0%であった。

Infusion reaction

ハーセプチン初回投与中に最もよくみられる症状は悪寒及び発熱で，臨床試験においては約 40%の患者で発現した。これらの症状は，（ハーセプチン投与速度の減速の有無に関わらず）アセトアミノフェン，ジフェンヒドラミン及びメペリジンにより治療された；Infusion reaction によるハーセプチンの投与中止例は，1%未満であった。他の徴候及び／又は症状としては，悪心，嘔吐，疼痛（一部の症例では腫瘍部位における疼痛），悪寒，頭痛，浮動性めまい，呼吸困難，低血圧，血圧上昇，発疹，及び無力症等が発現する可能性がある。2 回目以降のハーセプチン投与における Infusion reaction は，単独療法及び化学療法との併用療法で，それぞれ，患者の 21%及び 35%にみられ，患者の 1.4%及び 9%において重度であった。市販後調査において，過敏症，アナフィラキシー，血管浮腫を含む重度の Infusion reaction が報告されている。

貧血

無作為化比較臨床試験において，貧血［30% vs. 21%（試験 5）］，NCI-CTC グレード 2～5 の貧血［12.3% vs. 6.7%（試験 1）］，輸血を要する貧血［0.1% vs. 0 例（試験 2）］の発現率は，化学療法剤とハーセプチンを併用投与された患者の方が，化学療法剤を単独投与された患者より高かった。ハーセプチンの単剤投与（試験 6）後の NCI-CTC グレード 3 の貧血の発現率は 1%未満であった。試験 7（遠隔転移を伴う胃癌）において，貧血の発現率は，化学療法群で 21%であったのに対しハーセプチン併用群では 28%であり，NCI-CTC グレード 3/4 の貧血は化学療法群で 10.3%であったのに対しハーセプチン併用群は 12.2%であった。

好中球減少症

術後補助療法に関する無作為化比較臨床試験において，NCI-CTC グレード 4～5 の好中球減少症［1.7% vs. 0.8%（試験 2）］，グレード 2～5 の好中球減少症［6.4% vs. 4.3%（試験 1）］の発現率は，化学療法剤とハーセプチンを併用投与された患者の方が，化学療法剤を単独投与された患者より高かった。遠隔転移を伴う乳癌患者を対象とした無作為化比較試験において，NCI-CTC グレード 3/4 の好中球減少症（32% vs. 22%）及び発熱性好中球減少症（23% vs. 17%）の発現率もまた，骨髄抑制作用を有する化学療法剤とハーセプチンを併用投与する群に割り付けられた患者の方が，化学療法剤を単独投与する群に割り付けられた患者より高かった。試験 7（遠隔転移を伴う胃癌）において，NCI-CTC グレード 3/4 の好中球減少症の発現率は化学療法群で 28.9%であったのに対し，ハーセプチン併用群では 36.8%であった。発熱性好中球減少症においては，化学療法群で 2.8%であったのに対し，ハーセプチン併用群では 5.1%であった。

感染

感染発現率［46% vs. 30%（試験 5）］，NCI-CTC グレード 2～5 の感染症／発熱性好中球減少症［24.3% vs. 13.4%（試験 1）］及びグレード 3～5 の感染症／発熱性好中球減少症［2.9% vs. 1.4%（試験 2）］の発現率はすべて，化学療法剤とハーセプチンを併用投与された患者の方が，化学療法剤を単独投与された患者より高かった。術後補助療法における感染症の好発部位は，上気道，皮膚及び尿路であった。

試験4における感染の発現率は，TCH ではなく AC-T とハーセプチンを併用することで高かった［44%（AC-TH），37%（TCH），38%（AC-T）］。NCI-CTC のグレード3～4の感染の発現率は3群で同様であった［25%（AC-TH），21%（TCH），23%（AC-T）］。

遠隔転移を伴う乳癌治療に関する無作為化比較試験において，発熱性好中球減少症の発現率は，骨髄抑制作用を有する化学療法剤とハーセプチンを併用投与された患者の方が，化学療法剤を単独投与された患者より高かった（23% vs. 17%）。

肺毒性

乳癌術後補助療法

乳癌の術後補助療法を受けている女性のうち，ハーセプチン投与及び化学療法を受けている患者では，化学療法のみの患者と比較して，NCI-CTC グレード 2～5 の肺毒性（14.3% vs. 5.4%［試験 1］），並びに NCI-CTC グレード 3～5 の肺毒性及び自発的に報告されたグレード 2 の呼吸困難（3.4% vs. 0.9%［試験 2］）の発現率が高かった。最もよくみられる肺毒性は呼吸困難（NCI-CTC グレード 2～5：11.8% vs. 4.6%［試験 1］；NCI-CTC グレード 2～5：2.4% vs. 0.2%［試験 2］）であった。

肺臓炎／肺浸潤は，化学療法剤を単独投与された患者では 0.3%に発現したのに対し，ハーセプチンを投与された患者では 0.7%に発現した。致死的な呼吸不全は，化学療法剤を単独投与された患者では 1 例に発現したのに対し，ハーセプチンを投与された患者では 3 例に発現し，そのうち 1 例は多臓器不全であった。

試験 3 では，追跡期間中央値 12.6 カ月の時点で間質性肺臓炎がハーセプチン 1 年投与群で 4 件発現していたのに対し，観察群では発現していなかった。

遠隔転移を伴う乳癌

遠隔転移を伴う乳癌の治療でハーセプチンを投与された女性でも，肺毒性の発現率は上昇した。市販後使用経験において，肺に関する有害事象は，Infusion reaction の複合症状の一部として報告されている。肺に関する事象は，気管支痙攣，低酸素症，呼吸困難，肺浸潤，胸水，非心原性肺水腫及び急性呼吸窮迫症候群等である。詳細な記載については，*「警告及び使用上の注意（5.4）」*を参照。

血栓症／塞栓症

4 つの無作為化比較臨床試験のうち，血栓症の有害事象の発現率は，3 つの試験において化学療法剤とハーセプチンを併用投与された患者の方が，化学療法剤を単独投与された患者よりも高かった（2.6% vs. 1.5%［試験 1］，2.5 %，3.7% vs. 2.2%［試験 4］，2.1% vs. 0%［試験 5］）。

下痢

乳癌術後補助療法としてハーセプチン投与を受けた女性では，NCI-CTC グレード 2～5 の下痢（6.7% vs. 5.4%［試験 1］）及びグレード 3～5 の下痢（2.2% vs. 0%［試験 2］），並びにグレード 1～4 の下痢（7% vs. 1%［試験 3：ハーセプチン 1 年投与群の追跡期間中央値は 12.6 カ月］）の発現率は，ハーセプチンを投与された患者の方が，対照群の患者より高かった。試験 4 ではハーセプチンを投与された患者で，グレード 3～4 の下痢（5.7% AC-TH，5.5% TCH vs. 3.0% AC-T），グレード 1～4 の下痢（51% AC-TH，63% TCH vs. 43% AC-T）の発現率が高かった。遠隔転移を伴う乳癌の治療でハーセプチン単独投与を受けた患者の 25%に下痢が発現した。遠隔転移を伴う乳癌の治療でハーセプチンと化学療法を併用投与された患者において，下痢の発現率上昇が認められた。

腎毒性

試験7（遠隔転移を伴う胃癌）において腎機能障害の発現率は，化学療法群で14.5%であったのに対し，ハーセプチン併用群では18%であった。重度（グレード3/4）の腎不全は，化学療法群で1.7%であったのに対し，ハーセプチン併用群では2.7%であった。腎機能不全／腎不全による治療の中止は，ハーセプチン併用群では2%，化学療法群では0.3%であった。

市販後において，糸球体症の病理学的証拠を伴うネフローゼ症候群のまれな症例が報告されている。発症までの期間は，ハーセプチン療法開始後 4 カ月から約 18 カ月までの範囲であった。病理学的所見として，膜性糸球体腎炎，巣状糸球体硬化症，及び線維性糸球体腎炎等があった。合併症として，体液量過負荷及びうっ血性心不全があった。

6.2　免疫原性

あらゆる治療用蛋白製剤同様，本剤にも免疫原性の可能性がある。遠隔転移を伴う乳癌女性 903 例のうち 1 例において，ハーセプチンに対するヒト抗ヒト抗体（HAHA）が，酵素免疫測定法（ELISA）で検出された。当該患者にアレルギー反応は発現しなかった。乳癌術後補助療法の試験では，HAHA の測定検体は採取されなかった。

抗体産生の発現率は，アッセイの感度と特異度によって大きく異なる。加えて，ELISA 法で認められた抗体（中和抗体を含む）の陽性率は，測定手法，試料の取扱い，試料採取のタイミン

グ，併用薬，及び基礎疾患等，複数の要因の影響を受ける可能性がある。これらの理由から，ハーセプチンに対する抗体発現率と他の製品に対する抗体発現率の比較は，誤解を招く可能性がある。

6.3 市販後使用経験

以下の副作用が，ハーセプチン承認後の使用時に特定されている。これらの副作用は規模が不明な集団から自発的に報告されたため，必ずしも確実に発現頻度の評価や，薬物投与との因果関係の評価が可能とは限らない。

- Infusion reaction *［警告及び使用上の注意（5.2）参照］*
- 羊水過少又は肺形成不全，骨格異常及び新生児死亡を含む羊水過少 *［警告及び使用上の注意（5.3）参照］*
- 糸球体症 *［副作用（6.1）参照］*
- 免疫性血小板減少症
- 腫瘍崩壊症候群（TLS）：TLS の可能性がある症例がハーセプチン群の患者で報告されている。全身腫瘍組織量が大きい患者（例えば，巨大転移）はリスクが高い可能性がある。患者は高尿酸血症，高リン酸塩血症，急性腎不全を呈する可能性があり，これは TLS の可能性がある。医療従事者は，臨床的に適応となる場合には，追加のモニタリング及び／又は治療を検討すべきである。

7 薬物相互作用

母集団薬物動態解析によるとトラスツズマブのウォッシュアウト期間は長いため，ハーセプチン投与中止後にアントラサイクリン系薬剤を投与された患者では心機能障害のリスクが上昇する可能性がある *［臨床薬理（12.3）参照］*。可能な限り，ハーセプチン投与中止後 7 カ月までは，アントラサイクリン系薬剤をベースとした治療は避けるべきである。やむを得ずアントラサイクリン系薬剤を使用する場合は，患者の心機能を注意深く観察しなければならない。

8 特別な集団への投与

8.1 妊婦

妊娠中の安全管理プログラム

ハーセプチンには妊娠中の安全管理プログラムがある。妊娠中にハーセプチンが投与された場合，若しくはハーセプチン投与中又はハーセプチンの最後の投与から 7 カ月以内に患者が妊娠した場合，医療従事者及び患者は直ちにハーセプチンへの曝露について Genentech（電話：1-888-835-2555）に報告すること。

リスクの要約

ハーセプチンは，妊娠している女性に投与した場合，胎児へ害を及ぼす可能性がある。市販後調査の報告において，妊娠中のハーセプチンの使用により羊水過少及び，肺形成不全，骨格異常及び新生児死亡を合併する羊水過少を発現した患者がいた *［データ参照］*。胎児に対する潜在的なリスクがあることを患者に知らせること。妊婦にハーセプチンを使用する場合，又は患者がハーセプチンの最終投与後 7 カ月以内に妊娠した場合，臨床上の考慮事項がある *［臨床上の考慮事項を参照］*。

対象集団における主な先天性欠損及び自然流産の推定背景リスクは不明である。米国の一般集団において，臨床的に認識された妊娠における主な先天性欠損及び自然流産の推定背景リスクは，それぞれ 2～4%及び 15～20%である。

臨床上の考慮事項

胎児／新生児に対する副作用

羊水過少がないか，妊娠中又は妊娠前 7 カ月以内にハーセプチンを投与された女性をモニタリングすること。羊水過少が発現した場合，妊娠期間に応じ，標準的治療と一致した胎児の試験を実施すべきである。

データ

ヒトにおけるデータ

市販後調査の報告において，妊娠中のハーセプチンの使用により，羊水過少及び，肺形成不全，骨格異常及び新生児死亡として胎児に現れる一連の羊水過少が発現した。これらの症例報告において羊水過少は，妊娠中の女性にハーセプチン単独又は化学療法併用時のいずれの場合でも報告された。いくつかの症例ではハーセプチンの投与中止後，羊水指数が増加した。ある症例では，羊水指数が向上した後にハーセプチン投与を再開し，その後羊水過少が再発した。

動物におけるデータ

器官形成期の妊娠中のカニクイザルにトラスツズマブ最大25 mg/kg を週2回（ヒトの1週間の推奨投与量2 mg/kg の最大25倍）投与した試験では，トラスツズマブは妊娠初期（妊娠20～50日目）及び妊娠後期（妊娠120～150日目）に胎盤関門を通過した。その結果，胎児血清中及び羊水中のトラスツズマブ濃度は，それぞれ母体血清中の濃度の約33%及び25%であったが，発育への有害作用は認められなかった。

8.2　授乳

リスクの要約

ヒト乳汁中のトラスツズマブの存在，母乳栄養の乳児への影響，又は乳汁産生への影響については，知見が得られていない。公表データでは，ヒト IgG はヒト乳汁中に存在するが，新生児及び乳児の循環系へ相当量が移行することはないことが示唆されている。トラスツズマブは授乳中のカニクイザルの乳汁中に存在するが，新生児毒性との関連はなかった*[データ参照]*。母親へのハーセプチン投与の臨床上の必要性及びハーセプチン又は母体の基礎疾患による母乳栄養児への潜在的な悪影響と併せて，発達及び健康上の母乳栄養の利点を考慮すること。この考慮に際しては，7 カ月間のトラスツズマブのウォッシュアウト期間も考慮すること*［臨床薬理（12.3）参照］*。

データ

授乳中のカニクイザルでは，トラスツズマブは，分娩前（妊娠 120 日目に開始）及び分娩後（分娩後 28 日目まで）に 1 週間 2 回 25 mg/kg を投与した後，母乳中に約 0.3%の血清濃度で存在した（ヒトの 1 週間のハーセプチン推奨投与量 2 mg/kg の 25 倍）。トラスツズマブの血清レベルが検出可能な乳児サルでは，出生から生後 1 カ月まで，成長又は発育に有害な影響は及ぼさなかった。

8.3　　生殖可能な男女

妊娠反応

生殖能を有する女性には，ハーセプチンの投与開始前に妊娠状況を確認すること。

避妊

女性

ハーセプチンは，妊婦に投与した場合，胚・胎児へ害を及ぼす可能性がある。生殖能を有する女性にはハーセプチンの治療期間中及び治療終了後 7 カ月間は有効な避妊方法を用いるように助言すること*［特別な集団への投与（8.1, 8.3）及び臨床薬理（12.3）参照］*。

8.4　小児への投与

ハーセプチンの小児における安全性及び有効性は確立していない。

8.5　高齢者への投与

ハーセプチンは 65 歳以上の 386 例（術後補助療法として 253 例及び遠隔転移を伴う乳癌として 133 例）の患者に投与されている。試験 5 及び 6 で転移性乳癌の治療を受けた患者及び，試験 1 及び 2 で術後補助療法を受けた患者のいずれにおいても，高齢者の方が若年者よりも心機能障害の危険性は上昇した。データ収集の制約やハーセプチン乳癌術後補助療法における 4 つの試験デザインが異なっていたため，高齢者と若年者で安全性プロファイルが異なっているかどうかを結論付けることはできない。報告された臨床経験は，転移性乳癌治療と術後補助療法について，ハーセプチンの治療効果の改善（ORR，TTP，OS，DFS）が高齢者と 65 歳未満の患者で差があるか否かを判断するには不十分である。

試験 7（遠隔転移を伴う胃癌）において，ハーセプチンを投与した 294 例中 108 例（37%）が 65 歳以上であり，13 例（4.4%）は 75 歳以上であった。全体的な安全性又は有効性に差は認められなかった。

10 過量投与

ヒトにおける臨床試験で過量投与の経験はない。8 mg/kg を超える単回投与は実施されていない。

1.6.2.2 欧州添付文書の和訳概要

本剤の代表的な外国添付文書として，欧州の添付文書（2020 年 8 月版）の和訳概要を以下に示す。

4. 臨床事項

4.1 治療の適応症

乳癌

遠隔転移を伴う乳癌

ハーセプチンは，HER2陽性の遠隔転移を伴う乳癌成人患者の治療に以下のように適応される：

（MBC）：

- 遠隔転移を伴う乳癌に対し少なくとも2レジメンの化学療法治療歴を有する患者の治療における単剤療法。前化学療法には，患者に治療が適さない場合を除き，少なくともアントラサイクリン系薬剤及びタキサン系薬剤が含まれていなければならない。ホルモン受容体陽性の患者では，患者にホルモン療法が適さない場合を除き，ホルモン療法を受けて無効となっていなければならない。
- 遠隔転移を伴う乳癌に対し化学療法未治療の患者で，アントラサイクリン系薬剤が適さない患者の治療におけるパクリタキセルとの併用療法。
- 遠隔転移を伴う乳癌に対し化学療法未治療の患者の治療におけるドセタキセルとの併用療法。
- トラスツズマブ未治療でホルモン受容体陽性の閉経後の MBC 患者の治療におけるアロマターゼ阻害剤との併用療法。

早期乳癌

ハーセプチンは，HER2陽性の早期乳癌成人患者の治療に以下のように適応される：（EBC）。

- 手術，化学療法（術前又は術後）及び放射線療法（適応となる場合）後（5.1項参照）。
- パクリタキセル又はドセタキセルと併用で投与するドキソルビシン及びシクロホスファミドによる術後補助化学療法後。
- ドセタキセルとカルボプラチンからなる術後補助化学療法との併用。
- 局所進行性（炎症性を含む）疾患又は直径2 cm を超える腫瘍に対する，術前補助療法後のハーセプチンによる術後補助化学療法との併用（4.4項及び5.1項参照）。

正確でバリデーション済みの検査法により HER2過剰発現又は HER2遺伝子増幅が確認された腫瘍を有する，遠隔転移を伴う又は早期乳癌患者に対してのみ，ハーセプチンを使用すること（4.4項及び5.1項参照）。

遠隔転移を伴う胃癌

ハーセプチンは，カペシタビン又は5-FU，及びシスプラチンとの併用により，転移病巣に対し抗癌剤未治療の HER2陽性の遠隔転移を伴う胃癌又は胃食道接合部癌の成人患者に適応される。

HER2過剰発現が IHC2+と判定され HER2遺伝子増幅が SISH 又は FISH 法により確認された腫

瘍，又は IHC3+と確認された腫瘍を有する遠隔転移を伴う胃癌患者（MGC）に対してのみ，ハーセプチンを使用すること。正確でバリデーション済みの検査法を使用すること（4.4項及び5.1項参照）。

4.2　用法・用量

ハーセプチン療法開始前に，HER2検査を必ず実施すること（4.4項及び5.1項参照）。ハーセプチン療法は，細胞毒性を有する化学療法剤の投与に十分な経験を持つ医師のもとでのみ開始し，医療従事者のみが投与すること（4.4項参照）。

製品表示を確認し，処方通りに正しい製剤（点滴静注又は皮下の固定用量）が患者に投与されているかどうかを確認することが重要である。ハーセプチンの静注製剤は皮下投与を目的としていないため，点滴静注のみで投与すること。

MO22982試験では，3週間に1回（q3w）の投与でハーセプチンの静注製剤から皮下製剤及び皮下製剤から静注製剤へと切り替えて投与する方法を検討した（4.8項参照）。

投薬過誤を防ぐには，バイアルのラベルをチェックして，調製及び投与する薬剤がカドサイラ（トラスツズマブ エムタンシン）ではなくハーセプチン（トラスツズマブ）であることを確認することが重要である。

用量

遠隔転移を伴う乳癌

3週間1回投与

推奨初回負荷用量は8 mg/kg（体重）である。3週間1回投与における推奨維持用量は6 mg/kg（体重）で，初回投与3週間後から投与を開始する。

1週間1回投与

ハーセプチンの推奨初回負荷用量は4 mg/kg（体重）である。ハーセプチンの1週間1回投与における推奨維持用量は2 mg/kg（体重）で，初回投与1週間後から投与を開始する。

パクリタキセル又はドセタキセルとの併用投与

主要な臨床試験（H0648g，M77001）において，パクリタキセル又はドセタキセルは，ハーセプチンの初回投与の翌日に（用量については，パクリタキセル又はドセタキセルに対する製品特性概要［SmPC］を参照），また前回のハーセプチン投与で忍容性が確認された場合は，次回投与時にはハーセプチン投与直後に投与された。

アロマターゼ阻害剤との併用投与

主要な臨床試験（BO16216）において，ハーセプチンとアナストロゾールは1日目より併用で投与された。ハーセプチンとアナストロゾールの投与のタイミングに関する制限は無かった（用量については，アナストロゾール又は他のアロマターゼ阻害剤の SmPC を参照）。

早期乳癌

3週間1回投与及び1週間1回投与

ハーセプチンの3週間1回投与における推奨初回負荷用量は8 mg/kg（体重）である。ハーセプチンの3週間1回投与における推奨維持用量は6 mg/kg（体重）で，初回投与3週間後から投与を開始する。

1週間1回投与（初回負荷用量4 mg/kg の後，1週間1回2 mg/kg）では，ドキソルビシン及びシクロホスファミドによる化学療法後にパクリタキセルと併用。
化学療法との併用投与については，5.1項を参照。

遠隔転移を伴う胃癌
3週間1回投与
推奨初回負荷用量は8 mg/kg（体重）である。3週間1回投与における推奨維持用量は6 mg/kg（体重）で，初回投与3週間後から投与を開始する。

乳癌及び胃癌
投与期間
遠隔転移を伴う乳癌，遠隔転移を伴う胃癌の患者は病勢進行までハーセプチンを投与すること。早期乳癌の患者には1年間又は再発のいずれか早い方までハーセプチンを投与すること。EBCの治療を，1年を超えて延長することは推奨されない（5.1項を参照）。

減量
臨床試験中に，ハーセプチンの減量は行われなかった。可逆的な化学療法誘発性骨髄抑制発現中においてもハーセプチン療法を継続できるが，この期間中は，好中球減少症の合併症に関して慎重に患者を観察すること。パクリタキセル，ドセタキセル，アロマターゼ阻害剤の減量又は投与延期に関する情報については，それぞれの SmPC を参照。

左室駆出率（LVEF）が投与前値から10ポイント以上低下し，かつ50%未満の場合は，投与を延期し，約3週間以内に LVEF を再評価すること。LVEF が改善しない場合や更に低下した場合，又は症候性うっ血性心不全（CHF）が発症した場合は，その患者に対する有益性が危険性を上回るとみなされない限り，ハーセプチンの投与中止を強く考慮すべきである。このような患者に対しては，心臓専門医による評価とフォローアップを勧めること。

投与が行われなかった場合
ハーセプチンの投与スケジュールから外れた期間が1週間以下であれば，できるだけ早く通常の維持用量（1週間1回投与：2 mg/kg；3週間1回投与：6 mg/kg）を投与すること。次に予定されていたサイクルまで待たないこと。その後，1週間1回又は3週間1回のスケジュールに従って，維持用量をそれぞれ7日後又は21日後に投与する。
ハーセプチンの投与スケジュールから外れた期間が1週間を超える場合，できるだけ早くハーセプチンを約90分かけて（1週間1回投与：4 mg/kg；3週間1回投与：8 mg/kg）再投与する。その後，ハーセプチンの維持用量（1週間1回投与：2 mg/kg；3週間1回投与：6 mg/kg）を1週間1回又は3週間1回のスケジュールに従って，それぞれ7日後又は21日後に投与する。

特別な患者集団
高齢者並びに腎又は肝機能障害を有する患者を対象とした個別の薬物動態試験は実施されていない。母集団薬物動態解析では，年齢及び腎機能障害はトラスツズマブの体内動態に影響を及ぼさなかった。

小児
小児におけるハーセプチンに関連する使用はない。

投与方法
ハーセプチンの負荷用量は，90分かけて点滴静注する。急速静注又は静脈内大量投与は行ってはならない。ハーセプチンの点滴静注は，アナフィラキシーを管理できる医療機関において投

与され，緊急時の処置が可能とすること。初回投与では投与開始後少なくとも6時間，2回目以降では投与開始後2時間は，発熱及び悪寒，その他の点滴静注に伴う症状を観察すること（4.4項及び4.8項参照）。このような症状が発生した場合，投与を中断又は投与速度を遅くすることで症状が改善する場合がある。症状が改善したら，投与を再開できる。
初回投与で忍容性が確認された場合，2回目以降の投与では投与時間を30分間に短縮できる。
投与前のハーセプチン静注製剤の溶解方法については，6.6項を参照のこと。

4.3　禁忌

- トラスツズマブ，マウス蛋白質，又は6.1項に記載されている添加剤に対し過敏症の既往歴のある患者。
- 進行性悪性腫瘍の合併により，安静時に重度の呼吸困難のある患者，又は酸素吸入療法を要する患者。

4.4　警告及び使用上の注意

トレーサビリティー

生物学的製剤のトレーサビリティーを向上させるため，投与した製品の商品名及びバッチ番号を明確に記録する必要がある。

HER2検査は，検査手順の適切なバリデーションを保証できる検査機関において実施すること（5.1項参照）。

術後補助療法としてハーセプチン投与歴のある患者の再投与に関する臨床試験データは，現時点では得られていない。

心機能障害

一般的注意事項

ハーセプチンの投与を受ける患者は，CHF（ニューヨーク心臓学会［NYHA］分類 II～IV）又は無症候性心機能障害を発症するリスクが高くなる。特にアントラサイクリン系薬剤（ドキソルビシン又はエピルビシン）を含む化学療法後に，ハーセプチン療法を単独で，あるいはパクリタキセル又はドセタキセルと併用で投与した患者において，これらの事象が認められた。これらは中等度から重度で，死亡例が認められた（4.8項参照）。さらに，心疾患リスク（例えば，高血圧，冠動脈疾患の既往歴，CHF，LVEF が55%未満，高齢）の高い患者の治療には注意が必要である。

ハーセプチン治療を予定するすべての患者において，特にアントラサイクリン系薬剤及びシクロホスファミド（AC）の治療歴を有する患者では，治療開始前に，病歴，身体学的検査，心電図（ECG），心エコー，及び・又は心臓スキャンマルチゲート収集法（MUGA）によるスキャン又は MRI 等の心臓評価を行うこと。モニタリングは心機能障害を起こした患者を特定するのに役立つ。ベースライン時に実施する心臓評価は，治療中は3カ月ごと，治療中止後は6カ月ごとに，ハーセプチンの最終投与から24カ月後まで繰り返し実施する必要がある。ハーセプチンによる治療を決定する前に，慎重なリスク-ベネフィット評価を行うこと。

トラスツズマブは，利用可能なすべてのデータの母集団薬物動態解析を踏まえると，ハーセプチン投与中止後最長7カ月間循環中に残存する可能性がある（5.2項参照）。ハーセプチン投与中止後にアントラサイクリン系薬剤の投与を受ける患者では，心機能障害の危険性が高くなる可能性がある。可能な限り，ハーセプチン投与中止後7カ月までは，アントラサイクリン系薬剤をベースとした治療は避けるべきである。やむを得ずアントラサイクリン系薬剤を使用する場合は，患者の心機能を注意深く観察しなければならない。

ベースラインのスクリーニングで心血管系事象の懸念があった患者については，正式な心臓病学的評価を実施すること。すべての患者で投与中に心機能をモニターすること（例えば，12週ごと）。モニタリングは心機能障害を起こした患者を特定するのに役立つ。無症候性心機能障害を有する患者では，モニタリングの回数を増やすことが有益である（例えば，6～8週ごと）。無症候性ではあるが，継続的な左心室機能低下が認められる患者については，ハーセプチン治療による臨床効果が認められなければ，治療中止を検討すること。

心機能障害が発現した患者におけるハーセプチン投与の継続又は投与再開の安全性についての，予測的な検討は行われていない。LVEF が投与前値から10ポイント以上低下し，かつ50%未満の場合は，投与を延期し，約3週間以内に LVEF を再評価すること。LVEF が改善しない場合や更に低下した場合，又は CHF が発症した場合は，その患者に対する有益性が危険性を上回るとみなされない限り，ハーセプチンの投与中止を強く考慮すべきである。このような患者に対しては，心臓専門医による評価とフォローアップを勧めること。

ハーセプチン療法中に症候性心不全が発現した場合は，CHF 用の標準的な製剤を使用して治療を実施すること。主要な臨床試験で CHF 又は無症候性心機能障害を発症した患者のほとんどは，アンジオテンシン変換酵素（ACE）阻害薬又はアンジオテンシン受容体遮断薬（ARB）と β 遮断薬からなる標準的な CHF 治療で改善した。心臓症状はあるもののハーセプチン治療による臨床効果のエビデンスもある患者のほとんどにおいて，新たな臨床的心イベントの発現なく，治療を継続できた。

遠隔転移を伴う乳癌
ハーセプチンとアントラサイクリン系薬剤は，遠隔転移を伴う乳癌では同時投与しないこと。過去にアントラサイクリン系薬剤の投与を受けた遠隔転移を伴う乳癌患者にも，ハーセプチン投与による心機能障害の危険性はあるが，両剤を同時投与した場合よりも危険性は低い。

早期乳癌
早期乳癌患者では，ベースライン時に実施する心臓評価は，治療中は3カ月ごと，治療中止後は6カ月ごとに，ハーセプチンの最終投与から24カ月後まで繰り返し実施する必要がある。アントラサイクリン系薬剤を含む化学療法を受けている患者ではさらなるモニタリングが推奨され，ハーセプチンの最終投与から5年までは年1回，LVEF の低下が引き続き認められる場合にはそれより長く実施する必要がある。

心筋梗塞（MI）の既往歴，治療を要する狭心症，CHF（NYHA 分類 II～IV）の既往歴又は既存，LVEF が55%未満，その他の心筋症，治療を要する不整脈，臨床的に重要な心臓弁膜症，コントロール不良の高血圧（標準的な治療で管理可能な高血圧），及び血行力学的に有効な心嚢液貯留は，EBC を対象としてハーセプチンを用いた術前及び術後補助療法による主要な臨床試験から除外されたため，このような患者への治療は推奨できない。

術後補助療法
術後補助療法では，ハーセプチンとアントラサイクリン系薬剤は同時投与しないこと。
早期乳癌患者では，アントラサイクリン系薬剤を含む化学療法後にハーセプチンを投与した場合，ドセタキセルとカルボプラチンの非アントラサイクリン系薬剤の投与と比較して，症候性及び無症候性の心事象の発現率が上昇し，ハーセプチンをタキサン系薬剤と同時投与した場合には，タキサン系薬剤の後に投与した場合よりも顕著であった。用いた投与法を問わず，ほとんどの症候性心事象は最初の18カ月以内に発現した。入手できた3つの主要な試験（追跡期間中央値：5.5年）のうちの1つ（BCIRG006）では，アントラサイクリン系薬剤による治療後にタキサン系薬剤とハーセプチンを同時投与した患者で，症候性心事象又は LVEF 事象の累積発

現率が2.37%まで継続的に上昇したのに対し，2つの対照群（アントラサイクリン + シクロホスファミドの後にタキサン系薬剤並びにタキサン系薬剤，カルボプラチン，及びハーセプチン）では約1%まで上昇した。

術後補助療法による4つの大規模試験で特定された心事象のリスク因子は，高齢（50歳超），ベースライン時あるいはパクリタキセル治療開始前又は開始後の LVEF が低い（55%未満），LVEF の10～15ポイントの低下，降圧剤の使用歴又は併用などであった。術後補助化学療法終了後にハーセプチンを投与した患者では，心機能障害のリスクは，ハーセプチン開始前に投与されたアントラサイクリン系薬剤の累積投与量が多いこと，及び肥満指数（BMI）が25 kg/m^{2}を超えていることと関連していた。

術前・術後補助療法

術前・術後補助療法の対象となる早期乳癌患者では，ハーセプチンは，化学療法未治療の患者においてのみアントラサイクリン系薬剤と同時投与し，低用量のアントラサイクリン系薬剤（最大累積投与量はドキソルビシン180 mg/m^{2}又はエピルビシン360 mg/m^2）のみを使用すること。

術前補助療法で低用量のアントラサイクリン系薬剤とハーセプチンの同時投与によるフルコース治療を行った場合は，術後に細胞毒性化学療法を追加で行うべきではない。その他の状況での，追加の細胞毒性化学療法の必要性については，個々の要因に基づいて決定される。

トラスツズマブと低用量アントラサイクリンの同時投与の経験は，現在のところ2つの臨床試験（MO16432及び BO22227）に限られている。

主要な臨床試験である MO16432試験では，ハーセプチンを3サイクルのドキソルビシン（累積投与量180 mg/m^2）を含む術前補助化学療法と同時投与した。

症候性心機能障害の発現率はハーセプチン群で1.7%であった。

主要な臨床試験である BO22227試験は，ハーセプチン静注製剤による治療に対するハーセプチン皮下製剤による治療の非劣性を，PK 及び有効性の複合主要評価項目（それぞれ投与前のサイクル8におけるトラスツズマブの C_{trough} 及び根治手術時の pCR 率）に基づいて実証することを目的としてデザインされた（ハーセプチン皮下製剤の SmPC の5.1.項を参照）。主要な臨床試験である BO22227試験では，4サイクルのエピルビシン（累積投与量300 mg/m^2）を含む術前補助化学療法とハーセプチンを同時投与した。追跡期間中央値が70カ月を超えた時点で，ハーセプチン点滴静注群の心不全／うっ血性心不全の発現率は0.3%であった。

65歳を超える患者を対象とした臨床経験は限られている。

<u>注入に伴う反応（IRR）及び過敏症</u>
ハーセプチン点滴静注に対する重篤な IRR として，呼吸困難，低血圧，喘鳴，高血圧，気管支痙攣，上室性頻脈性不整脈，酸素飽和度低下，アナフィラキシー，呼吸窮迫，蕁麻疹，及び血管浮腫が報告されている（4.8項参照）。これらの事象の発現リスクを低減させるため，前投薬を行ってもよい。これらの事象のほとんどは，初回点滴静注中又は点滴静注開始後2.5時間以内に生じる。Infusion reaction が生じたら，点滴静注を中断するか点滴速度を遅らせ，認められたすべての症状が消失するまで患者を観察すること（4.2項参照）。これらの症状は，メペリジンやパラセタモールなどの鎮痛剤／解熱剤又はジフェンヒドラミンなどの抗ヒスタミン剤

で治療できる。ほとんどの患者で症状が消失し，その後ハーセプチン点滴静注が再開された。重篤な副作用は，酸素吸入，β 作動薬，副腎皮質ホルモン等の支持療法で治療された。まれに，これらの反応の臨床経過の最終転帰が死亡に至る場合もある。進行性悪性腫瘍の合併及び併存疾患により安静時呼吸困難のある患者は，致死性の Infusion reaction を起こす危険性が高い。したがって，こうした患者にハーセプチンによる治療を実施すべきではない（4.3項参照）。

初期に改善した後の臨床的悪化，及び急激な臨床的悪化を伴う遅延反応も報告された。死亡は点滴静注後数時間以内から1週間までに生じた。極めてまれに，ハーセプチン点滴静注開始後6時間以上を過ぎてから，点滴症状及び肺症状が発現した。遅発性の症状が生じる可能性があることを患者に警告し，こうした症状が発生した場合は，医師に連絡するよう患者に指示すること。

肺障害

市販後において，重度の肺障害が報告されている（4.8項参照）。これらの事象はときに致死的であった。さらに，肺浸潤，急性呼吸窮迫症候群，肺炎，肺臓炎，胸水，呼吸窮迫，急性肺水腫，呼吸不全といった間質性肺疾患の症例が報告されている。間質性肺疾患に関連するリスク因子として，タキサン系薬剤，ゲムシタビン，ビノレルビン，放射線療法など，間質性肺疾患に関連することが知られている他の抗悪性腫瘍療法による治療歴又は併用が挙げられる。これらの事象は点滴静注に伴う反応の一部として，あるいは遅発性に生じることがある。進行性悪性腫瘍の合併及び併存疾患により安静時呼吸困難のある患者は，肺障害を起こす危険性が高い。したがって，こうした患者にハーセプチンによる治療を実施すべきではない（4.3項参照）。特にタキサン系薬剤との併用治療を実施している患者においては，肺臓炎に注意すること。

4.5　薬物間相互作用及びその他の相互作用

薬物間相互作用を検討した正式な試験は行われていない。ハーセプチンと臨床試験で使用された併用薬との間には，臨床的に重要な相互作用は認められていない。

トラスツズマブが他の抗悪性腫瘍剤の薬物動態に及ぼす影響

HER2陽性遠隔転移を伴う乳癌女性患者を対象とした BO15935試験及び M77004試験の薬物動態データでは，パクリタキセル及びドキソルビシン（及びそれらの主要代謝物である6α-ヒドロキシパクリタキセル［POH］及びドキソルビシノール［DOL］）への曝露は，トラスツズマブの存在下では変化しないことが示唆された（それぞれ負荷用量8 mg/kg 又は4 mg/kg を点滴静注した後，6 mg/kg を3週間1回又は2 mg/kg を1週間1回で点滴静注）。

しかし，トラスツズマブは，1種類のドキソルビシン代謝物（7-デオキシ-13ジヒドロドキソルビシノン［D7D］）の全体的な曝露量を増加させる可能性がある。D7D の生理活性とこの代謝物の増加の臨床的影響は不明であった。

HER2陽性遠隔転移を伴う乳癌を有する日本人女性を対象に，ハーセプチン（負荷用量4 mg/kg を点滴静注，2 mg/kg を1週間1回点滴静注）とドセタキセル（60 mg/m^{2}を点滴静注）の単群試験である JP16003試験のデータでは，ハーセプチンの併用投与はドセタキセルの単回投与の薬物動態に影響を及ぼさないことが示唆された。JP19959試験は BO18255試験（ToGA）のサブ試験であり，進行胃癌を有する日本人男女を対象として，カペシタビンとシスプラチンをハーセプチンとの併用又は非併用で投与した場合の薬物動態を検討するために実施された。このサブ試験の結果では，カペシタビンの生理活性代謝物（例えば，5-FU）への曝露は，シスプラチンの同時投与やシスプラチン + ハーセプチンの同時投与によっては影響を受けないことが示唆された。ただし，カペシタビン自体はハーセプチンとの併用時の方が濃度が高く，半減期が長かった。また，シスプラチンの薬物動態がカペシタビンの同時投与やカペシタビン + ハーセプチンの同時投与によって影響を受けないこともデータから示唆された。

遠隔転移を伴う又は局所進行性の手術不能な HER2陽性癌患者を対象とした H4613g/GO01305試験の薬物動態データでは，トラスツズマブがカルボプラチンの薬物動態に影響を及ぼさないことが示唆された。

抗悪性腫瘍剤がトラスツズマブの薬物動態に及ぼす影響
ハーセプチン単剤療法（負荷用量4 mg/kg，2 mg/kg 1週間1回点滴静注）後のシミュレートされた血清中トラスツズマブ濃度と，HER2陽性遠隔転移を伴う乳癌を有する日本人女性で観察された血清中濃度を比較した結果（JP16003試験），ドセタキセルの同時投与がトラスツズマブの薬物動態に及ぼす薬物動態効果を示すエビデンスは認められなかった。

HER2陽性遠隔転移を伴う乳癌女性患者を対象としてハーセプチンとパクリタキセルを併用投与した2つの第 II 相試験（BO15935及び M77004）及び1つの第 III 相試験（H0648g）と，ハーセプチンを単剤投与した2つの第 II 相試験（W016229及び MO16982）の薬物動態の結果を比較したところ，トラスツズマブの個別のトラフ血清中濃度及び平均値には試験内でも試験間でもばらつきがみられたが，パクリタキセルの併用投与がトラスツズマブの薬物動態に与える明確な影響はなかったことが示された。HER2陽性遠隔転移を伴う乳癌女性患者にハーセプチン，パクリタキセル，及びドキソルビシンを併用投与した M77004試験におけるトラスツズマブの薬物動態データと，ハーセプチンを単剤投与した試験（H0649g），若しくはアントラサイクリン系薬剤 + シクロホスファミド又はパクリタキセルと併用投与した試験（H0648g 試験）におけるトラスツズマブの薬物動態データを比較したところ，ドキソルビシンとパクリタキセルはトラスツズマブの薬物動態に影響を及ぼしていないことが示唆された。

H4613g/GO01305試験の薬物動態データでは，カルボプラチンはトラスツズマブの薬物動態に影響を与えないことが示唆された。

アナストロゾールの併用投与はトラスツズマブの薬物動態に影響を与えていないと思われた。

4.6　生殖，妊娠及び授乳
妊娠可能な女性
生殖能を有する女性にはハーセプチンの治療期間中及び治療終了後7カ月間は有効な避妊方法を用いるように助言すること（5.2項参照）。

妊娠
カニクイザルを用いて，ヒトの1週間1回投与におけるハーセプチン静注製剤の維持用量 2 mg/kg の25倍を最大用量として実施された生殖試験において，生殖能への影響又は胎児への障害は認められなかった。妊娠早期（妊娠20～50日）及び後期（妊娠120日～150日）の胎児発達期間におけるトラスツズマブの胎盤通過が認められた。ハーセプチンが生殖能に影響を及ぼす可能性があるかは不明である。動物での生殖試験から必ずしもヒトでの反応を予測できるとは限らないので，母親に対する潜在的な有益性が胎児に対する潜在的な危険性を上回らない限り，妊娠中におけるハーセプチンの使用を避けること。

市販後において，ハーセプチンを投与した妊婦で，羊水過少を伴う胎児の腎臓の成長障害及び／又は腎機能障害の症例が報告され，数例において致命的な胎児の肺形成不全が認められた。妊娠中の女性には胎児へ害を及ぼす可能性があることを助言すること。妊婦にハーセプチンを投与する場合，若しくはハーセプチン投与中又はハーセプチンの最終投与後7カ月以内に妊娠した場合には，集学的チームにより注意深く観察することが望ましい。

母乳栄養法

授乳中のカニクイザルを用いて，ヒトの1週間1回投与におけるハーセプチン静注製剤の維持用量2 mg/kg の25倍の用量で実施された試験において，トラスツズマブが乳汁中に移行することが認められた。幼若サルの血清中にトラスツズマブが認められたが，誕生から1カ月齢までの成長又は発達に有害な影響は及ぼさなかった。トラスツズマブがヒトの母乳中に移行するかどうかは不明である。ヒト IgG1はヒトの母乳中に移行するが，胎児を障害する可能性があるかどうかは不明であるため，ハーセプチン療法中，及び最終投与後7カ月間は授乳を避けるべきである。

受胎能
受胎能に関する利用可能なデータはない。

4.7　運転及び機械の操作能力に対する影響

ハーセプチンは運転及び機械の操作能力に軽微な影響を与える（4.8項参照）。ハーセプチンの治療中に浮動性めまいや傾眠が起こる可能性がある（4.8項参照）。点滴静注に伴う症状（4.4項参照）を生じた患者には，症状が軽快するまで運転や機械の操作を行わないよう助言すること。

4.8　望ましくない効果

安全性プロファイルの要約

ハーセプチンのこれまでの使用経験（静注製剤及び皮下製剤）で最も重篤かつ／又はよくみられる副作用は，心機能障害，注入に伴う反応，血液毒性（特に好中球減少），感染及び肺障害である。

副作用一覧
本項では，頻度のカテゴリーとして次のものが用いられている：“very common”（≥ 1/10），“common”（≥ 1/100 ～<1/10），“uncommon”（≥ 1/1,000 ～<1/100），“rare”（≥ 1/10,000 ～<1/1,000），“very rare”（<1/10,000），“not known”（入手可能なデータからは算出不可）。副作用は，各頻度の中では重篤度の高いものから順に記載している。

表1に示された副作用は，主要な臨床試験及び市販後において単剤又は化学療法との併用でのハーセプチンの点滴静注に関連しているとして報告された副作用である。

事象名はいずれも，主要な臨床試験でみられた最も高い頻度に基づき記載されている。また，市販後調査で報告された用語が表1に含まれている。

表1 主要な臨床試験（N = 8386）及び市販後調査において，点滴静注によるハーセプチン単剤療法又は化学療法との併用療法で報告された望ましくない影響

器官別大分類	副作用	発現頻度
感染症および寄生虫症	感染	Very common
	上咽頭炎	Very common
	好中球減少性敗血症	Common
	膀胱炎	Common
	インフルエンザ	Common
	副鼻腔炎	Common
	皮膚感染	Common
	鼻炎	Common
	上気道感染	Common
	尿路感染	Common
	咽頭炎	Common
良性，悪性および詳細不明の新生物（嚢胞およびポリープを含む）	悪性新生物進行	Not known
	新生物進行	Not known
血液およびリンパ系障害	発熱性好中球減少症	Very common
	貧血	Very common
	好中球減少症	Very common
	白血球数減少／白血球減少症	Very common
	血小板減少症	Very common
	低プロトロンビン血症	Not known
	免疫性血小板減少症	Not known
免疫系障害	過敏症	Common
	[+]アナフィラキシー反応	Rare
	[+]アナフィラキシーショック	Rare
代謝および栄養障害	体重減少	Very common
	食欲不振	Very common
	腫瘍崩壊症候群	Not known
	高カリウム血症	Not known
精神障害	不眠症	Very common
	不安	Common
	うつ病	Common
神経系障害	[1]振戦	Very common
	浮動性めまい	Very common
	頭痛	Very common
	錯感覚	Very common
	味覚不全	Very common
	末梢性ニューロパチー	Common

器官別大分類	副作用	発現頻度
	筋緊張亢進	Common
	傾眠	Common
眼障害	結膜炎	Very common
	流涙増加	Very common
	ドライアイ	Common
	視神経乳頭浮腫	Not known
	網膜出血	Not known
耳および迷路障害	難聴	Uncommon
心障害	[1] 血圧低下	Very common
	[1] 血圧上昇	Very common
	[1] 心拍異常	Very common
	[1] 心粗動	Very common
	駆出率減少*	Very common
	[+]心不全（うっ血性）	Common
	[+1]上室性頻脈性不整脈	Common
	心筋症	Common
	[1] 動悸	Common
	心嚢液貯留	Uncommon
	心原性ショック	Not known
	ギャロップ・リズム陽性	Not known
血管障害	ほてり	Very common
	[+1]低血圧	Common
	血管拡張	Common
呼吸器，胸郭および縦隔障害		
	[+]呼吸困難	Very common
	咳嗽	Very common
	鼻出血	Very common
	鼻漏	Very common
	[+]肺炎	Common
	喘息	Common
	肺障害	Common
	[+]胸水	Common
	[+1]喘鳴	Uncommon
	肺臓炎	Uncommon
	[+]肺線維症	Not known
	[+]呼吸窮迫	Not known
	[+]呼吸不全	Not known
	[+]肺浸潤	Not known
	[+]急性肺水腫	Not known

器官別大分類	副作用	発現頻度
	[+]急性呼吸窮迫症候群	Not known
	[+]気管支痙攣	Not known
	[+]低酸素症	Not known
	[+]酸素飽和度低下	Not known
	喉頭浮腫	Not known
	起坐呼吸	Not known
	肺水腫	Not known
	間質性肺疾患	Not known
胃腸障害	下痢	Very common
	嘔吐	Very common
	悪心	Very common
	[1] 口唇腫脹	Very common
	腹痛	Very common
	消化不良	Very common
	便秘	Very common
	口内炎	Very common
	痔核	Common
	口内乾燥	Common
肝胆道系障害	肝細胞損傷	Common
	肝炎	Common
	肝圧痛	Common
	黄疸	Rare
皮膚および皮下組織障害	紅斑	Very common
	発疹	Very common
	[1] 顔面腫脹	Very common
	脱毛症	Very common
	爪の障害	Very common
	手掌・足底発赤知覚不全症候群	Very common
	ざ瘡	Common
	皮膚乾燥	Common
	斑状出血	Common
	多汗症	Common
	斑状丘疹状皮疹	Common
	そう痒症	Common
	爪破損	Common
	皮膚炎	Common
	蕁麻疹	Uncommon
	血管浮腫	Not known
筋骨格系および結合組織障害	関節痛	Very common
	[1]筋緊張	Very common
	筋肉痛	Very common
	関節炎	Common
	背部痛	Common

器官別大分類	副作用	発現頻度
	骨痛	Common
	筋痙縮	Common
	頚部痛	Common
	四肢痛	Common
腎および尿路障害	腎障害	Common
	膜性糸球体腎炎	Not known
	糸球体腎症	Not known
	腎不全	Not known
妊娠，産褥および周産期の状態	羊水過少	Not known
	腎発育不全	Not known
	肺低形成	Not known
生殖系および乳房障害	乳房炎症／乳腺炎	Common
全身障害および投与局所様態	無力症	Very common
	胸痛	Very common
	悪寒	Very common
	疲労	Very common
	インフルエンザ様症候群	Very common
	注入に伴う反応	Very common
	疼痛	Very common
	発熱	Very common
	粘膜の炎症	Very common
	末梢性浮腫	Very common
	倦怠感	Common
	浮腫	Common
傷害，中毒および処置合併症	挫傷	Common

+ 転帰が死亡に至ったと報告されている副作用

1 注入に伴う反応との関連が強いものとして報告されている副作用。これらの事象の発現率（%）については不明である。

* アントラサイクリン系薬剤投与後の併用療法及びタキサン系薬剤との併用療法で発現

本剤に特徴的な副作用

心機能障害

NYHA 分類 II～IV のうっ血性心不全は，ハーセプチン投与に関連してよくみられる事象であり，死亡例が認められている（4.4項参照）。ハーセプチン投与群では，呼吸困難，起坐呼吸，咳嗽増加，肺水腫，S3ギャロップ，又は心室駆出率低下などの心機能障害の徴候及び症状が認められている（4.4項参照）。

化学療法とハーセプチンの併用投与による術後補助療法の3つの主要な臨床試験において，グレード3/4の心機能障害（特に症候性うっ血性心不全）の発現率は，化学療法単独（すなわちハーセプチンを投与しなかった）投与患者とタキサン系薬剤の後にハーセプチンを順次投与した患者で同程度であった（0.3～0.4%）。発現率はタキサン系薬剤とハーセプチンを同時投与した患者で最も高かった（2.0%）。術前補助療法では，ハーセプチンと低用量のアントラサイクリン系薬剤の同時投与の経験は限られている（4.4項参照）。

術後補助化学療法の終了後にハーセプチンを投与した場合，NYHA 分類 III～IV の心不全が追

跡期間中央値12カ月後に1年投与群の0.6%の患者に認められた。BO16348試験では，追跡期間中央値が8年後の，ハーセプチン1年投与群における重度の CHF（NYHA 分類 III 及び IV）の発現率は0.8%であり，軽度の症候性及び無症候性の左室機能不全の発現率は4.6%であった。

ハーセプチン投与群患者の71.4%で，重度の CHF の可逆性（事象発現後に50%以上の LVEF 値が連続で2回以上続くものと定義）が明らかであった。軽度の症候性及び無症候性の左室機能不全は患者の79.5%で可逆性が実証された。心機能障害に関連する事象の約17%はハーセプチン投与終了後に発現した。

ハーセプチン点滴静注による主要な遠隔転移を伴うの臨床試験において，心機能障害の発現率は，パクリタキセルとの併用投与では9%から12%であったのに対し，パクリタキセル単剤投与では1%から4%であった。単剤療法では発現率は6%～9%であった。心機能障害の発現率が最も高かったのは，ハーセプチンとアントラサイクリン系薬剤／シクロホスファミドの併用投与を受けた患者（27%）であり，アントラサイクリン系薬剤／シクロホスファミド単剤投与（7%～10%）よりも有意に高かった。心機能を前向きにモニタリングしたその後の臨床試験では，ハーセプチンとドセタキセルを投与した患者では，症候性 CHF の発現率が2.2%であったのに対し，ドセタキセルを単剤投与した患者では0%であった。これらの臨床試験で心機能障害を発症した患者（79%）のほとんどは，CHF に対する標準治療を受けた後に改善がみられた。

Infusion reaction，アレルギー様反応及び過敏症
ハーセプチン投与患者の約40%において注入に伴う反応が現れると推定されている。しかしながら，注入に伴う反応のほとんどは軽度～中等度（NCI-CTC グレード分類）であり，投与の初期，つまり1，2，3回目の投与時に発現し，2回目以降の投与では発現頻度が減少する傾向がある。症状は，悪寒，発熱，呼吸困難，低血圧，喘鳴，気管支痙攣，頻脈，酸素飽和度低下，呼吸窮迫，発疹，悪心，嘔吐，頭痛などである（4.4項参照）。すべてのグレードの注入に伴う反応の割合は，適応症，データ収集方法，トラスツズマブを化学療法と同時投与したか単剤投与したかによって試験間でばらつきがあった。

早急に追加の治療が必要となる重度のアナフィラキシー反応は，通常ハーセプチンの初回又は2回目投与中に発現し（4.4項参照），死亡に至ることがある。

アナフィラキシー様反応が単独の症例で認められている。

血液毒性
発熱性好中球減少症，白血球減少症，貧血，血小板減少症，及び好中球減少症が非常に多くみられた。低プロトロンビン血症の発現頻度は不明である。アントラサイクリン療法後にトラスツズマブをドセタキセルと併用投与した場合，好中球減少症のリスクがわずかに上昇する可能性がある。

肺障害
重度の肺障害はハーセプチン投与と関連があり，死亡に至ることがある。事象には以下のもの等が含まれる：肺浸潤，急性呼吸窮迫症候群，肺炎，肺臓炎，胸水，呼吸窮迫，急性肺水腫，呼吸不全（4.4項参照）。

欧州-リスクマネジメントプランと一致したリスク最小化法の詳細については，警告及び使用上の注意（4.4項）に示している。

免疫原性

早期乳癌に対して術前・術後補助療法を行った試験（BO22227）では，追跡期間中央値が70カ月を超えた時点で，ハーセプチン点滴静注群の患者の10.1%（296例中30例）でトラスツズマブに対する抗体が発現していた。ハーセプチン点滴静注群の30例中2例のベースライン後の検体から抗トラスツズマブ中和抗体が検出された。

これらの抗体の臨床上の関連性は不明である。抗トラスツズマブ抗体の存在は，薬物動態，有効性（病理学的完全奏効率［pCR］及び無事象生存率［EFS］で評価），及びハーセプチン点滴静注の投与に伴う反応（ARR）の発現率で評価される安全性に影響しなかった。

胃癌におけるハーセプチンの入手可能な免疫原性データはない。

ハーセプチンの静注製剤から皮下製剤及び皮下製剤から静注製剤への切り替え

MO22982試験では，トラスツズマブの点滴静注と皮下投与のどちらが患者にとって好ましいかを評価することを主な目的として，ハーセプチンの静注製剤と皮下製剤の切り替えについて検討した。本臨床試験では，2つのコホート（バイアル入りの皮下製剤を使用するコホート及び投与システムで皮下製剤を使用するコホート）を2群クロスオーバーデザインで検討し，488例を2種類の異なる3週間ごとのハーセプチン投与順序（点滴静注［サイクル1～4］から皮下投与［サイクル5～8］，又は皮下投与［サイクル1～4］から点滴静注［サイクル5～8］）のいずれかに無作為に割り付けた。患者は，ハーセプチン点滴静注による治療が未経験（20.3%）であるか，以前に治療を受けたことがあるか（79.7%）のいずれかであった。点滴静注から皮下投与への順序（バイアル入りの皮下製剤を使用するコホート及び投与システムで皮下製剤を使用するコホートの併合）では，有害事象発現率（全グレード）は，切り替え前（サイクル1～4）が53.8%，切り替え後（サイクル5～8）が56.4%であった。皮下投与から点滴静注への順序（バイアル入りの皮下製剤を使用するコホート及び投与システムで皮下製剤を使用するコホートの併合）では，有害事象発現率（全グレード）は，切り替え前が65.4%，切り替え後が48.7%であった。
重篤な有害事象，グレード3の有害事象，及び有害事象による治療中止の発現率は，切り替え前（サイクル1～4）は低く（5%未満），切り替え後（サイクル5～8）と同程度であった。グレード4又はグレード5の有害事象は報告されなかった。

疑わしい副作用の報告

医薬品の承認後，疑わしい副作用を報告することは重要である。これにより，医薬品のベネフィットとリスクのバランスを継続的に監視できる。医療従事者は，副作用が疑われる場合，付録 V に記載されている国の報告システムを介して報告することが求められる。

4.9　過量投与

ヒトにおける臨床試験で過量投与の経験はない。臨床試験において，10 mg/kg より高用量でのハーセプチン単独単回投与は実施されていない。遠隔転移を伴う胃癌患者を対象とした臨床試験では，負荷用量8 mg/kg に続く維持用量10 mg/kg の3週間1回投与が検討されている。このレベル以下の用量では，忍容性は良好であった。

1.6.3 米国の添付文書

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

HERCEPTIN® (trastuzumab) for injection, for intravenous use
Initial U.S. Approval: 1998

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

See full prescribing information for complete boxed warning
Cardiomyopathy: Herceptin can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy. (2.3, 5.1)

Infusion Reactions, Pulmonary Toxicity: Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

Embryo-Fetal Toxicity: Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.3)

----------INDICATIONS AND USAGE----------
Herceptin is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer. (1.1, 1.2)
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. (1.3)

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin (1, 2.1).

----------DOSAGE AND ADMINISTRATION----------
For intravenous (IV) infusion only. Do not administer as an IV push or bolus. (2.2)
Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine. (2.2)
Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency. (1, 2.1)

Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.2)
Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose of Herceptin, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy, or
- Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30–90 minutes IV infusion every three weeks for 52 weeks.

Metastatic HER2-Overexpressing Breast Cancer (2.2)

- Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.

Metastatic HER2-Overexpressing Gastric Cancer (2.2)

- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

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

- For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution

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

- None. (4)

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

- Exacerbation of Chemotherapy-Induced Neutropenia. (5.5, 6.1)

----------ADVERSE REACTIONS----------
Adjuvant Breast Cancer

- Most common adverse reactions (≥ 5%) are headache, diarrhea, nausea, and chills. (6.1)

Metastatic Breast Cancer

- Most common adverse reactions (≥ 10%) are fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash. (6.1)

Metastatic Gastric Cancer

- Most common adverse reactions (≥ 10%) are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. (6.1)

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

----------USE IN SPECIFIC POPULATIONS----------
Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of Herceptin (8.3).

See 17 for PATIENT COUNSELING INFORMATION.
Revised: 02/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

Cardiomyopathy

Herceptin administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving Herceptin with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and withhold Herceptin in patients with metastatic disease for clinically significant decrease in left ventricular function *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].*

Infusion Reactions; Pulmonary Toxicity

Herceptin administration can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of Herceptin administration. Interrupt Herceptin infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome *[see Warnings and Precautions (5.2, 5.4)].*

Embryo-Fetal Toxicity

Exposure to Herceptin during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)].*

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature *[see Clinical Studies (14.1)]*) breast cancer

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- as part of a treatment regimen with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

1.2 Metastatic Breast Cancer

Herceptin is indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

1.3 Metastatic Gastric Cancer

Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens *[see Indications and Usage (1) and Clinical Studies (14)]*. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

2.2 Recommended Doses and Schedules

- **Do not administer as an intravenous push or bolus. Do not mix Herceptin with other drugs.**
- **Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine.**

Adjuvant Treatment, Breast Cancer

Administer according to one of the following doses and schedules for a total of 52 weeks of Herceptin therapy:

During and following paclitaxel, docetaxel, or docetaxel/carboplatin:

- Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.

As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens:

- Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes
- Subsequent doses at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks *[see Dosage and Administration (2.3)]*.
- Extending adjuvant treatment beyond one year is not recommended *[see Adverse Reactions (6.1)]*.

Metastatic Treatment, Breast Cancer

- Administer Herceptin, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as a 90-minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30-minute intravenous infusions until disease progression.

Metastatic Gastric Cancer

- Administer Herceptin at an initial dose of 8 mg/kg as a 90-minute intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks until disease progression *[see Dosage and Administration (2.3)]*.

2.3 Important Dosing Considerations

If the patient has missed a dose of Herceptin by one week or less, then the usual maintenance dose (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent Herceptin maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of Herceptin by more than one week, a re-loading dose of Herceptin should be administered over approximately 90 minutes (weekly schedule: 4 mg/kg; three-weekly schedule: 8 mg/kg) as soon as possible. Subsequent Herceptin maintenance doses (weekly schedule: 2 mg/kg; three-weekly schedule 6 mg/kg) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

Infusion Reactions

[See Boxed Warning, Warnings and Precautions (5.2)]

- Decrease the rate of infusion for mild or moderate infusion reactions
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Discontinue Herceptin for severe or life-threatening infusion reactions.

Cardiomyopathy

[See Boxed Warning, Warnings and Precautions (5.1)]

Assess left ventricular ejection fraction (LVEF) prior to initiation of Herceptin and at regular intervals during treatment. Withhold Herceptin dosing for at least 4 weeks for either of the following:

- ≥ 16% absolute decrease in LVEF from pre-treatment values
- LVEF below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values.

Herceptin may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤ 15%.

Permanently discontinue Herceptin for a persistent (> 8 weeks) LVEF decline or for suspension of Herceptin dosing on more than 3 occasions for cardiomyopathy.

2.4 Preparation for Administration

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin (trastuzumab) and not ado-trastuzumab emtansine.

<u>150 mg Single-dose vial</u>

Reconstitution

Reconstitute each 150 mg vial of Herceptin with 7.4 mL of Sterile Water for Injection (SWFI) (not supplied) to yield a single-dose solution containing 21 mg/mL trastuzumab that delivers 7.15 mL (150 mg trastuzumab).

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject 7.4 mL of SWFI (not supplied) into the vial containing the lyophilized powder of Herceptin, which has a cake-like appearance. The stream of diluent should be directed into the cake. The reconstituted vial yields a solution for single-dose use, containing 21 mg/mL trastuzumab.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE**.
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for

particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
- Use the Herceptin solution immediately following reconstitution with SWFI, as it contains no preservative and is intended for single-dose only. If not used immediately, store the reconstituted Herceptin solution for up to 24 hours at 2°C to 8°C (36°F to 46°F); discard any unused Herceptin after 24 hours. **Do not freeze.**

Dilution
- Determine the dose (mg) of Herceptin *[see Dosage and Administration (2.1)]*.
- Calculate the volume of the 21 mg/mL reconstituted Herceptin solution needed.
- Withdraw this amount from the vial using a sterile needle and syringe and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP.
  DO NOT USE DEXTROSE (5%) SOLUTION.
- Gently invert the bag to mix the solution.
- The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C (36°F to 46°F) for no more than 24 hours prior to use. Discard after 24 hours. This storage time is additional to the time allowed for the reconstituted vials. **Do not freeze**.

3 DOSAGE FORMS AND STRENGTHS
- For injection: 150 mg lyophilized powder in a single-dose vial

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy
Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death *[see Boxed Warning: Cardiomyopathy]*. Herceptin can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).

There is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving Herceptin as a single agent or in combination therapy compared with those not receiving Herceptin. The highest absolute incidence occurs when Herceptin is administered with an anthracycline.

Withhold Herceptin for ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values *[see Dosage and Administration (2.3)]*. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

Patients who receive anthracycline after stopping Herceptin may also be at increased risk of cardiac dysfunction *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

Cardiac Monitoring

Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:
- Baseline LVEF measurement immediately prior to initiation of Herceptin
- LVEF measurements every 3 months during and upon completion of Herceptin
- Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction *[see Dosage and Administration (2.3)]*

- LVEF measurements every 6 months for at least 2 years following completion of Herceptin as a component of adjuvant therapy.

In Study 1, 15% (158/1031) of patients discontinued Herceptin due to clinical evidence of myocardial dysfunction or significant decline in LVEF after a median follow-up duration of 8.7 years in the AC-TH arm. In Study 3 (one-year Herceptin treatment), the number of patients who discontinued Herceptin due to cardiac toxicity at 12.6 months median duration of follow-up was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) of patients in the TCH arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) of patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase) discontinued Herceptin due to cardiac toxicity.

Among 64 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive heart failure, one patient died of cardiomyopathy, one patient died suddenly without documented etiology, and 33 patients were receiving cardiac medication at last follow-up. Approximately 24% of the surviving patients had recovery to a normal LVEF (defined as ≥ 50%) and no symptoms on continuing medical management at the time of last follow-up. Incidence of congestive heart failure (CHF) is presented in Table 1. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

Table 1

Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

		Incidence of CHF	
Study	Regimen	Herceptin	Control
1 & 2[a]	AC[b]→Paclitaxel+Herceptin	3.2% (64/2000)[c]	1.3% (21/1655)
3[d]	Chemo → Herceptin	2% (30/1678)	0.3% (5/1708)
4	AC[b]→Docetaxel+Herceptin	2% (20/1068)	0.3% (3/1050)
4	Docetaxel+Carbo+Herceptin	0.4% (4/1056)	0.3% (3/1050)

[a] Median follow-up duration for studies 1 and 2 combined was 8.3 years in the AC→TH arm.

[b] Anthracycline (doxorubicin) and cyclophosphamide.

[c] Includes 1 patient with fatal cardiomyopathy and 1 patient with sudden death without documented etiology.

[d] Includes NYHA II-IV and cardiac death at 12.6 months median duration of follow-up in the one-year Herceptin arm.

In Study 3 (one-year Herceptin treatment), at a median follow-up duration of 8 years, the incidence of severe CHF (NYHA III & IV) was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Table 2
Incidence of Cardiac Dysfunction[a] in Metastatic Breast Cancer Studies

		Incidence			
		NYHA I–IV		NYHA III–IV	
Study	Event	Herceptin	Control	Herceptin	Control
5 (AC)[b]	Cardiac Dysfunction	28%	7%	19%	3%
5 (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
6	Cardiac Dysfunction[c]	7%	N/A	5%	N/A

[a] Congestive heart failure or significant asymptomatic decrease in LVEF.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[c] Includes 1 patient with fatal cardiomyopathy.

In Study 4, the incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the Herceptin containing regimens (AC-TH: 0.3% (3/1068) and TCH: 0.2% (2/1056)) as compared to none in AC-T.

5.2 Infusion Reactions

Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia *[see Adverse Reactions (6.1)]*.

In post-marketing reports, serious and fatal infusion reactions have been reported. Severe reactions, which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable, including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction.

Interrupt Herceptin infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered (which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen). Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Herceptin after experiencing a severe infusion reaction. Prior to resumption of Herceptin infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated Herceptin infusions, others had recurrent severe infusion reactions despite pre-medications.

5.3 Embryo-Fetal Toxicity

Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

Verify the pregnancy status of females of reproductive potential prior to the initiation of Herceptin. Advise pregnant women and females of reproductive potential that exposure to Herceptin during pregnancy or within 7 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 7 months

following the last dose of Herceptin *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.3)]*.

5.4 Pulmonary Toxicity

Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions *[see Warnings and Precautions (5.2)]*. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

5.5 Exacerbation of Chemotherapy-Induced Neutropenia

In randomized, controlled clinical trials, the per-patient incidences of NCI-CTC Grade 3–4 neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received Herceptin and those who did not *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cardiomyopathy *[see Warnings and Precautions (5.1)]*
- Infusion Reactions *[see Warnings and Precautions (5.2)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.3)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.4)]*
- Exacerbation of Chemotherapy-Induced Neutropenia *[see Warnings and Precautions (5.5)]*

The most common adverse reactions in patients receiving Herceptin in the adjuvant and metastatic breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of Herceptin treatment include CHF, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity *[see Dosage and Administration (2.3)]*.

In the metastatic gastric cancer setting, the most common adverse reactions (≥ 10%) that were increased (≥ 5% difference) in the Herceptin arm as compared to the chemotherapy alone arm were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. The most common adverse reactions which resulted in discontinuation of treatment on the Herceptin-containing arm in the absence of disease progression were infection, diarrhea, and febrile neutropenia.

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adjuvant Breast Cancer Studies

The data below reflect exposure to one-year Herceptin therapy across three randomized, open-label studies, Studies 1, 2, and 3, with (n = 3678) or without (n = 3363) trastuzumab in the adjuvant treatment of breast cancer.

The data summarized in Table 3 below, from Study 3, reflect exposure to Herceptin in 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18. Among the 3386 patients enrolled in the observation and one-year Herceptin arms of Study 3 at a

median duration of follow-up of 12.6 months in the Herceptin arm, the median age was 49 years (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.

Table 3
Adverse Reactions for Study 3[a], All Grades[b]

Adverse Reaction	One Year Herceptin (n = 1678)	Observation (n = 1708)
Cardiac		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias[c]	40 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	4 (0.2%)	0 (0%)
Respiratory Thoracic Mediastinal Disorders		
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Pneumonitis	4 (0.2%)	0 (0%)
Gastrointestinal Disorders		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
Musculoskeletal & Connective Tissue Disorders		
Arthralgia	137 (8%)	98 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
Nervous System Disorders		
Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
Skin & Subcutaneous Tissue Disorders		
Rash	70 (4%)	10 (0.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritus	40 (2%)	10 (0.6%)

Table 3 (cont'd)
Adverse Reactions for Study 3[a], All Grades[b]

Adverse Reaction	One Year Herceptin (n = 1678)	Observation (n = 1708)
General Disorders		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Asthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (0.06%)	0 (0%)
Infections		
Nasopharyngitis	135 (8%)	43 (3%)
UTI	39 (3%)	13 (0.8%)
Immune System Disorders		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

[a] Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.
[b] The incidence of Grade 3 or higher adverse reactions was <1% in both arms for each listed term.
[c] Higher level grouping term.

In Study 3, a comparison of 3-weekly Herceptin treatment for two years versus one year was also performed. The rate of asymptomatic cardiac dysfunction was increased in the 2-year Herceptin treatment arm (8.1% versus 4.6% in the one-year Herceptin treatment arm). More patients experienced at least one adverse reaction of Grade 3 or higher in the 2-year Herceptin treatment arm (20.4%) compared with the one-year Herceptin treatment arm (16.3%).

The safety data from Studies 1 and 2 were obtained from 3655 patients, of whom 2000 received Herceptin; the median treatment duration was 51 weeks. The median age was 49 years (range: 24–80); 84% of patients were White, 7% Black, 4% Hispanic, and 3% Asian.

In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving Herceptin plus chemotherapy as compared to chemotherapy alone: fatigue (29.5% vs. 22.4%), infection (24.0% vs. 12.8%), hot flashes (17.1% vs. 15.0%), anemia (12.3% vs. 6.7%), dyspnea (11.8% vs. 4.6%), rash/desquamation (10.9% vs. 7.6%), leukopenia (10.5% vs. 8.4%), neutropenia (6.4% vs. 4.3%), headache (6.2% vs. 3.8%), pain (5.5% vs. 3.0%), edema (4.7% vs. 2.7%), and insomnia (4.3% vs. 1.5%). The majority of these events were Grade 2 in severity.

In Study 2, data collection was limited to the following investigator-attributed treatment-related adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes, motor neuropathy, and sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (12.2% vs. 9.1%), nail changes (11.5% vs. 6.8%), dyspnea (2.4% vs. 0.2%), and diarrhea (2.2% vs. 0%). The majority of these events were Grade 2 in severity.

Safety data from Study 4 reflect exposure to Herceptin as part of an adjuvant treatment regimen from 2124 patients receiving at least one dose of study treatment [AC-TH: n = 1068; TCH: n=1056].

The overall median treatment duration was 54 weeks in both the AC-TH and TCH arms. The median number of infusions was 26 in the AC-TH arm and 30 in the TCH arm, including weekly infusions during the chemotherapy phase and every three week dosing in the monotherapy period. Among these patients, the median age was 49 years (range 22 to 74 years). In Study 4, the toxicity profile was similar to that reported in Studies 1, 2, and 3 with the exception of a low incidence of CHF in the TCH arm.

Metastatic Breast Cancer Studies

The data below reflect exposure to Herceptin in one randomized, open-label study, Study 5, of chemotherapy with (n = 235) or without (n = 234) trastuzumab in patients with metastatic breast cancer, and one single-arm study (Study 6; n = 222) in patients with metastatic breast cancer. Data in Table 4 are based on Studies 5 and 6.

Among the 464 patients treated in Study 5, the median age was 52 years (range: 25–77 years). Eighty-nine percent were White, 5% Black, 1% Asian, and 5% other racial/ethnic groups. All patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months and ≥ 12 months were 58% and 9%, respectively.

Among the 352 patients treated in single agent studies (213 patients from Study 6), the median age was 50 years (range 28–86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months and ≥ 12 months were 31% and 16%, respectively.

Table 4

Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6)

	Single Agent[a] n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC[b] n = 143	AC[b] Alone n = 135
Body as a Whole					
Pain	47%	61%	62%	57%	42%
Asthenia	42%	62%	57%	54%	55%
Fever	36%	49%	23%	56%	34%
Chills	32%	41%	4%	35%	11%
Headache	26%	36%	28%	44%	31%
Abdominal pain	22%	34%	22%	23%	18%
Back pain	22%	34%	30%	27%	15%
Infection	20%	47%	27%	47%	31%
Flu syndrome	10%	12%	5%	12%	6%
Accidental injury	6%	13%	3%	9%	4%
Allergic reaction	3%	8%	2%	4%	2%
Cardiovascular					
Tachycardia	5%	12%	4%	10%	5%
Congestive heart failure	7%	11%	1%	28%	7%

Table 4 (cont'd)

Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6)

	Single Agent[a] n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC[b] n = 143	AC[b] Alone n = 135
Digestive					
Nausea	33%	51%	9%	76%	77%
Diarrhea	25%	45%	29%	45%	26%
Vomiting	23%	37%	28%	53%	49%
Nausea and vomiting	8%	14%	11%	18%	9%
Anorexia	14%	24%	16%	31%	26%
Heme & Lymphatic					
Anemia	4%	14%	9%	36%	26%
Leukopenia	3%	24%	17%	52%	34%
Metabolic					
Peripheral edema	10%	22%	20%	20%	17%
Edema	8%	10%	8%	11%	5%
Musculoskeletal					
Bone pain	7%	24%	18%	7%	7%
Arthralgia	6%	37%	21%	8%	9%
Nervous					
Insomnia	14%	25%	13%	29%	15%
Dizziness	13%	22%	24%	24%	18%
Paresthesia	9%	48%	39%	17%	11%
Depression	6%	12%	13%	20%	12%
Peripheral neuritis	2%	23%	16%	2%	2%
Neuropathy	1%	13%	5%	4%	4%
Respiratory					
Cough increased	26%	41%	22%	43%	29%
Dyspnea	22%	27%	26%	42%	25%
Rhinitis	14%	22%	5%	22%	16%
Pharyngitis	12%	22%	14%	30%	18%
Sinusitis	9%	21%	7%	13%	6%
Skin					
Rash	18%	38%	18%	27%	17%
Herpes simplex	2%	12%	3%	7%	9%
Acne	2%	11%	3%	3%	< 1%
Urogenital					
Urinary tract infection	5%	18%	14%	13%	7%

[a] Data for Herceptin single agent were from 4 studies, including 213 patients from Study 6.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

Metastatic Gastric Cancer

The data below are based on the exposure of 294 patients to Herceptin in combination with a fluoropyrimidine (capecitabine or 5-FU) and cisplatin (Study 7). In the Herceptin plus chemotherapy arm, the initial dose of Herceptin 8 mg/kg was administered on Day 1 (prior to

chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was administered at 80 mg/m^2 on Day 1 and the fluoropyrimidine was administered as either capecitabine 1000 mg/m^2 orally twice a day on Days 1–14 or 5-fluorouracil 800 mg/m^2/day as a continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin infusions administered was eight.

Table 5
Study 7: Per Patient Incidence of Adverse Reactions of All Grades
(Incidence ≥ 5% between Arms) or Grade 3/4 (Incidence > 1% between Arms)
and Higher Incidence in Herceptin Arm

	Herceptin + FC (N = 294) N (%)		FC (N = 290) N (%)	
Body System/Adverse Event	All Grades	Grades 3/4	All Grades	Grades 3/4
Investigations				
Neutropenia	230 (78)	101 (34)	212 (73)	83 (29)
Hypokalemia	83 (28)	28 (10)	69 (24)	16 (6)
Anemia	81 (28)	36 (12)	61 (21)	30 (10)
Thrombocytopenia	47 (16)	14 (5)	33 (11)	8 (3)
Blood and Lymphatic System Disorders				
Febrile Neutropenia	—	15 (5)	—	8 (3)
Gastrointestinal Disorders				
Diarrhea	109 (37)	27 (9)	80 (28)	11 (4)
Stomatitis	72 (24)	2 (1)	43 (15)	6 (2)
Dysphagia	19 (6)	7 (2)	10 (3)	1 (≤ 1)
Body as a Whole				
Fatigue	102 (35)	12 (4)	82 (28)	7 (2)
Fever	54 (18)	3 (1)	36 (12)	0 (0)
Mucosal Inflammation	37 (13)	6 (2)	18 (6)	2 (1)
Chills	23 (8)	1 (≤ 1)	0 (0)	0 (0)
Metabolism and Nutrition Disorders				
Weight Decrease	69 (23)	6 (2)	40 (14)	7 (2)
Infections and Infestations				
Upper Respiratory Tract Infections	56 (19)	0 (0)	29 (10)	0 (0)
Nasopharyngitis	37 (13)	0 (0)	17 (6)	0 (0)
Renal and Urinary Disorders				
Renal Failure and Impairment	53 (18)	8 (3)	42 (15)	5 (2)
Nervous System Disorders				
Dysgeusia	28 (10)	0 (0)	14 (5)	0 (0)

The following subsections provide additional detail regarding adverse reactions observed in clinical trials of adjuvant breast cancer, metastatic breast cancer, metastatic gastric cancer, or post-marketing experience.

Cardiomyopathy

Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and 2, 7.9 years in the AC-T arm, 8.3 years in the AC-TH arm. In Studies 1 and 2, 6% of all randomized patients with post-AC LVEF evaluation were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF < LLN or ≥ 16 point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients receiving one-year Herceptin monotherapy compared to observation in Study 3 (see Table 6, Figures 1 and 2). The per-patient incidence of new-onset cardiac dysfunction, as measured by LVEF, remained similar when compared to the analysis performed at a median follow-up of 2.0 years in the AC-TH arm. This analysis also showed evidence of reversibility of left ventricular dysfunction, with 64.5% of patients who experienced symptomatic CHF in the AC-TH group being asymptomatic at latest follow-up, and 90.3% having full or partial LVEF recovery.

Table 6[a]

Per-patient Incidence of New Onset
Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4

	LVEF < 50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF < 50%	≥ 10% decrease	≥ 16% decrease	< 20% and ≥ 10%	≥ 20%
Studies 1 & 2[b,c]					
AC→TH (n = 1856)	23.1% (428)	18.5% (344)	11.2% (208)	37.9% (703)	8.9% (166)
AC→T (n = 1170)	11.7% (137)	7.0% (82)	3.0% (35)	22.1% (259)	3.4% (40)
Study 3[d]					
Herceptin (n = 1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n = 1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
Study 4[e]					
TCH (n = 1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n = 1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n = 1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

[a] For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization.

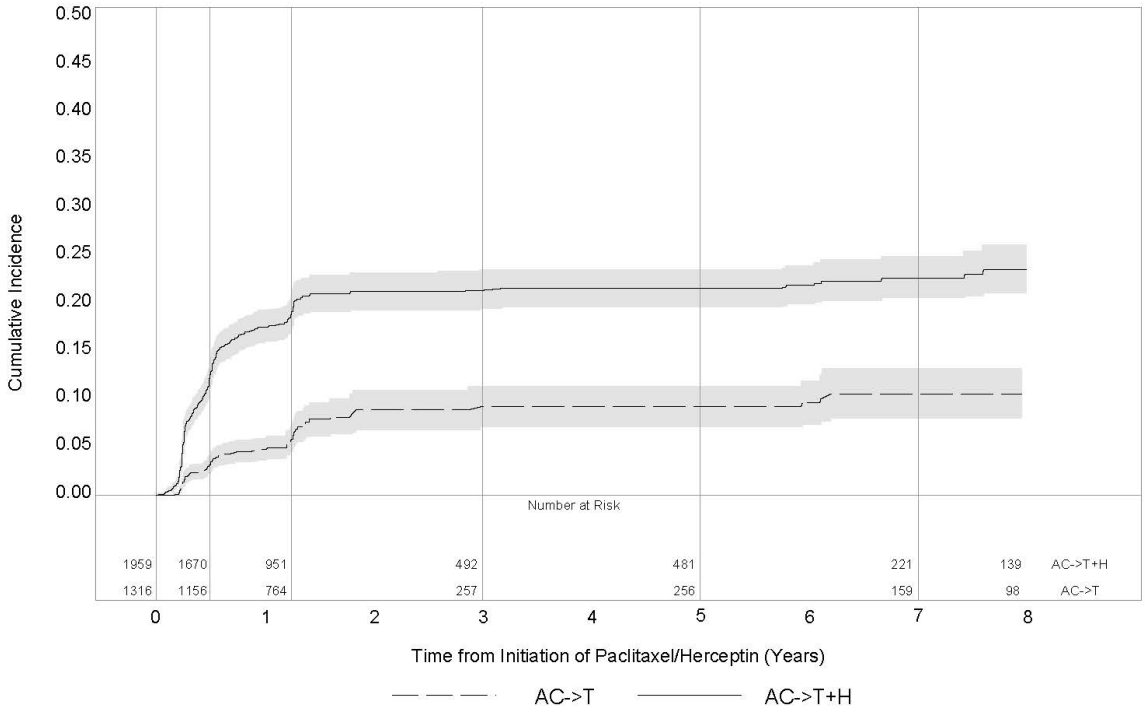
[b] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

[c] Median duration of follow-up for Studies 1 and 2 combined was 8.3 years in the AC→TH arm.

[d] Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.

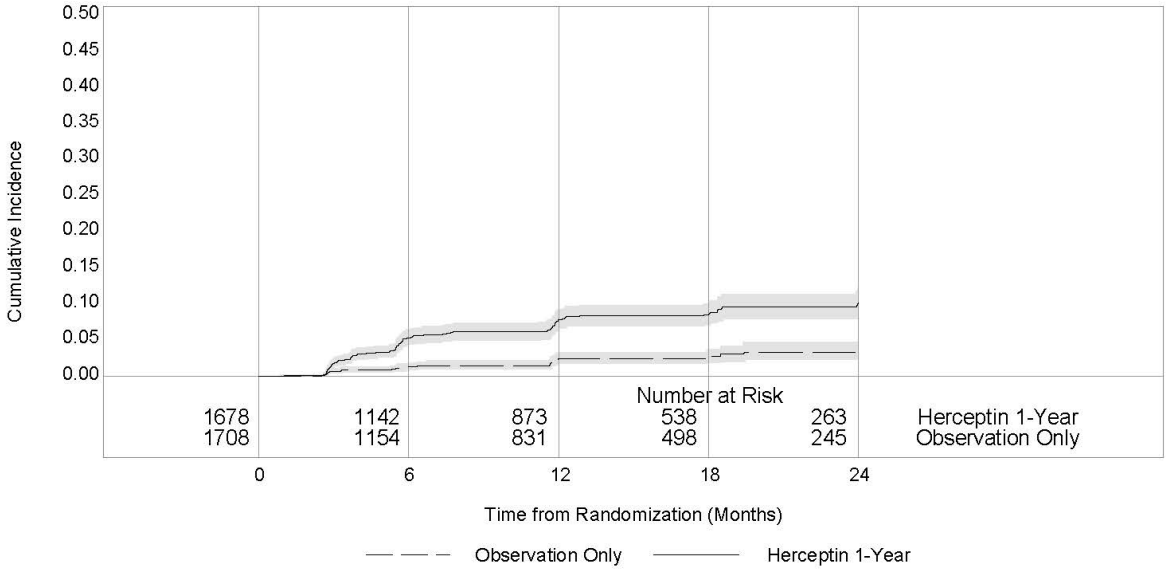
[e] Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

Figure 1
Studies 1 and 2: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



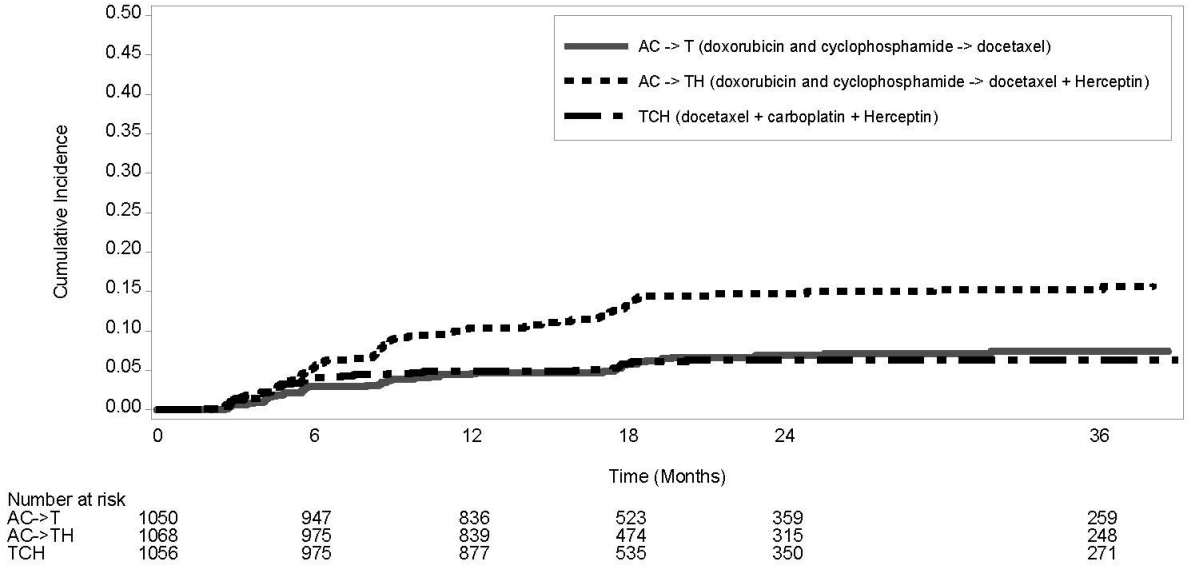
Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

Figure 2
Study 3: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization.

Figure 3
Study 4: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization.

The incidence of treatment emergent congestive heart failure among patients in the metastatic breast cancer trials was classified for severity using the New York Heart Association classification system (I–IV, where IV is the most severe level of cardiac failure) (see Table 2). In the metastatic breast cancer trials, the probability of cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracyclines.

In Study 7, 5.0% of patients in the Herceptin plus chemotherapy arm compared to 1.1% of patients in the chemotherapy alone arm had LVEF value below 50% with a ≥10% absolute decrease in LVEF from pretreatment values.

Infusion Reactions

During the first infusion with Herceptin, the symptoms most commonly reported were chills and fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of Herceptin infusion); permanent discontinuation of Herceptin for infusion reactions was required in < 1% of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. Infusion reactions occurred in 21% and 35% of patients, and were severe in 1.4% and 9% of patients, on second or subsequent Herceptin infusions administered as monotherapy or in combination with chemotherapy, respectively. In the post-marketing setting, severe infusion reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported.

Anemia

In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]), of selected NCI-CTC Grade 2−5 anemia (12.3% vs. 6.7% [Study 1]), and of anemia requiring transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. Following the administration of Herceptin as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was < 1%. In Study 7 (metastatic gastric cancer), on the Herceptin containing arm as compared to the chemotherapy alone arm, the overall incidence of anemia was 28% compared to 21% and of NCI-CTC Grade 3/4 anemia was 12.2% compared to 10.3%.

Neutropenia

In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI-CTC Grade 4–5 neutropenia (1.7% vs. 0.8% [Study 2]) and of selected Grade 2–5 neutropenia (6.4% vs. 4.3% [Study 1]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7 (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone arm, the incidence of NCI-CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile neutropenia 5.1% compared to 2.8%.

Infection

The overall incidences of infection (46% vs. 30% [Study 5]), of selected NCI-CTC Grade 2–5 infection/febrile neutropenia (24.3% vs. 13.4% [Study 1]) and of selected Grade 3–5 infection/febrile neutropenia (2.9% vs. 1.4% [Study 2]) were higher in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. The most common site of infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract.

In Study 4, the overall incidence of infection was higher with the addition of Herceptin to AC-T but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC Grade 3–4 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms.

In a randomized, controlled trial in treatment of metastatic breast cancer, the reported incidence of febrile neutropenia was higher (23% vs. 17%) in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone.

Pulmonary Toxicity

Adjuvant Breast Cancer

Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC Grade 2–5 pulmonary toxicity (14.3% vs. 5.4% [Study 1]) and of selected NCI-CTC Grade 3–5 pulmonary toxicity and spontaneous reported Grade 2 dyspnea (3.4% vs. 0.9% [Study 2]) was higher in patients receiving Herceptin and chemotherapy compared with chemotherapy alone. The most common pulmonary toxicity was dyspnea (NCI-CTC Grade 2–5: 11.8% vs. 4.6% [Study 1]; NCI-CTC Grade 2–5: 2.4% vs. 0.2% [Study 2]).

Pneumonitis/pulmonary infiltrates occurred in 0.7% of patients receiving Herceptin compared with 0.3% of those receiving chemotherapy alone. Fatal respiratory failure occurred in 3 patients receiving Herceptin, one as a component of multi-organ system failure, as compared to 1 patient receiving chemotherapy alone.

In Study 3, there were 4 cases of interstitial pneumonitis in the one-year Herceptin treatment arm compared to none in the observation arm at a median follow-up duration of 12.6 months.

Metastatic Breast Cancer

Among women receiving Herceptin for treatment of metastatic breast cancer, the incidence of pulmonary toxicity was also increased. Pulmonary adverse events have been reported in the post-marketing experience as part of the symptom complex of infusion reactions. Pulmonary events include bronchospasm, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see *Warnings and Precautions (5.4)*.

Thrombosis/Embolism

In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies (2.6% vs. 1.5% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]).

Diarrhea

Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC Grade 2–5 diarrhea (6.7% vs. 5.4% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (2.2% vs. 0% [Study 2]), and of Grade 1–4 diarrhea (7% vs. 1% [Study 3; one-year Herceptin treatment at 12.6 months median duration of follow-up]) were higher in patients receiving Herceptin as compared to controls. In Study 4, the incidence of Grade 3–4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving Herceptin. Of patients receiving Herceptin as a single agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was observed in patients receiving Herceptin in combination with chemotherapy for treatment of metastatic breast cancer.

Renal Toxicity

In Study 7 (metastatic gastric cancer) on the Herceptin-containing arm as compared to the chemotherapy alone arm the incidence of renal impairment was 18% compared to 14.5%. Severe (Grade 3/4) renal failure was 2.7% on the Herceptin-containing arm compared to 1.7% on the chemotherapy only arm. Treatment discontinuation for renal insufficiency/failure was 2% on the Herceptin-containing arm and 0.3% on the chemotherapy only arm.

In the post-marketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18 months from initiation of Herceptin therapy. Pathologic findings included membranous

glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Among 903 women with metastatic breast cancer, human anti-human antibody (HAHA) to Herceptin was detected in one patient using an enzyme-linked immunosorbent assay (ELISA). This patient did not experience an allergic reaction. Samples for assessment of HAHA were not collected in studies of adjuvant breast cancer.

The incidence of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Herceptin with the incidence of antibodies to other products may be misleading.

6.3 Post-Marketing Experience

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

- Infusion reaction *[see Warnings and Precautions (5.2)]*
- Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal abnormalities, and neonatal death *[see Warnings and Precautions (5.3)]*
- Glomerulopathy *[see Adverse Reactions (6.1)]*
- Immune thrombocytopenia
- Tumor lysis syndrome (TLS): Cases of possible TLS have been reported in patients treated with Herceptin. Patients with significant tumor burden (e.g. bulky metastases) may be at a higher risk. Patients could present with hyperuricemia, hyperphosphatemia, and acute renal failure which may represent possible TLS. Providers should consider additional monitoring and/or treatment as clinically indicated.

7 DRUG INTERACTIONS

Patients who receive anthracycline after stopping Herceptin may be at increased risk of cardiac dysfunction because of trastuzumab's long washout period based on population PK analysis *[see Clinical Pharmacology (12.3)]*. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Pharmacovigilance Program

There is a pregnancy pharmacovigilance program for Herceptin. If Herceptin is administered during pregnancy, or if a patient becomes pregnant while receiving Herceptin or within 7 months following the last dose of Herceptin, health care providers and patients should immediately report Herceptin exposure to Genentech at 1-888-835-2555.

Risk Summary

Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death *[see Data]*. Apprise the patient of the potential risks to a fetus. There are clinical

considerations if Herceptin is used in a pregnant woman or if a patient becomes pregnant within 7 months following the last dose of Herceptin *[see Clinical Considerations]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received Herceptin during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting in the fetus as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. These case reports described oligohydramnios in pregnant women who received Herceptin either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin therapy resumed after amniotic index improved and oligohydramnios recurred.

Animal Data

In studies where trastuzumab was administered to pregnant Cynomolgus monkeys during the period of organogenesis at doses up to 25 mg/kg given twice weekly (up to 25 times the recommended weekly human dose of 2 mg/kg), trastuzumab crossed the placental barrier during the early (Gestation Days 20 to 50) and late (Gestation Days 120 to 150) phases of gestation. The resulting concentrations of trastuzumab in fetal serum and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum but were not associated with adverse developmental effects.

8.2 Lactation

Risk Summary

There is no information regarding the presence of trastuzumab in human milk, the effects on the breastfed infant, or the effects on milk production. Published data suggest human IgG is present in human milk but does not enter the neonatal and infant circulation in substantial amounts. Trastuzumab was present in the milk of lactating Cynomolgus monkeys but not associated with neonatal toxicity *[see Data]*. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for Herceptin treatment and any potential adverse effects on the breastfed child from Herceptin or from the underlying maternal condition. This consideration should also take into account the trastuzumab wash out period of 7 months *[see Clinical Pharmacology (12.3)]*.

Data

In lactating Cynomolgus monkeys, trastuzumab was present in breast milk at about 0.3% of maternal serum concentrations after pre- (beginning Gestation Day 120) and post-partum (through Post-partum Day 28) doses of 25 mg/kg administered twice weekly (25 times the recommended weekly human dose of 2 mg/kg of Herceptin). Infant monkeys with detectable serum levels of trastuzumab did not exhibit any adverse effects on growth or development from birth to 1 month of age.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of Herceptin.

Contraception

Females

Herceptin can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment with Herceptin and for 7 months following the last dose of Herceptin *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

The safety and effectiveness of Herceptin in pediatric patients have not been established.

8.5 Geriatric Use

Herceptin has been administered to 386 patients who were 65 years of age or over (253 in the adjuvant treatment and 133 in metastatic breast cancer treatment settings). The risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients in both those receiving treatment for metastatic disease in Studies 5 and 6, or adjuvant therapy in Studies 1 and 2. Limitations in data collection and differences in study design of the 4 studies of Herceptin in adjuvant treatment of breast cancer preclude a determination of whether the toxicity profile of Herceptin in older patients is different from younger patients. The reported clinical experience is not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of Herceptin treatment in older patients is different from that observed in patients < 65 years of age for metastatic disease and adjuvant treatment.

In Study 7 (metastatic gastric cancer), of the 294 patients treated with Herceptin, 108 (37%) were 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or effectiveness were observed.

10 OVERDOSAGE

There is no experience with overdosage in human clinical trials. Single doses higher than 8 mg/kg have not been tested.

11 DESCRIPTION

Trastuzumab is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture.

Herceptin (trastuzumab) for injection is a sterile, white to pale yellow, preservative-free lyophilized powder with a cake-like appearance, for intravenous administration.

Each single-dose vial of Herceptin delivers 150 mg trastuzumab, 136.2 mg α,α-trehalose dihydrate, 3.4 mg L-histidine HCl monohydrate, 2.2 mg L-histidine, and 0.6 mg polysorbate 20. Reconstitution with 7.4 mL of sterile water for injection (SWFI) yields a solution containing 21 mg/mL trastuzumab that delivers 7.15 mL (150 mg trastuzumab), at a pH of approximately 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Herceptin has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Herceptin is a mediator of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, Herceptin-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumors. Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumors.

12.3 Pharmacokinetics

The pharmacokinetics of trastuzumab was evaluated in a pooled population pharmacokinetic (PK) model analysis of 1,582 subjects with primarily breast cancer and metastatic gastric cancer (MGC) receiving intravenous Herceptin. Total trastuzumab clearance increases with decreasing concentrations due to parallel linear and non-linear elimination pathways.

Although the average trastuzumab exposure was higher following the first cycle in breast cancer patients receiving the three-weekly schedule compared to the weekly schedule of Herceptin, the average steady-state exposure was essentially the same at both dosages. The average trastuzumab exposure following the first cycle and at steady state as well as the time to steady state was higher in breast cancer patients compared to MGC patients at the same dosage; however, the reason for this exposure difference is unknown. Additional predicted trastuzumab exposure and PK parameters following the first Herceptin cycle and at steady state exposure are described in Tables 7 and 8, respectively.

Population PK based simulations indicate that following discontinuation of Herceptin, concentrations in at least 95% of breast cancer and MGC patients will decrease to approximately 3% of the population predicted steady-state trough serum concentration (approximately 97% washout) by 7 months *[see Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1, 8.3)]*.

Table 7

Population Predicted Cycle 1 PK Exposures (Median with 5^{th} – 95^{th} Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	C_{min} (µg/mL)	C_{max} (µg/mL)	$AUC_{0\text{-}21days}$ (µg.day/mL)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	29.4 (5.8 - 59.5)	178 (117 - 291)	1373 (736 - 2245)
	MGC	274	23.1 (6.1 - 50.3)	132 (84.2 - 225)	1109 (588 - 1938)
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	37.7 (12.3 - 70.9)	88.3 (58 - 144)	1066 (586 - 1754)

Table 8
Population Predicted Steady State PK Exposures (Median with 5th - 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	$C_{min,ss}$[a] (µg/mL)	$C_{max,ss}$[b] (µg/mL)	$AUC_{ss,\ 0\text{-}21\ days}$ (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	47.4 (5 - 115)	179 (107 - 309)	1794 (673 - 3618)	12	0.173 - 0.283
	MGC	274	32.9 (6.1 - 88.9)	131 (72.5 - 251)	1338 (557 - 2875)	9	0.189 - 0.337
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	66.1 (14.9 - 142)	109 (51.0 - 209)	1765 (647 - 3578)	12	0.201 - 0.244

[a] Steady-state trough serum concentration of trastuzumab
[b] Maximum steady-state serum concentration of trastuzumab

Specific Populations
Based on a population pharmacokinetic analysis, no clinically significant differences were observed in the pharmacokinetics of trastuzumab based on age (< 65 (n = 1294); ≥ 65 (n = 288)), race (Asian (n = 264); non-Asian (n = 1324)) and renal impairment (mild (creatinine clearance [CLcr] 60 to 90 mL/min) (n = 636) or moderate (CLcr 30 to 60 mL/min) (n = 133)). The pharmacokinetics of trastuzumab in patients with severe renal impairment, end-stage renal disease with or without hemodialysis, or hepatic impairment is unknown.

Drug Interaction Studies
There have been no formal drug interaction studies performed with Herceptin in humans. Clinically significant interactions between Herceptin and concomitant medications used in clinical trials have not been observed.

Paclitaxel and doxorubicin: Concentrations of paclitaxel and doxorubicin and their major metabolites (i.e., 6-α hydroxyl-paclitaxel [POH], and doxorubicinol [DOL], respectively) were not altered in the presence of trastuzumab when used as combination therapy in clinical trials. Trastuzumab concentrations were not altered as part of this combination therapy.

Docetaxel and carboplatin: When Herceptin was administered in combination with docetaxel or carboplatin, neither the plasma concentrations of docetaxel or carboplatin nor the plasma concentrations of trastuzumab were altered.

Cisplatin and capecitabine: In a drug interaction substudy conducted in patients in Study 7, the pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered in combination with Herceptin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Herceptin has not been tested for carcinogenic potential.

No evidence of mutagenic activity was observed when trastuzumab was tested in the standard Ames bacterial and human peripheral blood lymphocyte mutagenicity assays at concentrations of up to 5000 mcg/mL. In an *in vivo* micronucleus assay, no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg of trastuzumab.

A fertility study was conducted in female Cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg of trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels.

14 CLINICAL STUDIES

14.1 Adjuvant Breast Cancer

The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were evaluated in an integrated analysis of two randomized, open-label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women at definitive Disease-Free Survival analysis for one-year Herceptin treatment versus observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4).

Studies 1 and 2

In Studies 1 and 2, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization (Study 2) or was required to be performed at a reference laboratory (Study 1). Patients with a history of active cardiac disease based on symptoms, abnormal electrocardiographic, radiologic, or left ventricular ejection fraction findings or uncontrolled hypertension (diastolic > 100 mm Hg or systolic > 200 mm Hg) were not eligible.

Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by paclitaxel (AC→paclitaxel) alone or paclitaxel plus Herceptin (AC→paclitaxel + Herceptin). In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2. Paclitaxel was administered either weekly (80 mg/m^2) or every 3 weeks (175 mg/m^2) for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in Study 2. Herceptin was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a dose of 2 mg/kg weekly for a total of 52 weeks. Herceptin treatment was permanently discontinued in patients who developed congestive heart failure, or persistent/recurrent LVEF decline *[see Dosage and Administration (2.3)]*. Radiation therapy, if administered, was initiated after the completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. The primary endpoint of the combined efficacy analysis was Disease-Free Survival (DFS), defined as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second primary cancer, or death. The secondary endpoint was overall survival (OS).

A total of 3752 patients were included in the joint efficacy analysis of the primary endpoint of DFS following a median follow-up of 2.0 years in the AC→paclitaxel + Herceptin arm. The pre-planned final OS analysis from the joint analysis included 4063 patients and was performed when 707 deaths had occurred after a median follow-up of 8.3 years in the AC→paclitaxel + Herceptin arm. The data from both arms in Study 1 and two of the three study arms in Study 2 were pooled for efficacy analyses. The patients included in the primary DFS analysis had a median age of 49 years (range, 22–80 years; 6% > 65 years), 84% were white, 7% black, 4% Hispanic, and 4% Asian/Pacific Islander. Disease characteristics included 90% infiltrating ductal histology, 38% T1, 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% ER+ and/or PR+ tumors. Similar demographic and baseline characteristics were reported for the efficacy evaluable population, after 8.3 years of median follow-up in the AC→paclitaxel + Herceptin arm.

Study 3

In Study 3, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH) as determined at a central laboratory. Patients with node-negative disease were required to have ≥ T1c primary tumor. Patients with a history of congestive heart failure or LVEF < 55%, uncontrolled arrhythmias, angina requiring medication, clinically significant

valvular heart disease, evidence of transmural infarction on ECG, poorly controlled hypertension (systolic > 180 mm Hg or diastolic > 100 mm Hg) were not eligible.

Study 3 was designed to compare one and two years of three-weekly Herceptin treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). Patients were randomized (1:1:1) upon completion of definitive surgery, and at least four cycles of chemotherapy to receive no additional treatment, or one year of Herceptin treatment or two years of Herceptin treatment. Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator discretion. Herceptin was administered with an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every three weeks. The main outcome measure was Disease-Free Survival (DFS), defined as in Studies 1 and 2.

A protocol specified interim efficacy analysis comparing one-year Herceptin treatment to observation was performed at a median follow-up duration of 12.6 months in the Herceptin arm and formed the basis for the definitive DFS results from this study. Among the 3386 patients randomized to the observation (n = 1693) and Herceptin one-year (n = 1693) treatment arms, the median age was 49 years (range 21–80), 83% were Caucasian, and 13% were Asian. Disease characteristics: 94% infiltrating ductal carcinoma, 50% ER+ and/or PgR+, 57% node positive, 32% node negative, and in 11% of patients, nodal status was not assessable due to prior neo-adjuvant chemotherapy. Ninety-six percent (1055/1098) of patients with node-negative disease had high-risk features: among the 1098 patients with node-negative disease, 49% (543) were ER– and PgR–, and 47% (512) were ER and/or PgR+ and had at least one of the following high-risk features: pathological tumor size greater than 2 cm, Grade 2–3, or age < 35 years. Prior to randomization, 94% of patients had received anthracycline-based chemotherapy regimens.

After the definitive DFS results comparing observation to one-year Herceptin treatment were disclosed, a prospectively planned analysis that included comparison of one year versus two years of Herceptin treatment at a median follow-up duration of 8 years was performed. Based on this analysis, extending Herceptin treatment for a duration of two years did not show additional benefit over treatment for one year [Hazard Ratios of two-years Herceptin versus one-year Herceptin treatment in the intent to treat (ITT) population for Disease-Free Survival (DFS) = 0.99 (95% CI: 0.87, 1.13), p-value = 0.90 and Overall Survival (OS) = 0.98 (0.83, 1.15); p-value = 0.78].

Study 4

In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only) as determined at a central laboratory. Patients were required to have either node-positive disease, or node-negative disease with at least one of the following high-risk features: ER/PR-negative, tumor size > 2 cm, age < 35 years, or histologic and/or nuclear Grade 2 or 3. Patients with a history of CHF, myocardial infarction, Grade 3 or 4 cardiac arrhythmia, angina requiring medication, clinically significant valvular heart disease, poorly controlled hypertension (diastolic > 100 mm Hg), any T4 or N2, or known N3 or M1 breast cancer were not eligible.

Patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by docetaxel (AC-T), doxorubicin and cyclophosphamide followed by docetaxel plus Herceptin (AC-TH), or docetaxel and carboplatin plus Herceptin (TCH). In both the AC-T and AC-TH arms, doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 were administered every 3 weeks for four cycles; docetaxel 100 mg/m^2 was administered every 3 weeks for four cycles. In the TCH arm, docetaxel 75 mg/m^2 and carboplatin (at a target AUC of 6 mg/mL/min as a 30- to 60-minute infusion) were administered every 3 weeks for six cycles. Herceptin was administered weekly (initial dose of 4 mg/kg followed by weekly dose of 2 mg/kg) concurrently with either T or TC, and then every 3 weeks (6 mg/kg) as monotherapy for a total of 52 weeks. Radiation therapy, if administered, was initiated after completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. Disease-Free Survival (DFS) was the main outcome measure.

Among the 3222 patients randomized, the median age was 49 (range 22 to 74 years; 6% ≥ 65 years). Disease characteristics included 54% ER+ and/or PR+ and 71% node positive. Prior to randomization, all patients underwent primary surgery for breast cancer.

The results for DFS for the integrated analysis of Studies 1 and 2, Study 3, and Study 4 and OS results for the integrated analysis of Studies 1 and 2, and Study 3 are presented in Table 9. For Studies 1 and 2, the duration of DFS following a median follow-up of 2.0 years in the AC→TH arm is presented in Figure 4, and the duration of OS after a median follow-up of 8.3 years in the AC→TH arm is presented in Figure 5. The duration of DFS for Study 4 is presented in Figure 6. Across all four studies, at the time of definitive DFS analysis, there were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect was different from that of the overall patient population: patients with low tumor grade, patients within specific ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients), and patients>65 years of age. For Studies 1 and 2, the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74). At 8.3 years of median follow-up [AC→TH], the survival rate was estimated to be 86.9% in the AC→TH arm and 79.4% in the AC→T arm. The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age, hormone receptor status, number of positive lymph nodes, tumor size and grade, and surgery/radiation therapy was consistent with the treatment effect in the overall population. In patients ≤ 50 years of age (n = 2197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in patients > 50 years of age (n = 1866), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive) (n = 2223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-negative disease (ER-negative and PR-negative) (n = 1830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤ 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80).

Table 9
Efficacy Results from Adjuvant Treatment of
Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	DFS Hazard ratio (95% CI) p-value	Deaths (OS events)	OS Hazard ratio p-value
Studies 1 + 2[a]				
AC→TH (n = 1872)[b] (n = 2031)[c]	133[b]	0.48[b,d] (0.39, 0.59) p< 0.0001[e]	289[c]	0.64[c,d] (0.55, 0.74) p< 0.0001[e]
AC→T (n = 1880)[b] (n = 2032)[c]	261[b]		418[c]	
Study 3[f]				
Chemo→ Herceptin (n = 1693)	127	0.54 (0.44, 0.67) p< 0.0001[g]	31	0.75 p = NS[h]
Chemo→ Observation (n = 1693)	219		40	
Study 4[i]				
TCH (n = 1075)	134	0.67 (0.54 – 0.84) p=0.0006[e,j]	56	
AC→TH (n = 1074)	121	0.60 (0.48 – 0.76) p< 0.0001[e,i]	49	
AC→T (n = 1073)	180		80	

CI = confidence interval.

[a] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

[b] Efficacy evaluable population, for the primary DFS analysis, following a median follow-up of 2.0 years in the AC→TH arm.

[c] Efficacy evaluable population, for the final OS analysis, following 707 deaths (8.3 years of median follow-up in the AC→TH arm).

[d] Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

[e] stratified log-rank test.

[f] At definitive DFS analysis with median duration of follow-up of 12.6 months in the one-year Herceptin treatment arm.

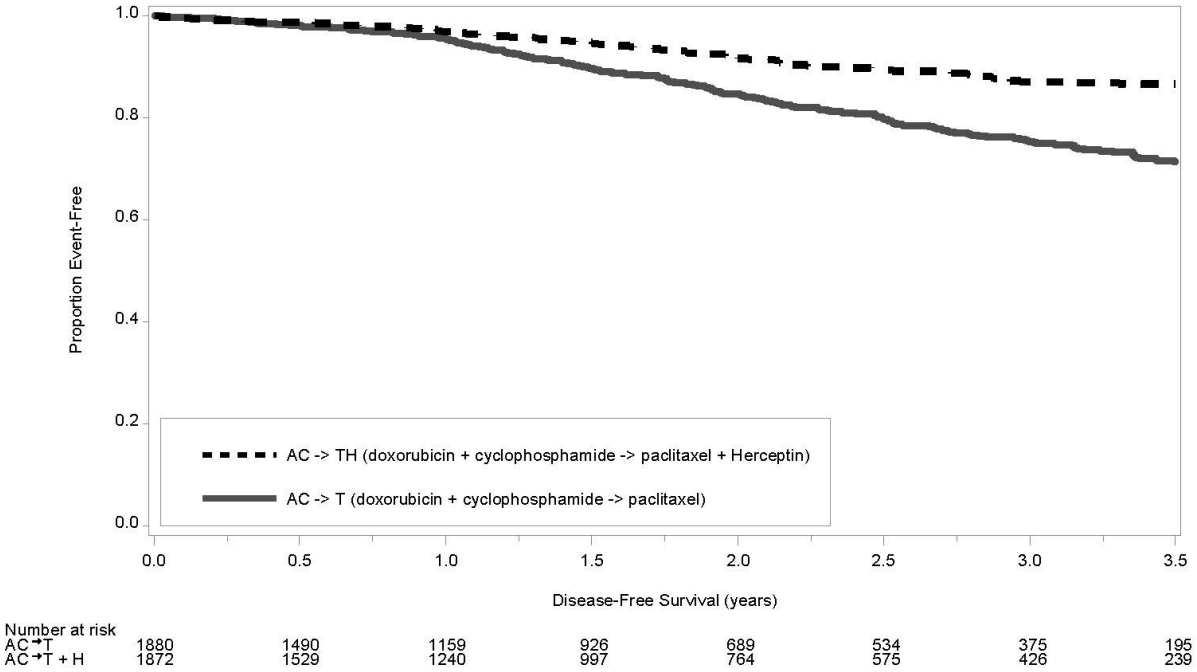
[g] log-rank test.

[h] NS = non-significant.

[i] Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

[j] A two-sided alpha level of 0.025 for each comparison.

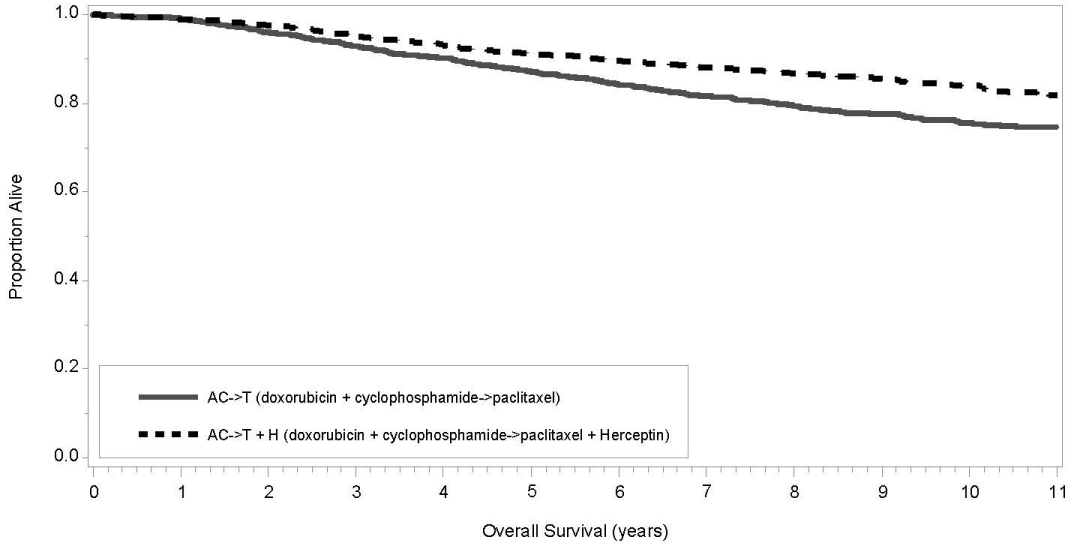
Figure 4
Duration of Disease-Free Survival in
Patients with Adjuvant Treatment of Breast Cancer (Studies 1 and 2)



Number at risk								
AC→T	1880	1490	1159	926	689	534	375	195
AC→T + H	1872	1529	1240	997	764	575	426	239

Figure 5

Duration of Overall Survival in Patients with
Adjuvant Treatment of Breast Cancer (Studies 1 and 2)

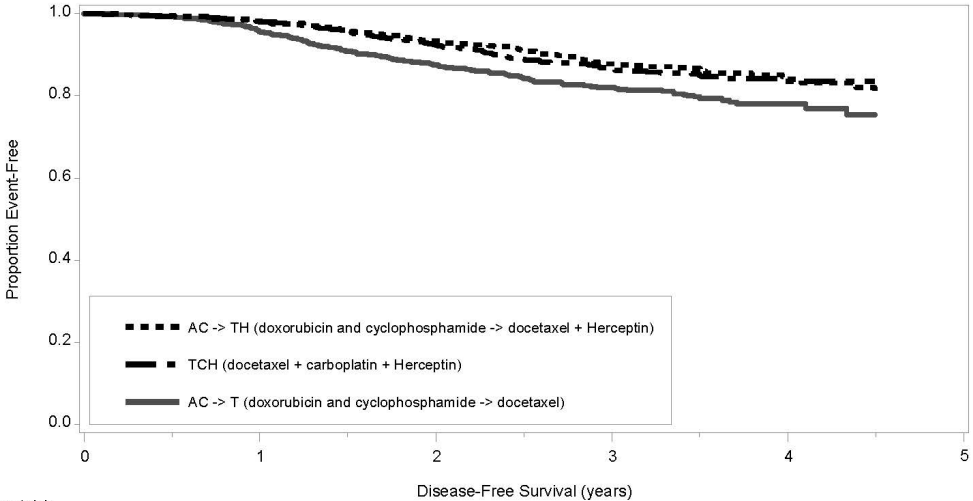


Number at risk

AC->T	2032	1961	1883	1806	1732	1643	1538	1377	979	630	399	151
AC->T + H	2031	1992	1957	1897	1843	1787	1714	1533	1127	787	485	159

Figure 6

Duration of Disease-Free Survival in Patients with
Adjuvant Treatment of Breast Cancer (Study 4)



Number at risk

AC->T	1073	971	802	417	103
AC->TH	1074	1023	885	457	126
TCH	1075	1018	877	447	126

AC=doxorubicin and cyclophosphamide; T=docetaxel; TCH=docetaxel, platinum salt, and Herceptin; TH=docetaxel and Herceptin.
Kaplan-Meier estimates are shown.

Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in Studies 2 and 3, where central laboratory testing data were available. The results are shown in Table 10. The number of events in Study 2 was small with the exception of

the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH+/IHC unknown subgroups.

Table 10
Treatment Outcomes in Studies 2 and 3 as a Function of HER2 Overexpression or Amplification

	Study 2		Study 3[c]	
HER2 Assay Result[a]	Number of Patients	Hazard Ratio DFS (95% CI)	Number of Patients	Hazard Ratio DFS (95% CI)
IHC 3+				
FISH (+)	1170	0.42 (0.27, 0.64)	91	0.56 (0.13, 2.50)
FISH (–)	51	0.71 (0.04, 11.79)	8	—
FISH Unknown	51	0.69 (0.09, 5.14)	2258	0.53 (0.41, 0.69)
IHC < 3+ / FISH (+)	174	1.01 (0.18, 5.65)	299[b]	0.53 (0.20, 1.42)
IHC unknown / FISH (+)	—	—	724	0.59 (0.38, 0.93)

[a] IHC by HercepTest, FISH by PathVysion (HER2/CEP17 ratio ≥ 2.0) as performed at a central laboratory.
[b] All cases in this category in Study 3 were IHC 2+.
[c] Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.

14.2 Metastatic Breast Cancer

The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n = 469 patients) and an open-label, single agent clinical trial (Study 6, n = 222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

Previously Untreated Metastatic Breast Cancer (Study 5)

Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or in combination with Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly doses of Herceptin at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to

receive chemotherapy alone in this study received Herceptin at the time of disease progression as part of a separate extension study.

Based upon the determination by an independent response evaluation committee, the patients randomized to Herceptin and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), and a longer median duration of response as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin and chemotherapy also had a longer median survival (see Table 11). These treatment effects were observed both in patients who received Herceptin plus paclitaxel and in those who received Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.

Table 11
Study 5: Efficacy Results in
First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Herceptin + All Chemo-therapy (n = 235)	All Chemo-therapy (n = 234)	Herceptin + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Herceptin + AC[a] (n = 143)	AC (n = 138)
Primary Endpoint						
Median TTP(mos)[b,c]	7.2	4.5	6.7	2.5	7.6	5.7
95% CI	7, 8	4, 5	5, 10	2, 4	7, 9	5, 7
p-value[d]	< 0.0001		< 0.0001		0.002	
Secondary Endpoints						
Overall Response Rate[b]	45	29	38	15	50	38
95% CI	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value[e]	< 0.001		< 0.001		0.10	
Median Resp Duration (mos)[b,c]	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% Quartile	6, 15	4, 8	5, 11	4, 7	6, 15	4, 8
Med Survival (mos)[c]	25.1	20.3	22.1	18.4	26.8	21.4
95% CI	22, 30	17, 24	17, 29	13, 24	23, 33	18, 27
p-value[d]	0.05		0.17		0.16	

[a] AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[b] Assessed by an independent Response Evaluation Committee.
[c] Kaplan-Meier Estimate.
[d] log-rank test.
[e] $\chi 2$-test.

Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see Table 12).

Table 12
Treatment Effects in Study 5 as a
Function of HER2 Overexpression or Amplification

HER2 Assay Result	Number of Patients (N)	Relative Risk[b] for Time to Disease Progression (95% CI)	Relative Risk[b] for Mortality (95% CI)
CTA 2+ or 3+	469	0.49 (0.40, 0.61)	0.80 (0.64, 1.00)
FISH (+)[a]	325	0.44 (0.34, 0.57)	0.70 (0.53, 0.91)
FISH (–)[a]	126	0.62 (0.42, 0.94)	1.06 (0.70, 1.63)
CTA 2+	120	0.76 (0.50, 1.15)	1.26 (0.82, 1.94)
FISH (+)	32	0.54 (0.21, 1.35)	1.31 (0.53, 3.27)
FISH (–)	83	0.77 (0.48, 1.25)	1.11 (0.68, 1.82)
CTA 3+	349	0.42 (0.33, 0.54)	0.70 (0.51, 0.90)
FISH (+)	293	0.42 (0.32, 0.55)	0.67 (0.51, 0.89)
FISH (–)	43	0.43 (0.20, 0.94)	0.88 (0.39, 1.98)

[a] FISH testing results were available for 451 of the 469 patients enrolled on study.
[b] The relative risk represents the risk of progression or death in the Herceptin plus chemotherapy arm versus the chemotherapy arm.

Previously Treated Metastatic Breast Cancer (Study 6)

Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of Herceptin at 2 mg/kg IV.

The ORR (complete response + partial response), as determined by an independent Response Evaluation Committee, was 14%, with a 2% complete response rate and a 12% partial response rate. Complete responses were observed only in patients with disease limited to skin and lymph nodes. The overall response rate in patients whose tumors tested as CTA 3+ was 18% while in those that tested as CTA 2+, it was 6%.

14.3 Metastatic Gastric Cancer

The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial, 594 patients were randomized 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil). All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients were also required to have adequate cardiac function (e.g., LVEF > 50%).

On the Herceptin-containing arm, Herceptin was administered as an IV infusion at an initial dose of 8 mg/kg followed by 6 mg/kg every 3 weeks until disease progression. On both study arms cisplatin was administered at a dose of 80 mg/m^2 Day 1 every 3 weeks for 6 cycles as a 2 hour IV

infusion. On both study arms, capecitabine was administered at 1000 mg/m^2 dose orally twice daily (total daily dose 2000 mg/m^2) for 14 days of each 21 day cycle for 6 cycles. Alternatively, continuous intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m^2/day from Day 1 through Day 5 every three weeks for 6 cycles.

The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1; 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant therapy, and 2% had received prior radiotherapy.

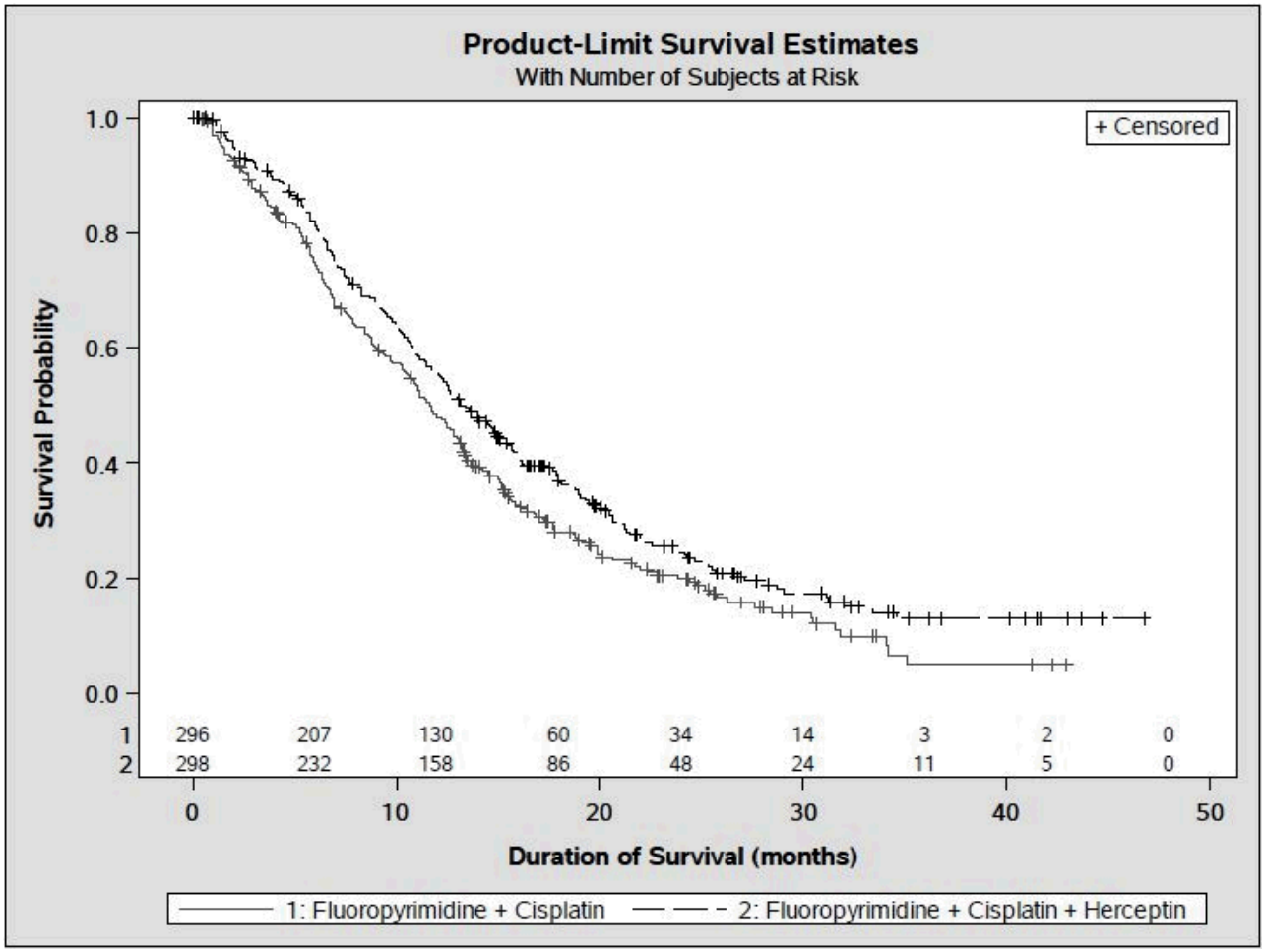
The main outcome measure of Study 7 was overall survival (OS), analyzed by the unstratified log-rank test. The final OS analysis based on 351 deaths was statistically significant (nominal significance level of 0.0193). An updated OS analysis was conducted at one year after the final analysis. The efficacy results of both the final and the updated analyses are summarized in Table 13 and Figure 7.

Table 13
Study 7: Overall Survival in ITT Population

	FC Arm N = 296	FC + H Arm N = 298
Definitive (Second Interim) Overall Survival		
No. Deaths (%)	184 (62.2%)	167 (56.0%)
Median	11.0	13.5
95% CI (mos.)	(9.4, 12.5)	(11.7, 15.7)
Hazard Ratio	0.73	
95% CI	(0.60, 0.91)	
p-value*, two-sided	0.0038	
Updated Overall Survival		
No. Deaths (%)	227 (76.7%)	221 (74.2%)
Median	11.7	13.1
95% CI (mos.)	(10.3, 13.0)	(11.9, 15.1)
Hazard Ratio	0.80	
95% CI	(0.67, 0.97)	

* Comparing with the nominal significance level of 0.0193.

Figure 7
Updated Overall Survival in Patients with Metastatic Gastric Cancer (Study 7)



An exploratory analysis of OS in patients based on HER2 gene amplification (FISH) and protein overexpression (IHC) testing is summarized in Table 14.

Table 14
Exploratory Analyses by HER2 Status Using Updated Overall Survival Results

	FC (N = 296)[a]	FC+H (N = 298)[b]
FISH+ / IHC 0, 1+ subgroup (N=133)		
No. Deaths / n (%)	57/71 (80%)	56/62 (90%)
Median OS Duration (mos.)	8.8	8.3
95% CI (mos.)	(6.4, 11.7)	(6.2, 10.7)
Hazard ratio (95% CI)	1.33 (0.92, 1.92)	
FISH+ / IHC2+ subgroup (N=160)		
No. Deaths / n (%)	65/80 (81%)	64/80 (80%)
Median OS Duration (mos.)	10.8	12.3
95% CI (mos.)	(6.8, 12.8)	(9.5, 15.7)
Hazard ratio (95% CI)	0.78 (0.55, 1.10)	
FISH+ or FISH- / IHC3+[c] subgroup (N=294)		
No. Deaths / n (%)	104/143 (73%)	96/151 (64%)
Median OS Duration (mos.)	13.2	18.0
95% CI (mos.)	(11.5, 15.2)	(15.5, 21.2)
Hazard ratio (95% CI)	0.66 (0.50, 0.87)	

[a] Two patients on the FC arm who were FISH+ but IHC status unknown were excluded from the exploratory subgroup analyses.

[b] Five patients on the Herceptin-containing arm who were FISH+, but IHC status unknown were excluded from the exploratory subgroup analyses.

[c] Includes 6 patients on chemotherapy arm, 10 patients on Herceptin arm with FISH–, IHC3+ and 8 patients on chemotherapy arm, 8 patients on Herceptin arm with FISH status unknown, IHC 3+.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

150 mg Single-dose vial

Herceptin (trastuzumab) for injection 150 mg/vial is supplied in a single-dose vial as a lyophilized sterile powder, under vacuum. Available in a carton containing one single-dose vial (NDC 50242-132-01) and a carton containing 10 single-dose vials (NDC 50242-132-10).

16.2 Storage

Store Herceptin vials in the refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution.

17 PATIENT COUNSELING INFORMATION

Cardiomyopathy

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness *[see Boxed Warning: Cardiomyopathy]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential that Herceptin exposure during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female

patients to contact their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

- Advise women who are exposed to Herceptin during pregnancy or who become pregnant within 7 months following the last dose of Herceptin that there is a pregnancy pharmacovigilance program that monitor pregnancy outcomes. Encourage these patients to report their pregnancy to Genentech *[see Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of Herceptin *[see Use in Specific Populations (8.3)]*.

HERCEPTIN® [trastuzumab]

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

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1.6.4 欧州の添付文書

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Herceptin 150 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 mg of trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures.

The reconstituted Herceptin solution contains 21 mg/mL of trastuzumab.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to pale yellow lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer

Metastatic breast cancer

Herceptin is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer: (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.

- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

Early breast cancer

Herceptin is indicated for the treatment of adult patients with HER2 positive early breast cancer. (EBC).

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).

- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.

- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.

- in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Herceptin should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

Metastatic gastric cancer

Herceptin in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Herceptin should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1).

4.2 Posology and method of administration

HER2 testing is mandatory prior to initiation of therapy (see sections 4.4 and 5.1). Herceptin treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy (see section 4.4), and should be administered by a healthcare professional only.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous fixed dose) is being administered to the patient, as prescribed. Herceptin intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only.

Switching treatment between Herceptin intravenous and Herceptin subcutaneous formulations and vice versa, using the three-weekly (q3w) dosing regimen, was investigated in study MO22982 (see section 4.8).

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin (trastuzumab) and not Kadcyla (trastuzumab emtansine).

Posology

Metastatic breast cancer

Three-weekly schedule

The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Weekly schedule

The recommended initial loading dose of Herceptin is 4 mg/kg body weight. The recommended weekly maintenance dose of Herceptin is 2 mg/kg body weight, beginning one week after the loading dose.

Administration in combination with paclitaxel or docetaxel

In the pivotal trials (H0648g, M77001), paclitaxel or docetaxel was administered the day following the first dose of Herceptin (for dose, see the Summary of Product Characteristics (SmPC) for paclitaxel or docetaxel) and immediately after the subsequent doses of Herceptin if the preceding dose of Herceptin was well tolerated.

Administration in combination with an aromatase inhibitor

In the pivotal trial (BO16216) Herceptin and anastrozole were administered from day 1. There were no restrictions on the relative timing of Herceptin and anastrozole at administration (for dose, see the SmPC for anastrozole or other aromatase inhibitors).

Early breast cancer

Three-weekly and weekly schedule

As a three-weekly regimen the recommended initial loading dose of Herceptin is 8 mg/kg body weight. The recommended maintenance dose of Herceptin at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.
As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

See section 5.1 for chemotherapy combination dosing.

Metastatic gastric cancer

Three-weekly schedule

The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Breast cancer and gastric cancer

Duration of treatment

Patients with MBC or MGC should be treated with Herceptin until progression of disease.
Patients with EBC should be treated with Herceptin for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended (see section 5.1).

Dose reduction

No reductions in the dose of Herceptin were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the SmPC for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.

If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

Missed doses

If the patient has missed a dose of Herceptin by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of Herceptin by more than one week, a re-loading dose of Herceptin should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent Herceptin maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively.

Special populations

Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. In a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition.

Paediatric population

There is no relevant use of Herceptin in the paediatric population.

Method of administration

Herceptin loading dose should be administered as a 90-minute intravenous infusion. Do not administer as an intravenous push or bolus. Herceptin intravenous infusion should be administered by a health-care provider prepared to manage anaphylaxis and an emergency kit should be available. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms (see sections 4.4 and 4.8). Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

For instructions on reconstitution of Herceptin intravenous formulation before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients listed in section 6.1
- Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

4.4 Special warnings and precautions for use

Traceability

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

HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures (see section 5.1).

Currently no data from clinical trials are available on re-treatment of patients with previous exposure to Herceptin in the adjuvant setting**.**

Cardiac dysfunction

General considerations

Patients treated with Herceptin are at increased risk for developing CHF (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving Herceptin therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. These may be moderate to severe and have been associated with death (see section 4.8). In addition, caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age.

All candidates for treatment with Herceptin, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help to identify patients who develop cardiac dysfunction. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Herceptin. A careful risk-benefit assessment should be made before deciding to treat with Herceptin.

Trastuzumab may persist in the circulation for up to 7 months after stopping Herceptin treatment based on population pharmacokinetic analysis of all available data (see section 5.2). Patients who receive anthracyclines after stopping Herceptin may possibly be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. In all patients cardiac function should be monitored during treatment (e.g. every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6 - 8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Herceptin therapy has been seen.

The safety of continuation or resumption of Herceptin in patients who experience cardiac dysfunction has not been prospectively studied. If LVEF percentage drops ≥10 points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic CHF has developed, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

If symptomatic cardiac failure develops during Herceptin therapy, it should be treated with standard medicinal products for CHF. Most patients who developed CHF or asymptomatic cardiac dysfunction in pivotal trials improved with standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued on therapy without additional clinical cardiac events.

Metastatic breast cancer

Herceptin and anthracyclines should not be given concurrently in combination in the MBC setting.

Patients with MBC who have previously received anthracyclines are also at risk of cardiac dysfunction with Herceptin treatment, although the risk is lower than with concurrent use of Herceptin and anthracyclines.

Early breast cancer

For patients with EBC, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Herceptin. In patients who receive anthracycline-containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of Herceptin, or longer if a continuous decrease of LVEF is observed.

Patients with history of myocardial infarction (MI), angina pectoris requiring medical treatment, history of or existing CHF (NYHA Class II –IV), LVEF of < 55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medical treatment eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant and neoadjuvant EBC pivotal trials with Herceptin and therefore treatment cannot be recommended in such patients.

Adjuvant treatment

Herceptin and anthracyclines should not be given concurrently in combination in the adjuvant treatment setting.

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Herceptin was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin and was more marked when Herceptin was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months. In one of the 3 pivotal studies conducted in which a median follow-up of 5.5 years was available (BCIRG006) a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events was observed in patients who were administered Herceptin concurrently with a taxane following anthracycline therapy up to 2.37% compared to approximately 1% in the two comparator arms (anthracycline plus cyclophosphamide followed by taxane and taxane, carboplatin and Herceptin).

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low LVEF (<55%) at baseline, prior to or following the initiation of paclitaxel treatment, decline in LVEF by 10-15 points, and prior or concurrent use of anti-hypertensive medicinal products. In patients receiving Herceptin after completion of adjuvant chemotherapy, the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Herceptin and a body mass index (BMI) >25 kg/m^2.

Neoadjuvant-adjuvant treatment

In patients with EBC eligible for neoadjuvant-adjuvant treatment, Herceptin should be used concurrently with anthracyclines only in chemotherapy-naive patients and only with low-dose anthracycline regimens i.e. maximum cumulative doses of doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2.

If patients have been treated concurrently with a full course of low-dose anthracyclines and Herceptin in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery. In other situations, the decision on the need for additional cytotoxic chemotherapy is determined based on individual factors.

Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited to two trials (MO16432 and BO22227).

In the pivotal trial MO16432, Herceptin was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2) .

The incidence of symptomatic cardiac dysfunction was 1.7% in the Herceptin arm .

The pivotal trial BO22227 was designed to demonstrate non-inferiority of treatment with Herceptin subcutaneous formulation versus treatment with Herceptin intravenous formulation based on co-primary PK and efficacy endpoints (trastuzumab C_{trough} at pre-dose Cycle 8, and pCR rate at definitive surgery, respectively) (See Section 5.1. of Herceptin subcutaneous formulation SmPC). In the pivotal trial BO22227, Herceptin was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m^2); at a median follow-up exceeding 70 months, the incidence of cardiac failure/congestive cardiac failure was 0.3% in the Herceptin intravenous arm.

Clinical experience is limited in patients above 65 years of age.

Infusion-related reactions (IRRs) and hypersensitivity

Serious IRRs to Herceptin infusion including dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema have been reported (see section 4.8). Pre-medication may be used to reduce risk of occurrence of these events. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms (see section 4.2). These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. The majority of patients experienced resolution of symptoms and subsequently received further infusions of Herceptin. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with Herceptin (see section 4.3).

Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than six hours after the start of the Herceptin infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

Pulmonary events

Severe pulmonary events have been reported with the use of Herceptin in the post-marketing setting (see section 4.8). These events have occasionally been fatal. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Herceptin (see section 4.3). Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed. Clinically significant interactions between Herceptin and the concomitant medicinal products used in clinical trials have not been observed.

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents

Pharmacokinetic data from studies BO15935 and M77004 in women with HER2-positive MBC suggested that exposure to paclitaxel and doxorubicin (and their major metabolites 6-α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) was not altered in the presence of trastuzumab (8 mg/kg or 4 mg/kg IV loading dose followed by 6 mg/kg q3w or 2 mg/kg q1w IV, respectively).
However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite was unclear.

Data from study JP16003, a single-arm study of Herceptin (4 mg/kg IV loading dose and 2 mg/kg IV weekly) and docetaxel (60 mg/m2 IV) in Japanese women with HER2- positive MBC, suggested that concomitant administration of Herceptin had no effect on the single dose pharmacokinetics of docetaxel. Study JP19959 was a substudy of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer to study the pharmacokinetics of capecitabine and cisplatin when used with or without Herceptin. The results of this substudy suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus Herceptin. However, capecitabine itself showed higher concentrations and a longer half-life when combined with Herceptin. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus Herceptin.

Pharmacokinetic data from Study H4613g/GO01305 in patients with metastatic or locally advanced inoperable HER2-positive cancer suggested that trastuzumab had no impact on the PK of carboplatin.

Effect of antineoplastic agents on trastuzumab pharmacokinetics

By comparison of simulated serum trastuzumab concentrations after Herceptin monotherapy (4 mg/kg loading/2 mg/kg q1w IV) and observed serum concentrations in Japanese women with HER2- positive MBC (study JP16003) no evidence of a PK effect of concurrent administration of docetaxel on the pharmacokinetics of trastuzumab was found.

Comparison of PK results from two Phase II studies (BO15935 and M77004) and one Phase III study (H0648g) in which patients were treated concomitantly with Herceptin and paclitaxel and two Phase II studies in which Herceptin was administered as monotherapy (W016229 and MO16982), in women with HER2-positive MBC indicates that individual and mean trastuzumab trough serum concentrations varied within and across studies but there was no clear effect of the concomitant administration of paclitaxel on the pharmacokinetics of trastuzumab. Comparison of trastuzumab PK data from Study M77004 in which women with HER2-positive MBC were treated concomitantly with Herceptin, paclitaxel and doxorubicin to trastuzumab PK data in studies where Herceptin was administered as monotherapy (H0649g) or in combination with anthracycline plus cyclophosphamide or paclitaxel (Study H0648g), suggested no effect of doxorubicin and paclitaxel on the pharmacokinetics of trastuzumab.

Pharmacokinetic data from Study H4613g/GO01305 suggested that carboplatin had no impact on the PK of trastuzumab.

The administration of concomitant anastrozole did not appear to influence the pharmacokinetics of trastuzumab.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for 7 months after treatment has concluded (see section 5.2).

Pregnancy

Reproduction studies have been conducted in Cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin intravenous formulation and have revealed no evidence of impaired fertility or harm to the foetus. Placental transfer of trastuzumab during the early (days 20–50 of gestation) and late (days 120–150 of gestation) foetal development period was observed. It is not known whether Herceptin can affect reproductive capacity. As animal reproduction studies are not always predictive of human response, Herceptin should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.

In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Herceptin, or if a patient becomes pregnant while receiving Herceptin or within 7 months following the last dose of Herceptin, close monitoring by a multidisciplinary team is desirable.

Breast-feeding

A study conducted in lactating Cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin intravenous formulation demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age. It is not known whether trastuzumab is secreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-feed during Herceptin therapy and for 7 months after the last dose.

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

Herceptin has a minor influence on the ability to drive or use machines (see section 4.8). Dizziness and somnolence may occur during treatment with Herceptin (see section 4.8). Patients experiencing infusion-related symptoms (see section 4.4) should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

Amongst the most serious and/or common adverse reactions reported in Herceptin usage (intravenous and subcutaneous formulations) to date are cardiac dysfunction, infusion-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.

Tabulated list of adverse reactions

In this section, the following categories of frequency have been used: very common (³ 1/10), common (³ 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Presented in Table 1 are adverse reactions that have been reported in association with the use of intravenous Herceptin alone or in combination with chemotherapy in pivotal clinical trials and in the post-marketing setting.

All the terms included are based on the highest percentage seen in pivotal clinical trials. In addition, terms reported in the post marketing setting are included in Table 1.

Table 1 Undesirable Effects Reported with Intravenous Herceptin Monotherapy or in Combination with Chemotherapy in Pivotal Clinical Trials (N = 8386) and in Post-Marketing

System organ class	**Adverse reaction**	**Frequency**
Infections and infestations	Infection	Very common
	Nasopharyngitis	Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Influenza	Common
	Sinusitis	Common
	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Pharyngitis	Common
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Blood and lymphatic system disorders	Febrile neutropenia	Very common
	Anaemia	Very common
	Neutropenia	Very common
	White blood cell count decreased/leukopenia	Very common
	Thrombocytopenia	Very common
	Hypoprothrombinaemia	Not known
	Immune thrombocytopenia	Not known
Immune system disorders	Hypersensitivity	Common
	[+]Anaphylactic reaction	Rare
	[+]Anaphylactic shock	Rare
Metabolism and nutrition disorders	Weight decreased/Weight loss	Very common
	Anorexia	Very common
	Tumour lysis syndrome	Not known
	Hyperkalaemia	Not known
Psychiatric disorders	Insomnia	Very common
	Anxiety	Common
	Depression	Common
Nervous system disorders	[1]Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Paraesthesia	Very common

System organ class	Adverse reaction	Frequency
	Dysgeusia	Very common
	Peripheral neuropathy	Common
	Hypertonia	Common
	Somnolence	Common
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and labyrinth disorders	Deafness	Uncommon
Cardiac disorders	[1] Blood pressure decreased	Very common
	[1] Blood pressure increased	Very common
	[1] Heart beat irregular	Very common
	[1]Cardiac flutter	Very common
	Ejection fraction decreased*	Very common
	[+]Cardiac failure (congestive)	Common
	[+1]Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	[1]Palpitation	Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Gallop rhythm present	Not known
Vascular disorders	Hot flush	Very common
	[+1] Hypotension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders		
	[+]Dyspnoea	Very common
	Cough	Very common
	Epistaxis	Very common
	Rhinorrhoea	Very common
	[+]Pneumonia	Common
	Asthma	Common
	Lung disorder	Common
	[+]Pleural effusion	Common
	[+1]Wheezing	Uncommon
	Pneumonitis	Uncommon
	[+]Pulmonary fibrosis	Not known
	[+]Respiratory distress	Not known
	[+]Respiratory failure	Not known
	[+]Lung infiltration	Not known
	[+]Acute pulmonary oedema	Not known
	[+]Acute respiratory distress syndrome	Not known
	[+]Bronchospasm	Not known
	[+]Hypoxia	Not known
	[+]Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	Orthopnoea	Not known

System organ class	Adverse reaction	Frequency
	Pulmonary oedema	Not known
	Interstitial lung disease	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	[1] Lip swelling	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular injury	Common
	Hepatitis	Common
	Liver tenderness	Common
	Jaundice	Rare
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	[1] Swelling face	Very common
	Alopecia	Very common
	Nail disorder	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Acne	Common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	[1]Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck Pain	Common
	Pain in extremity	Common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
Reproductive system and	Breast inflammation/mastitis	Common

System organ class	Adverse reaction	Frequency
breast disorders		
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like symptoms	Very common
	Infusion related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Mucosal inflammation	Very common
	Peripheral oedema	Very common
	Malaise	Common
	Oedema	Common
Injury, poisoning and procedural complications	Contusion	Common

+ Denotes adverse reactions that have been reported in association with a fatal outcome.
1 Denotes adverse reactions that are reported largely in association with Infusion-related reactions. Specific percentages for these are not available.
* Observed with combination therapy following anthracyclines and combined with taxanes

Description of selected adverse reactions

Cardiac dysfunction

Congestive heart failure (NYHA Class II – IV) is a common adverse reaction associated with the use of Herceptin and has been associated with a fatal outcome (see section 4.4). Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin (see section 4.4).

In 3 pivotal clinical trials of adjuvant Herceptin given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (specifically symptomatic Congestive Heart Failure) was similar in patients who were administered chemotherapy alone (ie did not receive Herceptin) and in patients who were administered Herceptin sequentially after a taxane (0.3-0.4 %). The rate was highest in patients who were administered Herceptin concurrently with a taxane (2.0 %). In the neoadjuvant setting, the experience of concurrent administration of Herceptin and low dose anthracycline regimen is limited (see section 4.4).

When Herceptin was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6 % of patients in the one-year arm after a median follow-up of 12 months. In study BO16348, after a median follow-up of 8 years the incidence of severe CHF (NYHA Class III & IV) in the Herceptin 1 year treatment arm was 0.8 %, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6 %.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥50 % after the event) was evident for 71.4 % of Herceptin-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5 % of patients. Approximately 17 % of cardiac dysfunction related events occurred after completion of Herceptin.

In the pivotal metastatic trials of intravenous Herceptin, the incidence of cardiac dysfunction varied between 9 % and 12 % when it was combined with paclitaxel compared with 1 % – 4 % for paclitaxel alone. For monotherapy, the rate was 6 % – 9 %. The highest rate of cardiac dysfunction was seen in patients receiving Herceptin concurrently with anthracycline/cyclophosphamide (27 %), and was significantly higher than for anthracycline/cyclophosphamide alone (7 % – 10 %). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic CHF was 2.2 % in patients receiving Herceptin and docetaxel, compared with 0 % in patients receiving docetaxel alone.

Most of the patients (79 %) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for CHF.

Infusion reactions, allergic-like reactions and hypersensitivity

It is estimated that approximately 40 % of patients who are treated with Herceptin will experience some form of infusion-related reaction. However, the majority of infusion-related reactions are mild to moderate in intensity (NCI-CTC grading system) and tend to occur earlier in treatment, i.e. during infusions one, two and three and lessen in frequency in subsequent infusions. Reactions include chills, fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting and headache (see section 4.4). The rate of infusion-related reactions of all grades varied between studies depending on the indication, the data collection methodology, and whether trastuzumab was given concurrently with chemotherapy or as monotherapy.

Severe anaphylactic reactions requiring immediate additional intervention can occur usually during either the first or second infusion of Herceptin (see section 4.4) and have been associated with a fatal outcome.

Anaphylactoid reactions have been observed in isolated cases.

Haematotoxicity

Febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred very commonly. The frequency of occurrence of hypoprothrombinemia is not known. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Pulmonary events

Severe pulmonary adverse reactions occur in association with the use of Herceptin and have been associated with a fatal outcome. These include, but are not limited to, pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency (see section 4.4).

Details of risk minimisation measures that are consistent with the EU Risk Management Plan are presented in (section 4.4) Warnings and Precautions.

Immunogenicity

In the neoadjuvant-adjuvant EBC study (BO22227), at a median follow-up exceeding 70 months, 10.1 % (30/296) of patients treated with Herceptin intravenous developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the Herceptin intravenous arm.

The clinical relevance of these antibodies is not known. The presence of anti-trastuzumab antibodies had no impact on pharmacokinetics, efficacy (determined by pathological Complete Response [pCR] and event free survival [EFS]) and safety determined by occurrence of administration related reactions (ARRs) of Herceptin intravenous.

There are no immunogenicity data available for Herceptin in gastric cancer.

Switching treatment between Herceptin intravenous and Herceptin subcutaneous formulation and vice versa

Study MO22982 investigated switching between the Herceptin intravenous and Herceptin subcutaneous formulation with a primary objective to evaluate patient preference for either

intravenous or the subcutaneous route of trastuzumab administration. In this trial, 2 cohorts (one using subcutaneous formulation in vial and one using subcutaneous formulation in administration system) were investigated using a 2-arm, cross-over design with 488 patients being randomized to one of two different three-weekly Herceptin treatment sequences (IV [Cycles 1-4]→ SC [Cycles 5-8], or SC [Cycles 1-4]→ IV [Cycles 5-8]). Patients were either naïve to Herceptin IV treatment (20.3%) or pre-exposed to Herceptin IV (79.7%). For the sequence IV→SC (SC vial and SC formulation in administration system cohorts combined), adverse event rates (all grades) were described pre-switching (Cycles 1-4) and post-switching (Cycles 5-8) as 53.8% vs. 56.4%, respectively; for the sequence SC→IV (SC vial and SC formulation in administration system cohorts combined), adverse event rates (all grades) were described pre- and post-switching as 65.4% vs. 48.7%, respectively. Pre-switching rates (Cycles 1-4) for serious adverse events, grade 3 adverse events and treatment discontinuations due to adverse events were low (<5%) and similar to post-switching rates (Cycles 5-8). No grade 4 or grade 5 adverse events were reported.

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

There is no experience with overdose in human clinical trials. Single doses of Herceptin alone greater than 10 mg/kg have not been administered in the clinical trials; a maintenance dose of 10 mg/kg q3w following a loading dose of 8 mg/kg has been studied in a clinical trial with metastatic gastric cancer patients. Doses up to this level were well tolerated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC03

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 is observed in 20 %-30 % of primary breast cancers. Studies of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8 % to 34.0 % for IHC and 7.1 % to 42.6 % for FISH. Studies indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. The extracellular domain of the receptor (ECD, p105) can be shed into the blood stream and measured in serum samples.

Mechanism of action

Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Detection of HER2 overexpression or HER2 gene amplification

Detection of HER2 overexpression or HER2 gene amplification in breast cancer
Herceptin should only be used in patients whose tumours have HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. HER2 overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks (see section 4.4). HER2 gene amplification should be detected using fluorescence *in situ* hybridisation (FISH) or chromogenic *in situ* hybridisation (CISH) of fixed tumour blocks. Patients are eligible for Herceptin treatment if they show strong HER2 overexpression as described by a 3+ score by IHC or a positive FISH or CISH result.

To ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures.

The recommended scoring system to evaluate the IHC staining patterns is as stated in Table 2:

Table 2 Recommended Scoring System to Evaluate the IHC Staining Patterns in Breast Cancer

Score	**Staining pattern**	**HER2 overexpression assessment**
0	No staining is observed or membrane staining is observed in < 10 % of the tumour cells	Negative
1+	A faint/barely perceptible membrane staining is detected in > 10 % of the tumour cells. The cells are only stained in part of their membrane.	Negative
2+	A weak to moderate complete membrane staining is detected in > 10 % of the tumour cells.	Equivocal
3+	Strong complete membrane staining is detected in > 10 % of the tumour cells.	Positive

In general, FISH is considered positive if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2, or if there are more than 4 copies of the HER2 gene per tumour cell if no chromosome 17 control is used.

In general, CISH is considered positive if there are more than 5 copies of the HER2 gene per nucleus in greater than 50 % of tumour cells.

For full instructions on assay performance and interpretation please refer to the package inserts of validated FISH and CISH assays. Official recommendations on HER2 testing may also apply.

For any other method that may be used for the assessment of HER2 protein or gene expression, the analyses should only be performed by laboratories that provide adequate state-of-the-art performance of validated methods. Such methods must clearly be precise and accurate enough to demonstrate overexpression of HER2 and must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) overexpression of HER2.

Detection of HER2 over expression or HER2 gene amplification in gastric cancer

Only an accurate and validated assay should be used to detect HER2 over expression or HER2 gene amplification. IHC is recommended as the first testing modality and in cases where HER2 gene amplification status is also required, either a silver-enhanced *in situ* hybridization (SISH) or a FISH technique must be applied. SISH technology is however, recommended to allow for the parallel evaluation of tumor histology and morphology. To ensure validation of testing procedures and the generation of accurate and reproducible results, HER2 testing must be performed in a laboratory staffed by trained personnel. Full instructions on assay performance and results interpretation should be taken from the product information leaflet provided with the HER2 testing assays used.

In the ToGA (BO18255) trial, patients whose tumours were either IHC3+ or FISH positive were defined as HER2 positive and thus included in the trial. Based on the clinical trial results, the beneficial effects were limited to patients with the highest level of HER2 protein overexpression, defined by a 3+ score by IHC, or a 2+ score by IHC and a positive FISH result.

In a method comparison study (study D008548) a high degree of concordance (>95 %) was observed for SISH and FISH techniques for the detection of HER2 gene amplification in gastric cancer patients.

HER2 over expression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks; HER2 gene amplification should be detected using *in situ* hybridisation using either SISH or FISH on fixed tumour blocks.

The recommended scoring system to evaluate the IHC staining patterns is as stated in Table 3:

Table 3 Recommended Scoring System to Evaluate the IHC Staining Patterns in Gastric Cancer

Score	**Surgical specimen - staining pattern**	**Biopsy specimen – staining pattern**	**HER2 overexpression assessment**
0	No reactivity or membranous reactivity in < 10 % of tumour cells	No reactivity or membranous reactivity in any tumour cell	Negative
1+	Faint/barely perceptible membranous reactivity in ≥ 10 % of tumour cells; cells are reactive only in part of their membrane	Tumour cell cluster with a faint/ barely perceptible membranous reactivity irrespective of percentage of tumour cells stained	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥ 10 % of tumour cells	Tumour cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in ≥ 10 % of tumour cells	Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Positive

In general, SISH or FISH is considered positive if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2.

Clinical efficacy and safety

Metastatic breast cancer

Herceptin has been used in clinical trials as monotherapy for patients with MBC who have tumours that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease (Herceptin alone).

Herceptin has also been used in combination with paclitaxel or docetaxel for the treatment of patients who have not received chemotherapy for their metastatic disease. Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m^2 infused over 3 hours) with or without Herceptin. In the pivotal trial of docetaxel (100 mg/m^2 infused over 1 hour) with or without Herceptin, 60 % of the patients had received prior anthracycline-based adjuvant chemotherapy. Patients were treated with Herceptin until progression of disease.

The efficacy of Herceptin in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been studied. However, Herceptin plus docetaxel was efficacious in patients whether or not they had received prior adjuvant anthracyclines.

The test method for HER2 overexpression used to determine eligibility of patients in the pivotal Herceptin monotherapy and Herceptin plus paclitaxel clinical trials employed immunohistochemical staining for HER2 of fixed material from breast tumours using the murine monoclonal antibodies CB11 and 4D5. These tissues were fixed in formalin or Bouin's fixative. This investigative clinical trial assay performed in a central laboratory utilised a 0 to 3+ scale. Patients classified as staining 2+ or 3+ were included, while those staining 0 or 1+ were excluded. Greater than 70 % of patients enrolled exhibited 3+ overexpression. The data suggest that beneficial effects were greater among those patients with higher levels of overexpression of HER2 (3+).

The main test method used to determine HER2 positivity in the pivotal trial of docetaxel, with or without Herceptin, was immunohistochemistry. A minority of patients was tested using fluorescence *in-situ* hybridisation (FISH). In this trial, 87 % of patients entered had disease that was IHC3+, and 95 % of patients entered had disease that was IHC3+ and/or FISH-positive.

Weekly dosing in metastatic breast cancer

The efficacy results from the monotherapy and combination therapy studies are summarised in Table 4:

Table 4 Efficacy Results from the Monotherapy and Combination Therapy Studies

Parameter	**Monotherapy**	**Combination Therapy**			
	Herceptin[1] **N=172**	**Herceptin plus paclitaxel[2]** **N=68**	**Paclitaxel[2]** **N=77**	**Herceptin plus docetaxel[3]** **N=92**	**Docetaxel[3]** **N=94**
Response rate (95 %CI)	18 % (13 - 25)	49 % (36 - 61)	17 % (9 - 27)	61 % (50-71)	34 % (25-45)
Median duration of response (months) (95 %CI)	9.1 (5.6-10.3)	8.3 (7.3-8.8)	4.6 (3.7-7.4)	11.7 (9.3 – 15.0)	5.7 (4.6-7.6)
Median TTP (months) (95 %CI)	3.2 (2.6-3.5)	7.1 (6.2-12.0)	3.0 (2.0-4.4)	11.7 (9.2-13.5)	6.1 (5.4-7.2)
Median Survival (months) (95 %CI)	16.4 (12.3-ne)	24.8 (18.6-33.7)	17.9 (11.2-23.8)	31.2 (27.3-40.8)	22.74 (19.1-30.8)

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.
1. Study H0649g: IHC3+ patient subset
2. Study H0648g: IHC3+ patient subset
3. Study M77001: Full analysis set (intent-to-treat), 24 months results

Combination treatment with Herceptin and anastrozole
Herceptin has been studied in combination with anastrozole for first line treatment of MBC in HER2 overexpressing, hormone-receptor (i.e. estrogen-receptor (ER) and/or progesterone-receptor (PR)) positive postmenopausal patients. Progression free survival was doubled in the Herceptin plus anastrozole arm compared to anastrozole (4.8 months versus 2.4 months). For the other parameters the improvements seen for the combination were for overall response (16.5 % versus 6.7 %); clinical benefit rate (42.7 % versus 27.9 %); time to progression (4.8 months versus 2.4 months). For time to response and duration of response no difference could be recorded between the arms. The median overall survival was extended by 4.6 months for patients in the combination arm. The difference was

not statistically significant, however more than half of the patients in the anastrozole alone arm crossed over to a Herceptin containing regimen after progression of disease.

Three -weekly dosing in metastatic breast cancer

The efficacy results from the non-comparative monotherapy and combination therapy studies are summarised in Table 5:

Table 5 Efficacy Results from the Non-Comparative Monotherapy and Combination Therapy Studies

Parameter	**Monotherapy**		**Combination Therapy**	
	Herceptin[1] **N=105**	**Herceptin[2]** **N=72**	**Herceptin plus paclitaxel[3]** **N=32**	**Herceptin plus docetaxel[4]** **N=110**
Response rate (95 %CI)	24 % (15 - 35)	27 % (14 - 43)	59 % (41-76)	73 % (63-81)
Median duration of response (months) (range)	10.1 (2.8-35.6)	7.9 (2.1-18.8)	10.5 (1.8-21)	13.4 (2.1-55.1)
Median TTP (months) (95 %CI)	3.4 (2.8-4.1)	7.7 (4.2-8.3)	12.2 (6.2-ne)	13.6 (11-16)
Median Survival (months) (95 %CI)	ne	ne	ne	47.3 (32-ne)

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.
1. Study WO16229: loading dose 8 mg/kg, followed by 6 mg/kg 3 weekly schedule
2. Study MO16982: loading dose 6 mg/kg weekly x 3; followed by 6 mg/kg 3-weekly schedule
3. Study BO15935
4. Study MO16419

Sites of progression
The frequency of progression in the liver was significantly reduced in patients treated with the combination of Herceptin and paclitaxel, compared to paclitaxel alone (21.8 % versus 45.7 %; p=0.004). More patients treated with Herceptin and paclitaxel progressed in the central nervous system than those treated with paclitaxel alone (12.6 % versus 6.5 %; p=0.377).

Early breast cancer (adjuvant setting)

Early breast cancer is defined as non-metastatic primary invasive carcinoma of the breast.
In the adjuvant treatment setting, Herceptin was investigated in 4 large multicentre, randomised, trials.

- Study BO16348 was designed to compare one and two years of three-weekly Herceptin treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). In addition, comparison of two years of Herceptin treatment versus one year of Herceptin treatment was performed. Patients assigned to receive Herceptin were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for either one or two years.
- The NSABP B-31 and NCCTG N9831 studies that comprise the joint analysis were designed to investigate the clinical utility of combining Herceptin treatment with paclitaxel following AC chemotherapy, additionally the NCCTG N9831 study also investigated adding Herceptin sequentially to AC→P chemotherapy in patients with HER2 positive EBC following surgery.
- The BCIRG 006 study was designed to investigate combining Herceptin treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2 positive EBC following surgery.

Early breast cancer in the HERA trial was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes positive or axillary nodes negative if tumors at least 1 cm in diameter.

In the joint analysis of the NSABP B-31 and NCCTG N9831 studies, EBC was limited to women with operable breast cancer at high risk, defined as HER2-positive and axillary lymph node positive or HER2 positive and lymph node negative with high risk features (tumor size > 1 cm and ER negative or tumor size > 2 cm, regardless of hormonal status).

In the BCIRG 006 study HER2 positive, EBC was defined as either lymph node positive or high risk node negative patients with no (pN0) lymph node involvement, and at least 1 of the following factors: tumour size greater than 2 cm, estrogen receptor and progesterone receptor negative, histological and/or nuclear grade 2-3, or age < 35 years).

The efficacy results from the BO16348 trial following 12 months* and 8 years** median follow-up are summarized in Table 6:

Table 6 Efficacy Results from Study BO16348

	Median follow-up 12 months*		Median follow-up 8 years**	
Parameter	Observation N=1693	Herceptin 1 Year N = 1693	Observation N= 1697***	Herceptin 1 Year N = 1702***
Disease-free survival				
- No. patients with event	219 (12.9 %)	127 (7.5 %)	570 (33.6 %)	471 (27.7 %)
- No. patients without event	1474 (87.1 %)	1566 (92.5 %)	1127 (66.4 %)	1231 (72.3 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.54		0.76	
Recurrence-free survival				
- No. patients with event	208 (12.3 %)	113 (6.7 %)	506 (29.8 %)	399 (23.4 %)
- No. patients without event	1485 (87.7 %)	1580 (93.3 %)	1191 (70.2 %)	1303 (76.6 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.51		0.73	
Distant disease-free survival				
- No. patients with event	184 (10.9 %)	99 (5.8 %)	488 (28.8 %)	399 (23.4 %)
- No. patients without event	1508 (89.1 %)	1594 (94.6 %)	1209 (71.2 %)	1303 (76.6 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.50		0.76	
Overall survival (death)				
- No. patients with event	40 (2.4 %)	31 (1.8 %)	350 (20.6 %)	278 (16.3 %)
- No. patients without event	1653 (97.6 %)	1662 (98.2 %)	1347 (79.4 %)	1424 (83.7 %)
P-value versus Observation	0.24		0.0005	
Hazard Ratio versus Observation	0.75		0.76	

*Co-primary endpoint of DFS of 1 year versus observation met the pre-defined statistical boundary
**Final analysis (including crossover of 52 % of patients from the observation arm to Herceptin)
*** There is a discrepancy in the overall sample size due to a small number of patients who were randomized after the cut-off date for the 12-month median follow-up analysis

The efficacy results from the interim efficacy analysis crossed the protocol pre-specified statistical boundary for the comparison of 1-year of Herceptin versus observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease free survival (DFS) was 0.54 (95 % CI 0.44, 0.67) which translates into an absolute benefit, in terms of a 2-year disease-free survival rate, of 7.6 percentage points (85.8 % versus 78.2 %) in favour of the Herceptin arm.

A final analysis was performed after a median follow-up of 8 years, which showed that 1 year Herceptin treatment is associated with a 24 % risk reduction compared to observation only (HR=0.76, 95 % CI 0.67, 0.86). This translates into an absolute benefit in terms of an 8 year disease free survival rate of 6.4 percentage points in favour of 1 year Herceptin treatment.

In this final analysis, extending Herceptin treatment for a duration of two years did not show additional benefit over treatment for 1 year [DFS HR in the intent to treat (ITT) population of 2 years versus 1 year=0.99 (95 % CI: 0.87, 1.13), p-value=0.90 and OS HR=0.98 (0.83, 1.15); p-value= 0.78]. The rate of asymptomatic cardiac dysfunction was increased in the 2-year treatment arm (8.1 % versus 4.6 % in the 1-year treatment arm). More patients experienced at least one grade 3 or 4 adverse event in the 2-year treatment arm (20.4 %) compared with the 1-year treatment arm (16.3 %).

In the NSABP B-31 and NCCTG N9831 studies Herceptin was administered in combination with paclitaxel, following AC chemotherapy.

Doxorubicin and cyclophosphamide were administered concurrently as follows:

- intravenous push doxorubicin, at 60 mg/ m^2, given every 3 weeks for 4 cycles.
- intravenous cyclophosphamide, at 600 mg/ m^2 over 30 minutes, given every 3 weeks for 4 cycles.

Paclitaxel, in combination with Herceptin, was administered as follows:

- intravenous paclitaxel - 80 mg/m^2 as a continuous intravenous infusion, given every week for 12 weeks.

or

- intravenous paclitaxel - 175 mg/m^2 as a continuous intravenous infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

The efficacy results from the joint analysis of the NSABP B-31 and NCCTG 9831 trials at the time of the definitive analysis of DFS* are summarized in Table 7. The median duration of follow up was 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm.

Table 7 Summary of Efficacy results from the joint analysis of the NSABP B-31 and NCCTG N9831 trials at the time of the definitive DFS analysis*

Parameter	AC→P (n=1679)	AC→PH (n=1672)	Hazard Ratio vs AC→P (95% CI) p-value
Disease-free survival No. patients with event (%)	261 (15.5)	133 (8.0)	0.48 (0.39, 0.59) p<0.0001
Distant Recurrence No. patients with event	193 (11.5)	96 (5.7)	0.47 (0.37, 0.60) p<0.0001
Death (OS event): No. patients with event	92 (5.5)	62 (3.7)	0.67 (0.48, 0.92) p=0.014**

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

* At median duration of follow up of 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm

** p value for OS did not cross the pre-specified statistical boundary for comparison of AC→PH vs. AC→P

For the primary endpoint, DFS, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 11.8 percentage points (87.2 % versus 75.4 %) in favour of the AC→PH (Herceptin) arm.

At the time of a safety update after a median of 3.5-3.8 years follow up, an analysis of DFS reconfirms the magnitude of the benefit shown in the definitive analysis of DFS. Despite the cross-over to Herceptin in the control arm, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The addition of Herceptin to paclitaxel chemotherapy also resulted in a 37 % decrease in the risk of death.

The pre-planned final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831 was performed when 707 deaths had occurred (median follow-up 8.3 years in the AC→P H group). Treatment with AC→PH resulted in a statistically significant improvement in OS compared with AC→P (stratified HR=0.64; 95% CI [0.55, 0.74]; log-rank p-value < 0.0001). At 8 years, the survival rate was estimated to be 86.9% in the AC→PH arm and 79.4% in the AC→P arm, an absolute benefit of 7.4% (95% CI 4.9%, 10.0%).
The final OS results from the joint analysis of studies NSABP B-31 and NCCTG N9831 are summarized in Table 8 below:

Table 8 Final Overall Survival Analysis from the joint analysis of trials NSABP B-31 and NCCTG N9831

Parameter	AC→P (N=2032)	AC→PH (N=2031)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)
Death (OS event): No. patients with event (%)	418 (20.6%)	289 (14.2%)	< 0.0001	0.64 (0.55, 0.74)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

DFS analysis was also performed at the final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831. The updated DFS analysis results (stratified HR = 0.61; 95% CI [0.54, 0.69]) showed a similar DFS benefit compared to the definitive primary DFS analysis, despite 24.8% patients in the AC→P arm who crossed over to receive Herceptin. At 8 years, the disease-free survival rate was estimated to be 77.2% (95% CI: 75.4, 79.1) in the AC→PH arm, an absolute benefit of 11.8% compared with the AC→P arm.

In the BCIRG 006 study Herceptin was administered either in combination with docetaxel, following AC chemotherapy (AC→DH) or in combination with docetaxel and carboplatin (DCarbH).

Docetaxel was administered as follows:

- intravenous docetaxel - 100 mg/m^2 as an intravenous infusion over 1 hour, given every 3 weeks for 4 cycles (day 2 of first docetaxel cycle, then day 1 of each subsequent cycle)

or

- intravenous docetaxel - 75 mg/m^2 as an intravenous infusion over 1 hour, given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each subsequent cycle)

which was followed by:

- carboplatin – at target AUC = 6 mg/mL/min administered by intravenous infusion over 30-60 minutes repeated every 3 weeks for a total of six cycles

Herceptin was administered weekly with chemotherapy and 3 weekly thereafter for a total of 52 weeks.

The efficacy results from the BCIRG 006 are summarized in Tables 9 and 10. The median duration of follow up was 2.9 years in the AC→D arm and 3.0 years in each of the AC→DH and DCarbH arms.

Table 9 Overview of Efficacy Analyses BCIRG 006 AC→D versus AC→DH

Parameter	AC→D (n=1073)	AC→DH (n=1074)	Hazard Ratio vs AC→D (95 % CI) p-value
Disease-free survival No. patients with event	195	134	0.61 (0.49, 0.77) p<0.0001
Distant recurrence No. patients with event	144	95	0.59 (0.46, 0.77) p<0.0001
Death (OS event) No. patients with event	80	49	0.58 (0.40, 0.83) p=0.0024

AC→D = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→DH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; CI = confidence interval

Table 10 Overview of Efficacy Analyses BCIRG 006 AC→D versus DCarbH

Parameter	AC→D (n=1073)	DCarbH (n=1074)	Hazard Ratio vs AC→D (95 % CI)
Disease-free survival No. patients with event	195	145	0.67 (0.54, 0.83) p=0.0003
Distant recurrence No. patients with event	144	103	0.65 (0.50, 0.84) p=0.0008
Death (OS event) No. patients with event	80	56	0.66 (0.47, 0.93) p=0.0182

AC→D = doxorubicin plus cyclophosphamide, followed by docetaxel; DCarbH = docetaxel, carboplatin and trastuzumab; CI = confidence interval

In the BCIRG 006 study for the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 5.8 percentage points (86.7 % versus 80.9 %) in favour of the AC→DH (Herceptin) arm and 4.6 percentage points (85.5 % versus 80.9 %) in favour of the DCarbH (Herceptin) arm compared to AC→D.

In study BCIRG 006, 213/1075 patients in the DCarbH (TCH) arm, 221/1074 patients in the AC® DH (AC® TH) arm, and 217/1073 in the AC→D (AC® T) arm had a Karnofsky performance status ≤90 (either 80 or 90). No disease-free survival (DFS) benefit was noticed in this subgroup of patients (hazard ratio = 1.16, 95 % CI [0.73, 1.83] for DCarbH (TCH) versus AC® D (AC® T); hazard ratio 0.97, 95 % CI [0.60, 1.55] for AC® DH (AC® TH) versus AC® D).

In addition a post-hoc exploratory analysis was performed on the data sets from the joint analysis (JA) NSABP B-31/NCCTG N9831* and BCIRG006 clinical studies combining DFS events and symptomatic cardiac events and summarised in Table 11:

Table 11 Post-Hoc Exploratory Analysis Results from the Joint Analysis NSABP B-31/NCCTG N9831* and BCIRG006 Clinical Studies Combining DFS Events and Symptomatic Cardiac Events

	AC® PH (vs. AC® P) (NSABP B-31 and NCCTG N9831)*	AC® DH (vs. AC® D) (BCIRG 006)	DCarbH (vs. AC® D) (BCIRG 006)
Primary efficacy analysis DFS Hazard ratios (95 % CI) p-value	 0.48 (0.39, 0.59) p<0.0001	 0.61 (0.49, 0.77) p< 0.0001	 0.67 (0.54, 0.83) p=0.0003
Long term follow-up efficacy analysis** DFS Hazard ratios (95 % CI) p-value	 0.61 (0.54, 0.69) p<0.0001	 0.72 (0.61, 0.85) p<0.0001	 0.77 (0.65, 0.90) p=0.0011
Post-hoc exploratory analysis with DFS and symptomatic cardiac events Long term follow-up** Hazard ratios (95 % CI)	 0.67 (0.60, 0.75)	 0.77 (0.66, 0.90)	 0.77 (0.66, 0.90)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; D: docetaxel; Carb: carboplatin; H: trastuzumab
CI = confidence interval
* At the time of the definitive analysis of DFS. Median duration of follow up was 1.8 years in the AC→P arm and 2.0 years in the AC→PH arm
** Median duration of long term follow-up for the Joint Analysis clinical studies was 8.3 years (range: 0.1 to 12.1) for the AC→PH arm and 7.9 years (range: 0.0 to 12.2) for the AC→P arm; Median duration of long term follow-up for the BCIRG 006 study was 10.3 years in both the AC→D arm (range: 0.0 to 12.6) arm and the DCarbH arm (range: 0.0 to 13.1), and was 10.4 years (range: 0.0 to 12.7) in the AC→DH arm

Early breast cancer (neoadjuvant-adjuvant setting)

So far, no results are available which compare the efficacy of Herceptin administered with chemotherapy in the adjuvant setting with that obtained in the neo-adjuvant/adjuvant setting.

In the neoadjuvant-adjuvant treatment setting, study MO16432, a multicentre randomised trial, was designed to investigate the clinical efficacy of concurrent administration of Herceptin with neoadjuvant chemotherapy including both an anthracycline and a taxane, followed by adjuvant Herceptin, up to a total treatment duration of 1 year. The study recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory EBC. Patients with HER2+ tumours were randomised to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant Herceptin, or neoadjuvant chemotherapy alone.

In study MO16432, Herceptin (8 mg/kg loading dose, followed by 6 mg/kg maintenance every 3 weeks) was administered concurrently with 10 cycles of neoadjuvant chemotherapy

as follows:

- Doxorubicin 60mg/m^2 and paclitaxel 150 mg/m^2, administered 3-weekly for 3 cycles,

which was followed by

- Paclitaxel 175 mg/m^2 administered 3-weekly for 4 cycles,

which was followed by

- CMF on day 1 and 8 every 4 weeks for 3 cycles

which was followed after surgery by

- additional cycles of adjuvant Herceptin (to complete 1 year of treatment)

The efficacy results from Study MO16432 are summarized in Table 12. The median duration of follow-up in the Herceptin arm was 3.8 years.

Table 12 Efficacy Results from MO16432

Parameter	Chemo + Herceptin (n=115)	Chemo only (n=116)	
Event-free survival No. patients with event	46	59	Hazard Ratio (95% CI) 0.65 (0.44, 0.96) p=0.0275
Total pathological complete response* (95 % CI)	40 % (31.0, 49.6)	20.7 % (13.7, 29.2)	P=0.0014
Overall survival No. patients with event	22	33	Hazard Ratio (95 % CI) 0.59 (0.35, 1.02) p=0.0555

* defined as absence of any invasive cancer both in the breast and axillary nodes

An absolute benefit of 13 percentage points in favour of the Herceptin arm was estimated in terms of 3-year event-free survival rate (65 % versus 52 %).

Metastatic gastric cancer

Herceptin has been investigated in one randomised, open-label phase III trial ToGA (BO18255) in combination with chemotherapy versus chemotherapy alone.

Chemotherapy was administered as follows:

- capecitabine - 1000 mg/m^2 orally twice daily for 14 days every 3 weeks for 6 cycles (evening of day 1 to morning of day 15 of each cycle)

or

- intravenous 5-fluorouracil - 800 mg/m^2/day as a continuous intravenous infusion over 5 days, given every 3 weeks for 6 cycles (days 1 to 5 of each cycle)

Either of which was administered with:

- cisplatin - 80 mg/m^2 every 3 weeks for 6 cycles on day 1 of each cycle.

The efficacy results from study BO18225 are summarized in Table 13:

Table 13 Efficacy Results from BO18225

Parameter	FP N = 290	FP +H N = 294	HR (95 % CI)	p-value
Overall Survival, Median months	11.1	13.8	0.74 (0.60-0.91)	0.0046
Progression-Free Survival, Median months	5.5	6.7	0.71 (0.59-0.85)	0.0002
Time to Disease Progression, Median months	5.6	7.1	0.70 (0.58-0.85)	0.0003
Overall Response Rate, %	34.5 %	47.3 %	1.70[a] (1.22, 2.38)	0.0017
Duration of Response, Median months	4.8	6.9	0.54 (0.40-0.73)	< 0.0001

FP + H: Fluoropyrimidine/cisplatin + Herceptin
FP: Fluoropyrimidine/cisplatin
a Odds ratio

Patients were recruited to the trial who were previously untreated for HER2-positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction not amenable to curative therapy. The primary endpoint was overall survival which was defined as the time from the date of randomization to the date of death from any cause. At the time of the analysis a total of 349 randomized patients had died: 182 patients (62.8 %) in the control arm and 167 patients (56.8 %) in the treatment arm. The majority of the deaths were due to events related to the underlying cancer.

Post-hoc subgroup analyses indicate that positive treatment effects are limited to targeting tumours with higher levels of HER2 protein (IHC 2+/FISH+ or IHC 3+). The median overall survival for the high HER2 expressing group was 11.8 months versus 16 months, HR 0.65 (95 % CI 0.51-0.83) and the median progression free survival was 5.5 months versus 7.6 months, HR 0.64 (95 % CI 0.51-0.79) for FP versus FP + H, respectively. For overall survival, the HR was 0.75 (95 % CI 0.51-1.11) in the IHC 2+/FISH+ group and the HR was 0.58 (95 % CI 0.41-0.81) in the IHC 3+/FISH+ group.

In an exploratory subgroup analysis performed in the TOGA (BO18255) trial there was no apparent benefit on overall survival with the addition of Herceptin in patients with ECOG PS 2 at baseline [HR 0.96 (95 % CI 0.51-1.79)], non measurable [HR 1.78 (95 % CI 0.87-3.66)] and locally advanced disease [HR 1.20 (95 % CI 0.29-4.97)].

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Herceptin in all subsets of the paediatric population for breast and gastric cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects, including patients with HER2 positive MBC, EBC, AGC or other tumor types, and healthy volunteers, in 18 Phase I, II and III trials receiving Herceptin IV. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to non-linear elimination, total clearance increased with decreasing concentration. Therefore, no constant value for half-life of trastuzumab can be deduced. The $t_{1/2}$ decreases with decreasing concentrations within a dosing interval (see Table 16). MBC and EBC patients had similar PK parameters (e.g. clearance (CL), the central compartment volume (V_c)) and population-predicted steady-state exposures (C_{min}, C_{max} and AUC). Linear clearance was 0.136 L/day for MBC, 0.112 L/day for EBC and 0.176 L/day for AGC. The non-linear elimination parameter values were 8.81 mg/day for the maximum elimination rate (V_{max}) and 8.92

µg/mL for the Michaelis-Menten constant (K_m) for the MBC, EBC, and AGC patients. The central compartment volume was 2.62 L for patients with MBC and EBC and 3.63 L for patients with AGC. In the final population PK model, in addition to primary tumor type, body-weight, serum aspartate aminotransferase and albumin were identified as a statistically significant covariates affecting the exposure of trastuzumab. However, the magnitude of effect of these covariates on trastuzumab exposure suggests that these covariates are unlikely to have a clinically meaningful effect on trastuzumab concentrations.

The population predicted PK exposure values (median with 5th - 95th Percentiles) and PK parameter values at clinically relevant concentrations (C_{max} and C_{min}) for MBC, EBC and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 14 (Cycle 1), Table 15 (steady-state), and Table 16 (PK parameters).

Table 14 Population Predicted Cycle 1 PK Exposure Values (median with 5th - 95th Percentiles) for Herceptin IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	Primary tumor type	N	C_{min} (µg/mL)	C_{max} (µg/mL)	$AUC_{0\text{-}21days}$ (µg.day/mL)
8mg/kg + 6mg/kg q3w	MBC	805	28.7 (2.9 - 46.3)	182 (134 - 280)	1376 (728 - 1998)
	EBC	390	30.9 (18.7 - 45.5)	176 (127 - 227)	1390 (1039 - 1895)
	AGC	274	23.1 (6.1 - 50.3)	132 (84.2 – 225)	1109 (588 – 1938)
4mg/kg + 2mg/kg qw	MBC	805	37.4 (8.7 - 58.9)	76.5 (49.4 - 114)	1073 (597 – 1584)
	EBC	390	38.9 (25.3 - 58.8)	76.0 (54.7 - 104)	1074 (783 - 1502)

Table 15 Population Predicted Steady State PK Exposure Values (median with 5th - 95th Percentiles) for Herceptin IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	Primary tumor type	N	$C_{min,ss}$* (µg/mL)	$C_{max,ss}$** (µg/mL)	$AUC_{ss,\ 0\text{-}21days}$ (µg.day/mL)	Time to steady-state*** (week)
8mg/kg + 6mg/kg q3w	MBC	805	44.2 (1.8 - 85.4)	179 (123 - 266)	1736 (618 - 2756)	12
	EBC	390	53.8 (28.7 - 85.8)	184 (134 - 247)	1927 (1332 -2771)	15
	AGC	274	32.9 (6.1 – 88.9)	131 (72.5 -251)	1338 (557 - 2875)	9
4mg/kg + 2mg/kg qw	MBC	805	63.1 (11.7 - 107)	107 (54.2 - 164)	1710 (581 - 2715)	12
	EBC	390	72.6 (46 - 109)	115 (82.6 - 160)	1893 (1309 -2734)	14

*$C_{min,ss}$ – C_{min} at steady state
**$C_{max,ss}$ = C_{max} at steady state
*** time to 90% of steady-state

Table 16 Population Predicted PK Parameter Values at Steady State for Herceptin IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	Primary tumor type	N	Total CL range from $C_{max,ss}$ to $C_{min,ss}$ (L/day)	$t_{1/2}$ range from $C_{max,ss}$ to $C_{min,ss}$ (day)
8mg/kg + 6mg/kg q3w	MBC	805	0.183 - 0.302	15.1 - 23.3
	EBC	390	0.158 - 0.253	17.5 – 26.6
	AGC	274	0.189 - 0.337	12.6 - 20.6
4mg/kg + 2mg/kg qw	MBC	805	0.213 - 0.259	17.2 - 20.4
	EBC	390	0.184 - 0.221	19.7 - 23.2

Trastuzumab washout

Trastuzumab washout period was assessed following q1w or q3w intravenous administration using the population PK model. The results of these simulations indicate that at least 95% of patients will reach concentrations that are <1 μg/mL (approximately 3% of the population predicted $C_{min,ss}$, or about 97% washout) by 7 months.

Circulating shed HER2 ECD

The exploratory analyses of covariates with information in only a subset of patients suggested that patients with greater shed HER2-ECD level had faster nonlinear clearance (lower K_m) ($P < 0.001$). There was a correlation between shed antigen and SGOT/AST levels; part of the impact of shed antigen on clearance may have been explained by SGOT/AST levels.

Baseline levels of the shed HER2-ECD observed in MGC patients were comparable to those in MBC and EBC patients and no apparent impact on trastuzumab clearance was observed.

5.3 Preclinical safety data

There was no evidence of acute or multiple dose-related toxicity in studies of up to 6 months, or reproductive toxicity in teratology, female fertility or late gestational toxicity/placental transfer studies. Herceptin is not genotoxic. A study of trehalose, a major formulation excipient did not reveal any toxicities.

No long-term animal studies have been performed to establish the carcinogenic potential of Herceptin, or to determine its effects on fertility in males.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine hydrochloride monohydrate
L-histidine
a,a-trehalose dihydrate
polysorbate 20

6.2 Incompatibilities

This medicinal product must not be mixed or diluted with other medicinal products except those mentioned under section 6.6.

Do not dilute with glucose solutions since these cause aggregation of the protein.

6.3 Shelf life

Unopened vial

4 years

Aseptic reconstitution and dilution:

After aseptic reconstitution with sterile water for injection, chemical and physical stability of the reconstituted solution has been demonstrated for 48 hours at 2°C – 8°C.

After aseptic dilution in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 9 mg/mL (0.9 %) solution for injection, chemical and physical stability of Herceptin has been demonstrated for up to 30 days at 2 °C – 8°C, and 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution and Herceptin infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, and would not normally be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place under controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze the reconstituted solution.

For storage conditions of the opened medicinal product, see section 6.3 and 6.6.

6.5 Nature and contents of container

Herceptin vial:

One 15 mL clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film containing 150 mg of trastuzumab.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Herceptin IV is provided in sterile, preservative-free, non-pyrogenic, single use vials.

Appropriate aseptic technique should be used for reconstitution and dilution procedures. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed.

Aseptic preparation, handling and storage:

Aseptic handling must be ensured when preparing the infusion. Preparation should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.

- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.
- followed by adequate storage of the prepared solution for intravenous infusion to ensure maintenance of the aseptic conditions

Each vial of Herceptin is reconstituted with 7.2 mL of sterile water for injection (not supplied). Use of other reconstitution solvents should be avoided.

This yields a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0. A volume overage of 4 % ensures that the labelled dose of 150 mg can be withdrawn from each vial.

Herceptin should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted solution may result in problems with the amount of Herceptin that can be withdrawn from the vial.

The reconstituted solution should not be frozen.

Instructions for aseptic reconstitution:

1) Using a sterile syringe, slowly inject 7.2 mL of sterile water for injection in the vial containing the lyophilised Herceptin, directing the stream into the lyophilised cake.
2) Swirl the vial gently to aid reconstitution. DO NOT SHAKE!

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Herceptin results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

Instructions for aseptic dilution of the reconstituted solution

Determine the volume of the solution required:

- based on a loading dose of 4 mg trastuzumab/kg body weight, or a subsequent weekly dose of 2 mg trastuzumab/kg body weight:

$$\textbf{Volume}\ (\text{mL}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{dose}\ (\textbf{4}\ \text{mg/kg for loading or}\ \textbf{2}\ \text{mg/kg for maintenance})}{\textbf{21}\ (\text{mg/mL, concentration of reconstituted solution})}$$

- based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent 3-weekly dose of 6 mg trastuzumab/kg body weight:

$$\textbf{Volume}\ (\text{mL}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{dose}\ (\textbf{8}\ \text{mg/kg for loading or}\ \textbf{6}\ \text{mg/kg for maintenance})}{\textbf{21}\ (\text{mg/mL, concentration of reconstituted solution})}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9 % sodium chloride solution. Do not use with glucose-containing solutions (see section 6.2). The bag should be gently inverted to mix the solution in order to avoid foaming.

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

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

No incompatibilities between Herceptin and polyvinylchloride, polyethylene or polypropylene bags have been observed.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/145/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 August 2000
Date of latest renewal: 28 August 2010

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

Herceptin 600 mg solution for injection in vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 5 mL contains 600 mg of trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear to opalescent solution, colourless to yellowish.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer

Metastatic breast cancer

Herceptin is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.

- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

Early breast cancer

Herceptin is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC).

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).

- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.

- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Herceptin should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

4.2 Posology and method of administration

HER2 testing is mandatory prior to initiation of therapy (see sections 4.4 and 5.1). Herceptin treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy (see section 4.4), and should be administered by a healthcare professional only.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous fixed dose) is being administered to the patient, as prescribed. Herceptin subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

Switching treatment between Herceptin intravenous and Herceptin subcutaneous formulations and vice versa, using the three-weekly (q3w) dosing regimen, was investigated in study MO22982 (see section 4.8).

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin (trastuzumab) and not Kadcyla (trastuzumab emtansine).

Posology

The recommended dose for Herceptin subcutaneous formulation is 600 mg irrespective of the patient's body weight. No loading dose is required. This dose should be administered subcutaneously over 2-5 minutes every three weeks.

In the pivotal trial (BO22227) Herceptin subcutaneous formulation was administered in the neoadjuvant/adjuvant setting in patients with early breast cancer. The preoperative chemotherapy regimen consisted of docetaxel (75 mg/m²) followed by FEC (5FU, epirubicin and cyclophosphamide) at a standard dose.

See section 5.1 for chemotherapy combination dosing.

Duration of treatment

Patients with MBC should be treated with Herceptin until progression of disease. Patients with EBC should be treated with Herceptin for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended (see section 5.1).

Dose reduction

No reductions in the dose of Herceptin were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression butthey should be monitored carefully for complications of neutropenia during this time. Refer to the Summary of Product Characteristics (SmPC) for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.

If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately

3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

Missed doses

If the patient misses a dose of Herceptin subcutaneous formulation, it is recommended to administer the next 600 mg dose (i.e. the missed dose) as soon as possible. The interval between consecutive Herceptin subcutaneous formulation administrations should not be less than three weeks.

Special populations

Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. In a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition.

Paediatric population

There is no relevant use of Herceptin in the paediatric population.

Method of administration

The 600 mg dose should be administered as a subcutaneous injection only over 2-5 minutes every three weeks. The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with Herceptin subcutaneous formulation other medicinal products for subcutaneous administration should preferably be injected at different sites. Patients should be observed for six hours after the first injection and for two hours after subsequent injections for signs or symptoms of administration-related reactions (see sections 4.4 and 4.8).

For instructions on use and handling of Herceptin subcutaneous formulation refer to section 6.6.

4.3 Contraindications

- Hypersensitivity to trastuzumab, murine proteins, hyaluronidase or to any of the other excipients listed in section 6.1.
- Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

4.4 Special warnings and precautions for use

Traceability

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

HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures (see section 5.1).

Currently no data from clinical trials are available on re-treatment of patients with previous exposure to Herceptin in the adjuvant setting.

Cardiac dysfunction

General considerations

Patients treated with Herceptin are at increased risk for developing CHF (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving Herceptin therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. These may be moderate to severe and have been associated with death (see section 4.8). In addition, caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age.

All candidates for treatment with Herceptin, but especially those with prior anthracycline and cyclophosphamide exposure, should undergo baseline cardiac assessment including history and physical examination and electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help to identify patients who develop cardiac dysfunction. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Herceptin. A careful risk-benefit assessment should be made before deciding to treat with Herceptin.

Trastuzumab may persist in the circulation for up to 7 months after stopping Herceptin treatment based on population pharmacokinetic analysis of all available data (see section 5.2). Patients who receive anthracyclines after stopping Herceptin may possibly be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. In all patients cardiac function should be monitored during treatment (e.g. every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6-8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Herceptin therapy has been seen.

The safety of continuation or resumption of Herceptin in patients who experience cardiac dysfunction has not been prospectively studied. If LVEF percentage drops ≥ 10 points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic CHF has developed, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

If symptomatic cardiac failure develops during Herceptin therapy, it should be treated with standard medicinal products for CHF. Most patients who developed CHF or asymptomatic cardiac dysfunction in pivotal trials improved with standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued on therapy without additional clinical cardiac events.

Metastatic breast cancer

Herceptin and anthracyclines should not be given concurrently in combination in the MBC setting.

Patients with MBC who have previously received anthracyclines are also at risk of cardiac dysfunction with Herceptin treatment, although the risk is lower than with concurrent use of Herceptin and anthracyclines.

Early breast cancer

For patients with EBC, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Herceptin. In patients who receive anthracycline-containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of Herceptin, or longer if a continuous decrease of LVEF is observed.

Patients with history of myocardial infarction (MI), angina pectoris requiring medical treatment, history of or existing CHF (NYHA Class II –IV), LVEF of < 55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medical treatment eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant and neoadjuvant EBC pivotal trials with Herceptin and therefore treatment cannot be recommended in such patients.

Adjuvant treatment

Herceptin and anthracyclines should not be given concurrently in the adjuvant treatment setting.

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Herceptin (intravenous formulation) was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin and was more marked when Herceptin (intravenous formulation) was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months. In one of the 3 pivotal studies conducted in which a median follow-up of 5.5 years was available (BCIRG006) a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events was observed (up to 2.37 %) in patients who were administered Herceptin concurrently with a taxane following anthracycline therapy, compared to approximately 1 % in the two comparator arms (anthracycline plus cyclophosphamide followed by taxane and taxane, carboplatin and Herceptin).

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low LVEF (<55%) at baseline, prior to or following the initiation of paclitaxel treatment, decline in LVEF by 10-15 points, and prior or concurrent use of anti-hypertensive medicinal products. In patients receiving Herceptin after completion of adjuvant chemotherapy, the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Herceptin and a body mass index (BMI) >25 kg/m^2.

Neoadjuvant-adjuvant treatment

In patients with EBC eligible for neoadjuvant-adjuvant treatment, Herceptin should be used concurrently with anthracyclines only in chemotherapy-naive patients and only with low-dose anthracycline regimens, i.e., with maximum cumulative doses of doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2.

If patients have been treated concurrently with a full course of low-dose anthracyclines and Herceptin in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery. In other situations, the decision on the need for additional cytotoxic chemotherapy is determined based on individual factors.

Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited to two trials (MO16432 and BO22227).

In the pivotal trial MO16432, Herceptin was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2) . The incidence of symptomatic cardiac dysfunction was 1.7% in the Herceptin arm .

In the pivotal trial BO22227, Herceptin was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m^2); at a median follow-up exceeding 70 months, the incidence of cardiac failure/congestive cardiac failure was 0.3% in the Herceptin intravenous arm and 0.7% in the Herceptin subcutaneous arm. In patients with lower body weights (<59 kg, the lowest body weight quartile) the fixed dose used in the Herceptin subcutaneous arm was not associated with an increased risk of cardiac events or significant drop in LVEF.

Clinical experience is limited in patients above 65 years of age.

Administration-related reactions

Administration-related reactions (ARRs) are known to occur with Herceptin subcutaneous formulation. Pre-medication may be used to reduce risk of occurrence of ARRs.

Although serious ARRs, including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, were not reported in the clinical trial with the Herceptin subcutaneous formulation, caution should be exercised as these have been associated with the intravenous formulation. Patients should be observed for ARRs for six hours after the first injection and for two hours after subsequent injections. They can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions to intravenous Herceptin have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions were associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal ARR. Therefore, these patients should not be treated with Herceptin (see section 4.3).

Pulmonary events

Caution is recommended with Herceptin subcutaneous formulation as severe pulmonary events have been reported with the use of the intravenous formulation in the post-marketing setting (see section 4.8). These events have occasionally been fatal and may occur as part of an infusion-related reaction or with delayed onset. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Herceptin (see section 4.3). Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed. Clinically significant interactions between Herceptin and the concomitant medicinal products used in clinical trials have not been observed.

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents

Pharmacokinetic data from studies BO15935 and M77004 in women with HER2-positive MBC suggested that exposure to paclitaxel and doxorubicin (and their major metabolites 6-α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) was not altered in the presence of trastuzumab (8 mg/kg or 4 mg/kg IV loading dose followed by 6 mg/kg q3w or 2 mg/kg q1w IV, respectively).

However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite was unclear.

Data from study JP16003, a single-arm study of Herceptin (4 mg/kg IV loading dose and 2 mg/kg IV weekly) and docetaxel (60 mg/m2 IV) in Japanese women with HER2- positive MBC, suggested that concomitant administration of Herceptin had no effect on the single dose pharmacokinetics of docetaxel. Study JP19959 was a substudy of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer to study the pharmacokinetics of capecitabine and cisplatin when used with or without Herceptin. The results of this substudy suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus Herceptin. However, capecitabine itself showed higher concentrations and a longer half-life when combined with Herceptin. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus Herceptin.

Pharmacokinetic data from Study H4613g/GO01305 in patients with metastatic or locally advanced inoperable HER2-positive cancer suggested that trastuzumab had no impact on the PK of carboplatin.

Effect of antineoplastic agents on trastuzumab pharmacokinetics

By comparison of simulated serum trastuzumab concentrations after Herceptin monotherapy (4 mg/kg loading/2 mg/kg q1w IV) and observed serum concentrations in Japanese women with HER2- positive MBC (study JP16003) no evidence of a PK effect of concurrent administration of docetaxel on the pharmacokinetics of trastuzumab was found.

Comparison of PK results from two Phase II studies (BO15935 and M77004) and one Phase III study (H0648g) in which patients were treated concomitantly with Herceptin and paclitaxel and two Phase II studies in which Herceptin was administered as monotherapy (W016229 and MO16982), in women with HER2-positive MBC indicates that individual and mean trastuzumab trough serum concentrations varied within and across studies but there was no clear effect of the concomitant administration of paclitaxel on the pharmacokinetics of trastuzumab. Comparison of trastuzumab PK data from Study M77004 in which women with HER2-positive MBC were treated concomitantly with Herceptin, paclitaxel and doxorubicin to trastuzumab PK data in studies where Herceptin was administered as monotherapy (H0649g) or in combination with anthracycline plus cyclophosphamide or paclitaxel (Study H0648g), suggested no effect of doxorubicin and paclitaxel on the pharmacokinetics of trastuzumab.

Pharmacokinetic data from Study H4613g/GO01305 suggested that carboplatin had no impact on the PK of trastuzumab.

The administration of concomitant anastrozole did not appear to influence the pharmacokinetics of trastuzumab.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception

Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for 7 months after treatment has concluded (see section 5.2).

Pregnancy

Reproduction studies have been conducted in Cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin intravenous formulation and have revealed no evidence of impaired fertility or harm to the fetus. Placental transfer of trastuzumab during the early (days 20-50 of gestation) and late (days 120-150 of gestation) fetal development period was observed.

It is not known whether Herceptin can affect reproductive capacity. As animal reproduction studies are not always predictive of human response, Herceptin should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

In the post-marketing setting, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving Herceptin. Women who become pregnant should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Herceptin, or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable.

Breast-feeding

A study conducted in lactating Cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin intravenous formulation demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age. It is not known whether trastuzumab is secreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-feed during Herceptin therapy and for 7 months after the last dose.

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

Herceptin has a minor influence on the ability to drive or use machines (see section 4.8). Dizziness and somnolence may occur during treatment with Herceptin (see section 4.8). Patients experiencing administration-related symptoms (see section 4.4) should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

Amongst the most serious and/or common adverse reactions reported in Herceptin usage (intravenous and subcutaneous formulations) to date are cardiac dysfunction, administration-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.

The safety profile of Herceptin subcutaneous formulation (evaluated in 298 and 297 patients treated with the intravenous and subcutaneous formulations respectively) from the pivotal trial in EBC was overall similar to the known safety profile of the intravenous formulation.

Severe adverse events (defined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE grade ≥3) version 3.0) were equally distributed between both Herceptin formulations (52.3 % versus 53.5 % in the intravenous formulation versus subcutaneous formulation respectively).

Some adverse events / reactions were reported with a higher frequency for the subcutaneous formulation:

- Serious adverse events (most of which were identified because of in-patient hospitalisation or prolongation of existing hospitalisation): 14.1 % for the intravenous formulation versus 21.5 % for the subcutaneous formulation. The difference in serious adverse event rates between formulations was mainly due to infections with or without neutropenia (4.4 % versus 8.1 %) and cardiac disorders (0.7 % versus 1.7 %);

- Post-operative wound infections (severe and/or serious): 1.7 % versus 3.0 % for the intravenous formulation versus subcutaneous formulation, respectively;
- Administration-related reactions: 37.2 % versus 47.8 % for the intravenous formulation versus subcutaneous formulation, respectively during the treatment phase;
- Hypertension: 4.7 % versus 9.8 % for the intravenous formulation versus subcutaneous formulation respectively.

Tabulated list of adverse reactions with the intravenous formulation

In this section, the following categories of frequency have been used: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Presented in Table 1 are adverse reactions that have been reported in association with the use of intravenous Herceptin alone or in combination with chemotherapy in pivotal clinical trials and in the post-marketing setting.

All the terms included are based on the highest percentage seen in pivotal clinical trials. In addition, terms reported in the post marketing setting are included in Table 1.

Table 1: Undesirable effects reported with intravenous Herceptin monotherapy or in combination with chemotherapy in pivotal clinical trials (N = 8386) and in post-marketing

System organ class	**Adverse reaction**	**Frequency**
Infections and infestations	Infection	Very common
	Nasopharyngitis	Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Influenza	Common
	Sinusitis	Common
	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Pharyngitis	Common
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Blood and lymphatic system disorders	Febrile neutropenia	Very common
	Anaemia	Very common
	Neutropenia	Very common
	White blood cell count decreased/leukopenia	Very common
	Thrombocytopenia	Very common
	Hypoprothrombinaemia	Not known
	Immune thrombocytopenia	Not known
Immune system disorders	Hypersensitivity	Common
	[+]Anaphylactic reaction	Rare
	[+]Anaphylactic shock	Rare
Metabolism and nutrition	Weight decreased/Weight loss	Very common

System organ class	Adverse reaction	Frequency
disorders	Anorexia	Very common
	Tumour lysis syndrome	Not known
	Hyperkalaemia	Not known
Psychiatric disorders	Insomnia	Very common
	Anxiety	Common
	Depression	Common
Nervous system disorders	[1]Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Paraesthesia	Very common
	Dysgeusia	Very common
	Peripheral neuropathy	Common
	Hypertonia	Common
	Somnolence	Common
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and labyrinth disorders	Deafness	Uncommon
Cardiac disorders	[1] Blood pressure decreased	Very common
	[1] Blood pressure increased	Very common
	[1] Heart beat irregular	Very common
	[1]Cardiac flutter	Very common
	Ejection fraction decreased*	Very common
	[+]Cardiac failure (congestive)	Common
	[+1]Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	[1]Palpitation	Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Gallop rhythm present	Not known
Vascular disorders	Hot flush	Very common
	[+1] Hypotension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders		
	[+]Dyspnoea	Very common
	Cough	Very common
	Epistaxis	Very common
	Rhinorrhoea	Very common
	[+]Pneumonia	Common
	Asthma	Common
	Lung disorder	Common
	[+]Pleural effusion	Common
	[+1]Wheezing	Uncommon
	Pneumonitis	Uncommon

System organ class	Adverse reaction	Frequency
	[+]Pulmonary fibrosis	Not known
	[+]Respiratory distress	Not known
	[+]Respiratory failure	Not known
	[+]Lung infiltration	Not known
	[+]Acute pulmonary oedema	Not known
	[+]Acute respiratory distress syndrome	Not known
	[+]Bronchospasm	Not known
	[+]Hypoxia	Not known
	[+]Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	Orthopnoea	Not known
	Pulmonary oedema	Not known
	Interstitial lung disease	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	[1] Lip swelling	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular Injury	Common
	Hepatitis	Common
	Liver Tenderness	Common
	Jaundice	Rare
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	[1] Swelling face	Very common
	Alopecia	Very common
	Nail disorder	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Acne	Common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	[1]Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common

System organ class	Adverse reaction	Frequency
	Neck pain	Common
	Pain in extremity	Common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like symptoms	Very common
	Infusion related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Mucosal inflammation	Very common
	Peripheral oedema	Very common
	Malaise	Common
	Oedema	Common
Injury, poisoning and procedural complications	Contusion	Common

+ Denotes adverse reactions that have been reported in association with a fatal outcome.
1 Denotes adverse reactions that are reported largely in association with administration-related reactions. Specific percentages for these are not available.
* Observed with combination therapy following anthracyclines and combined with taxanes

Description of selected adverse reactions

Cardiac dysfunction

Congestive heart failure (NYHA Class II-IV) is a common adverse reaction to Herceptin. It has been associated with a fatal outcome. Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin (see section 4.4).

In 3 pivotal EBC clinical trials of adjuvant intravenous Herceptin given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (specifically symptomatic congestive heart failure) was similar in patients who were administered chemotherapy alone (ie did not receive Herceptin) and in patients who were administered Herceptin sequentially after a taxane (0.3-0.4 %). The rate was highest in patients who were administered Herceptin concurrently with a taxane (2.0 %). In the neoadjuvant setting, the experience of concurrent administration of Herceptin and low dose anthracycline regimen is limited (see section 4.4).

When Herceptin was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6 % of patients in the one-year arm after a median follow-up of 12 months. In study BO16348, after a median follow-up of 8 years the incidence of severe CHF (NYHA Class III & IV) in the Herceptin 1 year treatment arm was 0.8 %, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6 %.
Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥50 % after the event) was evident for 71.4 % of Herceptin-treated patients. Reversibility of mild

symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5 % of patients. Approximately 17 % of cardiac dysfunction related events occurred after completion of Herceptin.

In the pivotal metastatic trials of intravenous Herceptin, the incidence of cardiac dysfunction varied between 9 % and 12 % when it was combined with paclitaxel compared with 1 % – 4 % for paclitaxel alone. For monotherapy, the rate was 6 % – 9 %. The highest rate of cardiac dysfunction was seen in patients receiving Herceptin concurrently with anthracycline/cyclophosphamide (27 %), and was significantly higher than for anthracycline/cyclophosphamide alone (7 % – 10 %). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic CHF was 2.2 % in patients receiving Herceptin and docetaxel, compared with 0 % in patients receiving docetaxel alone. Most of the patients (79 %) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for CHF.

Administration-related reactions/hypersensitivity

Administration-related reactions (ARRs)/hypersensitivity reactions such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting and headache were seen in Herceptin clinical trials (see section 4.4). The rate of ARRs of all grades varied between studies depending on the indication, the data collection methodology, and whether trastuzumab was given concurrently with chemotherapy or as monotherapy.

Anaphylactoid reactions have been observed in isolated cases.

Haematotoxicity

Febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred very commonly. The frequency of occurrence of hypoprothrombinemia is not known. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Pulmonary events

Severe pulmonary adverse reactions occur in association with the use of Herceptin and have been associated with a fatal outcome. These include, but are not limited to, pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency (see section 4.4).

Description of selected adverse reactions with the subcutaneous formulation

Administration-related reactions

In the pivotal trial, the rate of all grade ARRs was 37.2 % with the Herceptin intravenous formulation and 47.8 % with the Herceptin subcutaneous formulation; severe grade 3 reactions were reported in 2.0 % and 1.7 % of the patients, respectively during the treatment phase; no severe grade 4 or 5 reactions were observed. All of the severe ARRs with the Herceptin subcutaneous formulation occurred during concurrent administration with chemotherapy. The most frequent severe reaction was drug hypersensitivity.

The systemic reactions included hypersensitivity, hypotension, tachycardia, cough, and dyspnoea. The local reactions included erythema, pruritus, oedema, rash and pain at the site of the injection.

Infections

The rate of severe infections (NCI CTCAE grade ≥3) was 5.0 % versus 7.1 %, in the Herceptin intravenous formulation arm and the Herceptin subcutaneous formulation arm respectively.

The rate of serious infections (most of which were identified because of in-patient hospitalisation or prolongation of existing hospitalisation) was 4.4 % in the Herceptin intravenous formulation arm and 8.1 % in the Herceptin subcutaneous formulation arm. The difference between formulations was mainly observed during the adjuvant treatment phase (monotherapy) and was mainly due to postoperative wound infections, but also to various other infections such as respiratory tract infections, acute pyelonephritis and sepsis. They resolved within a mean of 13 days in the Herceptin intravenous treatment arm and a mean of 17 days in the Herceptin subcutaneous treatment arm.

Hypertensive events

In the pivotal trial BO22227, there were more than twice as many patients reporting all grade hypertension with the Herceptin subcutaneous formulation (4.7 % versus 9.8 % in the intravenous and subcutaneous formulations respectively), with a greater proportion of patients with severe events (NCI CTCAE grade ≥3) <1 % versus 2.0 % the intravenous and subcutaneous formulations respectively. All but one patient who reported severe hypertension had a history of hypertension before they entered the study. Some of the severe events occurred on the day of the injection.

Immunogenicity

In the neoadjuvant-adjuvant EBC study (BO22227), at a median follow-up exceeding 70 months, 10.1% (30/296) of patients treated with Herceptin intravenous and 15.9 % (47/295) of patients receiving Herceptin subcutaneous vial developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the Herceptin intravenous arm and 3 of 47 in the Herceptin subcutaneous arm. 21.0 % of patients treated with Herceptin subcutaneous formulation developed antibodies against the excipient hyaluronidase (rHuPH20).

The clinical relevance of these antibodies is not known.The presence of anti-trastuzumab antibodies had no impact on pharmacokinetics, efficacy (determined by pathological Complete Response [pCR] and event free survival [EFS]) and safety determined by occurrence of administration related reactions (ARRs) of Herceptin intravenous and Herceptin subcutaneous.

Details of risk minimisation measures that are consistent with the EU Risk Management Plan are presented in Section 4.4.

Switching treatment between Herceptin intravenous and Herceptin subcutaneous formulation and vice versa

Study MO22982 investigated switching between the Herceptin intravenous and Herceptin subcutaneous formulation with a primary objective to evaluate patient preference for either the intravenous or the subcutaneous route of trastuzumab administration. In this trial, 2 cohorts (one using subcutaneous formulation in vial and one using subcutaneous formulation in administration system) were investigated using a 2-arm, cross-over design with 488 patients being randomized to one of two different three-weekly Herceptin treatment sequences (IV [Cycles 1-4]→ SC [Cycles 5-8], or SC [Cycles 1-4]→ IV [Cycles 5-8]). Patients were either naïve to Herceptin IV treatment (20.3%) or pre-exposed to Herceptin IV (79.7%). For the sequence IV→SC (SC vial and SC formulation in administration system cohorts combined), adverse event rates (all grades) were described pre-switching (Cycles 1-4) and post-switching (Cycles 5-8) as 53.8% vs. 56.4%, respectively; for the sequence SC→IV (SC vial and SC formulation in administration system cohorts combined), adverse event rates (all grades) were described pre- and post-switching as 65.4% vs. 48.7%, respectively. Pre-switching rates (Cycles 1-4) for serious adverse events, grade 3 adverse events and treatment discontinuations due to adverse events were low (<5%) and similar to post-switching rates (Cycles 5-8). No grade 4 or grade 5 adverse events were reported.

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

Single doses of up to 960 mg of Herceptin subcutaneous formulation have been administered with no reported untoward effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC03

Herceptin subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 is observed in 20% - 30% of primary breast cancers. Studies indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. The extracellular domain of the receptor (ECD, p105) can be shed into the blood stream and measured in serum samples.

Mechanism of action

Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Detection of HER2 overexpression or HER2 gene amplification

Detection of HER2 overexpression or HER2 gene amplification in breast cancer

Herceptin should only be used in patients whose tumours have HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. HER2 overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks (see section 4.4). HER2 gene amplification should be detected using fluorescence *in situ* hybridisation (FISH) or chromogenic *in situ* hybridisation (CISH) of fixed tumour blocks. Patients are eligible for Herceptin treatment if they show strong HER2 overexpression as described by a 3+ score by IHC or a positive FISH or CISH result.

To ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures.

The recommended scoring system to evaluate the IHC staining patterns is as stated in Table 2:

Table 2: Recommended scoring system to evaluate the IHC staining patterns

Score	**Staining pattern**	**HER2 overexpression assessment**
0	No staining is observed or membrane staining is observed in < 10 % of the tumour cells	Negative
1+	A faint/barely perceptible membrane staining is detected in > 10 % of the tumour cells. The cells are only stained in part of their membrane.	Negative
2+	A weak to moderate complete membrane staining is detected in > 10 % of the tumour cells.	Equivocal
3+	Strong complete membrane staining is detected in > 10 % of the tumour cells.	Positive

In general, FISH is considered positive if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2, or if there are more than 4 copies of the HER2 gene per tumour cell if no chromosome 17 control is used.

In general, CISH is considered positive if there are more than 5 copies of the HER2 gene per nucleus in greater than 50 % of tumour cells.

For full instructions on assay performance and interpretation please refer to the package inserts of validated FISH and CISH assays. Official recommendations on HER2 testing may also apply.

For any other method that may be used for the assessment of HER2 protein or gene expression, the analyses should only be performed by laboratories that provide adequate state-of-the-art performance of validated methods. Such methods must clearly be precise and accurate enough to demonstrate overexpression of HER2 and must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) overexpression of HER2.

Clinical efficacy and safety

Metastatic breast cancer

Intravenous formulation

Herceptin has been used in clinical trials as monotherapy for patients with MBC who have tumours that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease (Herceptin alone).

Herceptin has also been used in combination with paclitaxel or docetaxel for the treatment of patients who have not received chemotherapy for their metastatic disease. Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m^2 infused over 3 hours) with or without Herceptin. In the pivotal trial of docetaxel (100 mg/m^2 infused over 1 hour) with or without Herceptin, 60 % of the patients had received prior anthracycline-based adjuvant chemotherapy. Patients were treated with Herceptin until progression of disease.

The efficacy of Herceptin in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been studied. However, Herceptin plus docetaxel was efficacious in patients whether or not they had received prior adjuvant anthracyclines.

The test method for HER2 overexpression used to determine eligibility of patients in the pivotal Herceptin monotherapy and Herceptin plus paclitaxel clinical trials employed immunohistochemical staining for HER2 of fixed material from breast tumours using the murine monoclonal antibodies CB11 and 4D5. These tissues were fixed in formalin or Bouin's fixative. This investigative clinical

trial assay performed in a central laboratory utilised a 0 to 3+ scale. Patients classified as staining 2+ or 3+ were included, while those staining 0 or 1+ were excluded. Greater than 70 % of patients enrolled exhibited 3+ overexpression. The data suggest that beneficial effects were greater among those patients with higher levels of overexpression of HER2 (3+).

The main test method used to determine HER2 positivity in the pivotal trial of docetaxel, with or without Herceptin, was immunohistochemistry. A minority of patients was tested using fluorescence *in-situ* hybridisation (FISH). In this trial, 87 % of patients entered had disease that was IHC3+, and 95 % of patients entered had disease that was IHC3+ and/or FISH-positive.

Weekly dosing in metatstatic breast cancer

The efficacy results from the monotherapy and combination therapy studies are summarised in Table 3:

Table 3: Efficacy results from the monotherapy and combination therapy studies

Parameter	**Monotherapy**	**Combination Therapy**			
	Herceptin[1] **N=172**	**Herceptin plus paclitaxel[2]** **N=68**	**Paclitaxel[2]** **N=77**	**Herceptin plus docetaxel[3]** **N=92**	**Docetaxel[3]** **N=94**
Response rate (95 %CI)	18 % (13-25)	49 % (36- 61)	17 % (9-27)	61 % (50-71)	34 % (25-45)
Median duration of response (months) (95 %CI)	9.1 (5.6-10.3)	8.3 (7.3-8.8)	4.6 (3.7-7.4)	11.7 (9.3–15.0)	5.7 (4.6-7.6)
Median TTP (months) (95 %CI)	3.2 (2.6-3.5)	7.1 (6.2-12.0)	3.0 (2.0-4.4)	11.7 (9.2-13.5)	6.1 (5.4-7.2)
Median Survival (months) (95 %CI)	16.4 (12.3-ne)	24.8 (18.6-33.7)	17.9 (11.2-23.8)	31.2 (27.3-40.8)	22.74 (19.1-30.8)

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.

1. Study H0649g: IHC3+ patient subset
2. Study H0648g: IHC3+ patient subset
3. Study M77001: Full analysis set (intent-to-treat), 24 months results

Combination treatment with Herceptin and anastrozole

Herceptin has been studied in combination with anastrozole for first line treatment of MBC in HER2 overexpressing, hormone-receptor (i.e. estrogen-receptor (ER) and/or progesterone-receptor (PR)) positive postmenopausal patients. Progression free survival was doubled in the Herceptin plus anastrozole arm compared to anastrozole (4.8 months versus 2.4 months). For the other parameters the improvements seen for the combination were for overall response (16.5 % versus 6.7 %); clinical benefit rate (42.7 % versus 27.9 %); time to progression (4.8 months versus 2.4 months). For time to response and duration of response no difference could be recorded between the arms. The median overall survival was extended by 4.6 months for patients in the combination arm. The difference was not statistically significant, however more than half of the patients in the anastrozole alone arm crossed over to a Herceptin containing regimen after progression of disease.

Three -weekly dosing in metastatic breast cancer

The efficacy results from the non-comparative monotherapy and combination therapy studies are summarised in Table 4:

Table 4: Efficacy results from the non-comparative monotherapy and combination therapy studies

Parameter	**Monotherapy**		**Combination Therapy**	
	Herceptin[1] **N=105**	**Herceptin[2]** **N=72**	**Herceptin plus paclitaxel[3]** **N=32**	**Herceptin plus docetaxel[4]** **N=110**
Response rate (95 %CI)	24 % (15-35)	27 % (14-43)	59 % (41-76)	73 % (63-81)
Median duration of response (months) (range)	10.1 (2.8-35.6)	7.9 (2.1-18.8)	10.5 (1.8-21)	13.4 (2.1-55.1)
Median TTP (months) (95 %CI)	3.4 (2.8-4.1)	7.7 (4.2-8.3)	12.2 (6.2-ne)	13.6 (11-16)
Median Survival (months) (95 %CI)	ne	ne	ne	47.3 (32-ne)

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.

1. Study WO16229: loading dose 8 mg/kg, followed by 6 mg/kg 3 weekly schedule
2. Study MO16982: loading dose 6 mg/kg weekly x 3; followed by 6 mg/kg 3-weekly schedule
3. Study BO15935
4. Study MO16419

Sites of progression

The frequency of progression in the liver was significantly reduced in patients treated with the combination of Herceptin and paclitaxel, compared to paclitaxel alone (21.8 % versus 45.7 %; p=0.004). More patients treated with Herceptin and paclitaxel progressed in the central nervous system than those treated with paclitaxel alone (12.6 % versus 6.5 %; p=0.377).

Early breast cancer (adjuvant setting)

Intravenous formulation

Early breast cancer is defined as non-metastatic primary invasive carcinoma of the breast.
In the adjuvant treatment setting, Herceptin was investigated in 4 large multicentre, randomised, trials.

- Study BO16348 was designed to compare one and two years of three-weekly Herceptin treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). In addition, comparison of two years of Herceptin treatment versus one year of Herceptin treatment was performed. Patients assigned to receive Herceptin were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for either one or two years.
- Studies NSABP B-31 and NCCTG N9831 that comprise the joint analysis were designed to investigate the clinical utility of combining Herceptin treatment with paclitaxel following AC chemotherapy, additionally the NCCTG N9831 study also investigated adding Herceptin sequentially to AC→P chemotherapy in patients with HER2 positive EBC following surgery.
- Study BCIRG 006 study was designed to investigate combining Herceptin treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2 positive EBC following surgery.

Early breast cancer in the BO16348 Study was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes positive or axillary nodes negative if tumors at least 1 cm in diameter.

In the joint analysis of the NSABP B-31 and NCCTG N9831 studies, EBC was limited to women with operable breast cancer at high risk, defined as HER2-positive and axillary lymph node positive or HER2 positive and lymph node negative with high risk features (tumor size > 1 cm and ER negative or tumor size > 2 cm, regardless of hormonal status).

In the BCIRG 006 study HER2 positive, EBC was defined as either lymph node positive or high risk node negative patients with no (pN0) lymph node involvement, and at least 1 of the following factors: tumour size greater than 2 cm, estrogen receptor and progesterone receptor negative, histological and/or nuclear grade 2-3, or age < 35 years.

The efficacy results from study BO16348 following 12 months* and 8 years** median follow-up are summarized in the Table 5:

Table 5: Efficacy results from study BO16348

	Median follow-up 12 months*		Median follow-up 8 years**	
Parameter	Observation N=1693	Herceptin 1 Year N = 1693	Observation N= 1697***	Herceptin 1 Year N = 1702***
Disease-free survival				
- No. patients with event	219 (12.9 %)	127 (7.5 %)	570 (33.6 %)	471 (27.7 %)
- No. patients without event	1474 (87.1 %)	1566 (92.5 %)	1127 (66.4 %)	1231 (72.3 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.54		0.76	
Recurrence-free survival				
- No. patients with event	208 (12.3 %)	113 (6.7 %)	506 (29.8 %)	399 (23.4 %)
- No. patients without event	1485 (87.7 %)	1580 (93.3 %)	1191 (70.2 %)	1303 (76.6 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.51		0.73	
Distant disease-free survival				
- No. patients with event	184 (10.9 %)	99 (5.8 %)	488 (28.8 %)	399 (23.4 %)
- No. patients without event	1508 (89.1 %)	1594 (94.6 %)	1209 (71.2 %)	1303 (76.6 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.50		0.76	
Overall survival (death)				
- No. patients with event	40 (2.4 %)	31 (1.8 %)	350 (20.6 %)	278 (16.3 %)
- No. patients without event	1653 (97.6 %)	1662 (98.2 %)	1347 (79.4 %)	1424 (83.7 %)
P-value versus Observation	0.24		0.0005	
Hazard Ratio versus Observation	0.75		0.76	

*Co-primary endpoint of DFS of 1 year versus observation met the pre-defined statistical boundary
**Final analysis (including crossover of 52 % of patients from the observation arm to Herceptin)
*** There is a discrepancy in the overall sample size due to a small number of patients who were randomized after the cut-off date for the 12-month median follow-up analysis

The efficacy results from the interim efficacy analysis crossed the protocol pre-specified statistical boundary for the comparison of 1-year of Herceptin versus observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease free survival (DFS) was 0.54 (95 % CI 0.44, 0.67) which translates into an absolute benefit, in terms of a 2-year disease-free survival rate, of 7.6 percentage points (85.8 % versus 78.2 %) in favour of the Herceptin arm.

A final analysis was performed after a median follow-up of 8 years, which showed that 1 year Herceptin treatment is associated with a 24 % risk reduction compared to observation only (HR=0.76, 95 % CI 0.67, 0.86). This translates into an absolute benefit in terms of an 8 year disease free survival rate of 6.4 percentage points in favour of 1 year Herceptin treatment.

In this final analysis, extending Herceptin treatment for a duration of two years did not show additional benefit over treatment for 1 year [DFS HR in the intent to treat (ITT) population of 2 years versus 1 year=0.99 (95 % CI: 0.87, 1.13), p-value=0.90 and OS HR=0.98 (0.83, 1.15); p-value= 0.78]. The rate of asymptomatic cardiac dysfunction was increased in the 2-year treatment arm (8.1 % versus 4.6 % in the 1-year treatment arm). More patients experienced at least one grade 3 or 4 adverse event in the 2-year treatment arm (20.4 %) compared with the 1-year treatment arm (16.3 %).

In the NSABP B-31 and NCCTG N9831 studies Herceptin was administered in combination with paclitaxel, following AC chemotherapy.

Doxorubicin and cyclophosphamide were administered concurrently as follows:

- intravenous push doxorubicin, at 60 mg/ m^2, given every 3 weeks for 4 cycles.
- intravenous cyclophosphamide, at 600 mg/ m^2 over 30 minutes, given every 3 weeks for 4 cycles.

Paclitaxel, in combination with Herceptin, was administered as follows:

- intravenous paclitaxel - 80 mg/m^2 as a continuous intravenous infusion, given every week for 12 weeks.

or

- intravenous paclitaxel - 175 mg/m^2 as a continuous intravenous infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

The efficacy results from the joint analysis of the NSABP B-31 and NCCTG 9831 trials at the time of the definitive analysis of DFS* are summarized in Table 6. The median duration of follow up was 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm.

Table 6: Summary of Efficacy results from the joint analysis studies NSABP B-31 and NCCTG N9831 at the time of the definitive DFS analysis*

Parameter	AC→P (n=1679)	AC→PH (n=1672)	Hazard Ratio vs AC→P (95 % CI) p-value
Disease-free survival No. patients with event (%)	261 (15.5)	133 (8.0)	0.48 (0.39, 0.59) p<0.0001
Distant Recurrence No. patients with event	193 (11.5)	96 (5.7)	0.47 (0.37, 0.60) p<0.0001
Death (OS event): No. patients with event	92 (5.5)	62 (3.7)	0.67 (0.48, 0.92) p=0.014**

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

* at median duration of follow up of 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm

** p value for OS did not cross the pre-specified statistical boundary for comparison of AC→PH vs. AC→P

For the primary endpoint, DFS, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The hazard ratio translates into an absolute benefit, in

terms of 3-year disease-free survival rate estimates of 11.8 percentage points (87.2 % versus 75.4 %) in favour of the AC→PH (Herceptin) arm.
At the time of a safety update after a median of 3.5-3.8 years follow up, an analysis of DFS reconfirms the magnitude of the benefit shown in the definitive analysis of DFS. Despite the cross-over to Herceptin in the control arm, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The addition of Herceptin to paclitaxel chemotherapy also resulted in a 37 % decrease in the risk of death.

The pre-planned final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831 was performed when 707 deaths had occurred (median follow-up 8.3 years in the AC→PH group). Treatment with AC→PH resulted in a statistically significant improvement in OS compared with AC® P (stratified HR=0.64; 95% CI [0.55, 0.74]; log-rank p-value < 0.0001). At 8 years, the survival rate was estimated to be 86.9% in the AC® PH arm and 79.4% in the AC® P arm, an absolute benefit of 7.4% (95% CI 4.9%, 10.0%).

The final OS results from the joint analysis of studies NSABP B-31 and NCCTG N9831 are summarized in Table 7:

Table 7: Final Overall Survival Analysis from the joint analysis of trials NSABP B-31 and NCCTG N9831

Parameter	AC→P (N=2032)	AC→PH (N=2031)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)
Death (OS event): No. patients with event (%)	418 (20.6%)	289 (14.2%)	< 0.0001	0.64 (0.55, 0.74)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

DFS analysis was also performed at the final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831. The updated DFS analysis results (stratified HR = 0.61; 95% CI [0.54, 0.69]) showed a similar DFS benefit compared to the definitive primary DFS analysis, despite 24.8% patients in the AC→P arm who crossed over to receive Herceptin. At 8 years, the disease-free survival rate was estimated to be 77.2% (95% CI: 75.4, 79.1) in the AC→PH arm, an absolute benefit of 11.8% compared with the AC→P arm.

In the BCIRG 006 study Herceptin was administered either in combination with docetaxel, following AC chemotherapy (AC→DH) or in combination with docetaxel and carboplatin (DCarbH).

Docetaxel was administered as follows:

- intravenous docetaxel - 100 mg/m^2 as an intravenous infusion over 1 hour, given every 3 weeks for 4 cycles (day 2 of first docetaxel cycle, then day 1 of each subsequent cycle)

or

- intravenous docetaxel - 75 mg/m^2 as an intravenous infusion over 1 hour, given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each subsequent cycle)

which was followed by:

- carboplatin – at target AUC = 6 mg/mL/min administered by intravenous infusion over 30-60 minutes repeated every 3 weeks for a total of six cycles

Herceptin was administered weekly with chemotherapy and 3 weekly thereafter for a total of 52 weeks.

The efficacy results from the BCIRG 006 are summarized in Tables 8 and 9. The median duration of follow up was 2.9 years in the AC→D arm and 3.0 years in each of the AC→DH and DCarbH arms.

Table 8: Overview of efficacy analyses BCIRG 006 AC→D versus AC→DH

Parameter	AC→D (n=1073)	AC→DH (n=1074)	Hazard Ratio vs AC→D (95 % CI) p-value
Disease-free survival No. patients with event	195	134	0.61 (0.49, 0.77) p<0.0001
Distant recurrence No. patients with event	144	95	0.59 (0.46, 0.77) p<0.0001
Death (OS event) No. patients with event	80	49	0.58 (0.40, 0.83) p=0.0024

AC→D = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→DH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; CI = confidence interval

Table 9: Overview of efficacy analyses BCIRG 006 AC→D versus DCarbH

Parameter	AC→D (n=1073)	DCarbH (n=1074)	Hazard Ratio vs AC→D (95 % CI)
Disease-free survival No. patients with event	195	145	0.67 (0.54, 0.83) p=0.0003
Distant recurrence No. patients with event	144	103	0.65 (0.50, 0.84) p=0.0008
Death (OS event) No. patients with event	80	56	0.66 (0.47, 0.93) p=0.0182

AC→D = doxorubicin plus cyclophosphamide, followed by docetaxel; DCarbH = docetaxel, carboplatin and trastuzumab; CI = confidence interval

In the BCIRG 006 study for the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 5.8 percentage points (86.7 % versus 80.9 %) in favour of the AC→DH (Herceptin) arm and 4.6 percentage points (85.5 % versus 80.9 %) in favour of the DCarbH (Herceptin) arm compared to AC→D.

In study BCIRG 006, 213/1075 patients in the DCarbH (TCH) arm, 221/1074 patients in the AC® DH (AC® TH) arm, and 217/1073 in the AC→D (AC® T) arm had a Karnofsky performance status ≤90 (either 80 or 90). No disease-free survival (DFS) benefit was noticed in this subgroup of patients (hazard ratio = 1.16, 95 % CI [0.73, 1.83] for DCarbH (TCH) versus AC® D (AC® T); hazard ratio 0.97, 95 % CI [0.60, 1.55] for AC® DH (AC® TH) versus AC® D).

In addition a post-hoc exploratory analysis was performed on the data sets from the joint analysis (JA) NSABP B-31/NCCTG N9831* and BCIRG006 clinical studies combining DFS events and symptomatic cardiac events and summarised in Table 10:

Table 10: Post-hoc exploratory analysis results from the joint analysis NSABP B-31/NCCTG N9831* and BCIRG006 clinical studies combining DFS events and symptomatic cardiac events

	AC® PH (vs. AC® P) (NSABP B-31 and NCCTG N9831)*	AC® DH (vs. AC® D) (BCIRG 006)	DCarbH (vs. AC® D) (BCIRG 006)
Primary efficacy analysis DFS Hazard ratios (95 % CI) p-value	 0.48 (0.39, 0.59) p<0.0001	 0.61 (0.49, 0.77) p< 0.0001	 0.67 (0.54, 0.83) p=0.0003
Long term follow-up efficacy analysis** DFS Hazard ratios (95 % CI) p-value	 0.61 (0.54, 0.69) p<0.0001	 0.72 (0.61, 0.85) p<0.0001	 0.77 (0.65, 0.90) p=0.0011
Post-hoc exploratory analysis with DFS and symptomatic cardiac events Long term follow-up** Hazard ratios (95 % CI)	 0.67 (0.60, 0.75)	 0.77 (0.66, 0.90)	 0.77 (0.66, 0.90)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; D: docetaxel; Carb: carboplatin; H: trastuzumab
CI = confidence interval
* At the time of the definitive analysis of DFS. Median duration of follow up was 1.8 years in the AC→P arm and 2.0 years in the AC→PH arm
** Median duration of long term follow-up for the Joint Analysis clinical studies was 8.3 years (range: 0.1 to 12.1) for the AC→PH arm and 7.9 years (range: 0.0 to 12.2) for the AC→P arm; Median duration of long term follow-up for the BCIRG 006 study was 10.3 years in both the AC→D arm (range: 0.0 to 12.6) and the DCarbH arm (range: 0.0 to 13.1), and was 10.4 years (range: 0.0 to 12.7) in the AC→DH arm

Early breast cancer – (neoadjuvant-adjuvant setting)

Intravenous formulation

So far, no results are available which compare the efficacy of Herceptin administered with chemotherapy in the adjuvant setting with that obtained in the neo-adjuvant/adjuvant setting.

In the neoadjuvant-adjuvant treatment setting, study MO16432, a multicentre randomised trial, was designed to investigate the clinical efficacy of concurrent administration of Herceptin with neoadjuvant chemotherapy including both an anthracycline and a taxane, followed by adjuvant Herceptin, up to a total treatment duration of 1 year. The study recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory EBC. Patients with HER2+ tumours were randomised to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant Herceptin, or neoadjuvant chemotherapy alone.

In study MO16432, Herceptin (8 mg/kg loading dose, followed by 6 mg/kg maintenance every 3 weeks) was administered concurrently with 10 cycles of neoadjuvant chemotherapy

as follows:

- Doxorubicin 60mg/m^2 and paclitaxel 150 mg/m^2, administered 3-weekly for 3 cycles,

which was followed by
- Paclitaxel 175 mg/m^2 administered 3-weekly for 4 cycles,

which was followed by
- CMF on day 1 and 8 every 4 weeks for 3 cycles

which was followed after surgery by
- additional cycles of adjuvant Herceptin (to complete 1 year of treatment)

The efficacy results from Study MO16432 are summarized in Table 11. The median duration of follow-up in the Herceptin arm was 3.8 years.

Table 11: Efficacy results from MO16432

Parameter	Chemo + Herceptin (n=115)	Chemo only (n=116)	
Event-free survival No. patients with event	46	59	Hazard Ratio (95 % CI) 0.65 (0.44, 0.96) p=0.0275
Total pathological complete response* (95 % CI)	40 % (31.0, 49.6)	20.7 % (13.7, 29.2)	P=0.0014
Overall survival No. patients with event	22	33	Hazard Ratio (95 % CI) 0.59 (0.35, 1.02) p=0.0555

* defined as absence of any invasive cancer both in the breast and axillary nodes

An absolute benefit of 13 percentage points in favour of the Herceptin arm was estimated in terms of 3-year event-free survival rate (65 % versus. 52 %).

Subcutaneous formulation

Study BO22227 was designed to demonstrate non-inferiority of treatment with Herceptin subcutaneous formulation versus Herceptin intravenous formulation based on co-primary PK and efficacy endpoints (trastuzumab C_{trough} at pre-dose Cycle 8, and pCR rate at definitive surgery, respectively). A total of 595 patients with HER2-positive, operable or locally advanced breast cancer (LABC) including inflammatory breast cancer received eight cycles of either Herceptin intravenous formulation or Herceptin subcutaneous formulation concurrently with chemotherapy (4 cycles of docetaxel, 75 mg/m^2 intravenous infusion, followed by 4 cycles of FEC ([5-Fluorouracil, 500 mg/m^2; epirubicin, 75 mg/m^2; cyclophosphamide, 500 mg/m^2 each intravenous bolus or infusion]), followed by surgery, and continued therapy with Herceptin intravenous formulation or Herceptin subcutaneous formulation as originally randomized for 10 additional cycles, for a total of one year of treatment.

The analysis of the efficacy co-primary endpoint, pCR, defined as absence of invasive neoplastic cells in the breast, resulted in rates of 40.7 % (95 % CI: 34.7, 46.9) in the Herceptin intravenous arm and 45.4 % (95 % CI: 39.2 %, 51.7 %) in the Herceptin subcutaneous arm, a difference of 4.7 percentage points in favour of the Herceptin subcutaneous arm. The lower boundary of the one-sided 97.5 %

confidence interval for the difference in pCR rates was -4.0, establishing the non-inferiority of Herceptin subcutaneous for the co-primary endpoint

Table 12: Summary of pathological Complete Response (pCR)

	Herceptin IV (N = 263)	Herceptin SC (N=260)
pCR (absence ofinvasive neoplastic cells in breast	107 (40.7%)	118 (45.4%)
Non-responders	156 (59.3%)	142 (54.6%)
Exact 95% CI for pCR Rate*	(34.7; 46.9)	(39.2; 51.7)
Difference in pCR (SC minus IV arm)	4.70	
Lower bound one-sided 97.5% CI for the difference in pCR**	-4.0	

*Confidence interval for one sample binomial using Pearson-Clopper method
**Continuity correction of Anderson and Hauck (1986) has been used in this calculation

Analyses with longer term follow-up of a median duration exceeding 40 months supported the non-inferior efficacy of Herceptin subcutaneous compared to Herceptin intravenous with comparable results of both EFS and OS (3-year EFS rates of 73% in the Herceptin intravenous arm and 76% in the Herceptin subcutaneous arm, and 3-year OS rates of 90% in the Herceptin intravenous arm and 92% in the Herceptin subcutaneous arm).

For non-inferiority of the PK co-primary endpoint, steady-state trastuzumab C_{trough} value at the end of treatment Cycle 7, refer to section 5.2. Pharmacokinetic Properties. For the comparative safety profile see section 4.8.

The final analysis at a median follow-up exceeding 70 months showed similar EFS and OS between patients who received Herceptin IV and those who received Herceptin SC. The 6-year EFS rate was 65% in both arms (ITT population: HR=0.98 [95% CI: 0.74;1.29]) and the OS rate, 84% in both arms (ITT population: HR=0.94 [95% CI: 0.61;1.45]).

Study MO28048 investigating the safety and tolerability of Herceptin subcutaneous formulation as adjuvant therapy in HER2 positive EBC patients who were enrolled in either a Herceptin subcutaneous vial cohort (N=1868 patients, including 20 patients receiving neoadjuvant therapy) or a Herceptin subcutaneous administration system cohort (N=710 patients, including 21 patients receiving neoadjuvant therapy) resulted in no new safety signals. Results were consistent with the known safety profile for Herceptin intravenous and Herceptin subcutaneous formulations. In addition, treatment of lower body weight patients with Herceptin subcutaneous fixed dose in adjuvant EBC was not associated with increased safety risk, adverse events and serious adverse events, compared to the higher body weight patients. The final results of study BO22227 at a median follow-up exceeding 70 months were also consistent with the known safety profile for Herceptin IV and Herceptin SC, and no new safety signals were observed.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Herceptin in all subsets of the paediatric population for breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of trastuzumab at a dose of 600 mg administered three-weekly by the subcutaneous route was compared to the intravenous route (8 mg/kg loading dose, 6 mg/kg maintenance every three weeks) in the phase III study BO22227. The pharmacokinetic results for the co primary endpoint, C_{trough} pre dose Cycle 8, showed non-inferiority of the Herceptin subcutaneous compared to the Herceptin intravenous dose adjusted by body weight.

The mean C_{trough} during the neoadjuvant treatment phase, at the pre dose Cycle 8 time point, was higher in the Herceptin subcutaneous arm (78.7 µg/mL) than the Herceptin intravenous arm (57.8 µg/mL) of the study. During the adjuvant phase of treatment, at the pre-dose Cycle 13 time point, the mean C_{trough} values were 90.4 µg/mL and 62.1 µg/mL, respectively. Based on the observed data in study BO22227, steady state with the intravenous formulation was reached at cycle 8. With Herceptin subcutaneous formulation, concentrations were approximately at steady-state following Cycle 7 dose (pre-dose Cycle 8) with small increase in concentration (<15%) up to cycle 13. The mean C_{trough} at the subcutaneous pre- dose cycle 18 was 90.7 µg/mL and is similar to that of cycle 13, suggesting no further increase after cycle 13.

The median T_{max} following subcutaneous administration was approximately 3 days, with high interindividual variability (range 1-14 days). The mean C_{max} was expectedly lower in the Herceptin subcutaneous formulation (149 µg/mL) than in the intravenous arm (end of infusion value: 221 µg/mL).

The mean $AUC_{0\text{-}21\ days}$ following the Cycle 7 dose was approximately 10 % higher with the Herceptin subcutaneous formulation as compared to the Herceptin intravenous formulation, with mean AUC values of 2268 µg/mL•day and 2056 µg/mL•day, respectively. The $AUC_{0\text{-}21\ days}$ following Cycle 12 dose was approximately 20 % higher with the Herceptin subcutaneous formulation than the Herceptin intravenous dose, with mean AUC values of 2610 µg/mL•day and 2179 µg/mL•day, respectively. Due to the significant impact of body weight on trastuzumab clearance and the use of a fixed dose for the subcutaneous administration the difference in exposure between subcutaneous and intravenous administration was dependent on body weight: in patients with a body weight < 51 kg, mean steady state AUC of trastuzumab was about 80% higher after subcutaneous than after intravenous treatment whereas in the highest BW group (> 90 kg) AUC was 20% lower after subcutaneous than after intravenous treatment.

A population PK model with parallel linear and nonlinear elimination from the central compartment was constructed using pooled Herceptin SC and Herceptin IV PK data from the phase III study BO22227 to describe the observed PK concentrations following Herceptin IV and Herceptin SC administration in EBC patients. Bioavailability of trastuzumab given as the subcutaneous formulation was estimated to be 77.1%, and the first order absorption rate constant was estimated to be 0.4 day-1. Linear clearance was 0.111 L/day and the central compartment volume (V_c) was 2.91 L. The Michaelis-Menten parameter values were 11.9 mg/day and 33.9 µg/mL for V_{max} and K_m, respectively. Body weight and serum alanine aminotransferase (SGPT/ALT) showed a statistically significant influence on PK, however, simulations demonstrated that no dose adjustments are required in EBC patients. The population predicted PK exposure parameter values (median with 5th - 95th Percentiles) for Herceptin SC dosing regimens in EBC patients are shown in Table 13 below.

Table 13 Population Predicted PK Exposure Values (median with 5th - 95th Percentiles) for the Herceptin SC 600 mg Q3W Dosing Regimen in EBC patients

Primary tumor type and Regimen	**Cycle**	**N**	**C_{min} (µg/mL)**	**C_{max} (µg/mL)**	**$AUC_{0\text{-}21days}$ (µg.day/mL)**
EBC 600 mg Herceptin SC q3w	Cycle 1	297	28.2 (14.8 - 40.9)	79.3 (56.1 - 109)	1065 (718 - 1504)
	Cycle 7 (steady state)	297	75.0 (35.1 - 123)	149 (86.1 - 214)	2337 (1258 - 3478)

Trastuzumab washout

Trastuzumab washout period was assessed following subcutaneous administration using the population PK model. The results of these simulations indicate that at least 95% of patients will reach concentrations that are <1 μg/mL (approximately 3% of the population predicted $C_{min,ss}$, or about 97% washout) by 7 months.

5.3 Preclinical safety data

Herceptin Intravenous

There was no evidence of acute or multiple dose-related toxicity in studies of up to 6 months, or reproductive toxicity in teratology, female fertility or late gestational toxicity/placental transfer studies. Herceptin is not genotoxic. A study of trehalose, a major formulation excipient did not reveal any toxicities.

No long-term animal studies have been performed to establish the carcinogenic potential of Herceptin, or to determine its effects on fertility in males.

Herceptin Subcutaneous

A single dose study in rabbits and a 13-week repeat dose toxicity study in Cynomolgus monkeys were conducted. The rabbit study was performed to specifically examine local tolerance aspects. The 13-week study was performed to confirm that the change in route of administration and the use of the novel excipient recombinant human hyaluronidase (rHuPH20) did not have an effect on the Herceptin safety characteristics. Herceptin subcutaneous formulation was locally and systemically well tolerated.

Hyaluronidase is found in most tissues of the human body. Non-clinical data for recombinant human hyaluronidase reveal no special hazard for humans based on conventional studies of repeated dose toxicity including safety pharmacology endpoints. Reproductive toxicology studies with rHuPH20 revealed embryofetal toxicity in mice at high systemic exposure, but did not show teratogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Recombinant human hyaluronidase (rHuPH20)
L-histidine
L-histidine hydrochloride monohydrate
α,α-trehalose dihydrate
L-methionine
Polysorbate 20
Water for injections

6.2 Incompatibilities

Herceptin subcutaneous formulation is a ready to use solution which should not be mixed or diluted with other products.

No incompatibilities between Herceptin subcutaneous formulation and polypropylene or polycarbonate syringe material or stainless steel transfer and injection needles and polyethylene Luer cone stoppers have been observed.

6.3 Shelf life

21 months.

Once transferred from the vial to the syringe the medicinal product is physically and chemically stable for 28 days at 2°C – 8°C and for 6 hours (cumulative time in the vial and the syringe) at ambient temperature (max. 30°C) in diffused daylight.
As Herceptin does not contain any antimicrobial-preservative, from a microbiological point of view, the medicine should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Once removed from the refrigerator Herceptin subcutaneous formulation must be administered within 6 hours and should not be kept above 30°C.

For storage conditions of the opened medicinal product, see section 6.3 and 6.6.

6.5 Nature and contents of container

One 6 mL clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film containing 5 mL of solution (600 mg of trastuzumab).

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Herceptin should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

Herceptin is for single-use only.

As Herceptin does not contain any antimicrobial-preservative, from a microbiological point of view, the medicine should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. After transfer of the solution to the syringe, it is recommended to replace the transfer needle by a syringe closing cap to avoid drying of the solution in the needle and not compromise the quality of the medicinal product. The hypodermic injection needle must be attached to the syringe immediately prior to administration followed by volume adjustment to 5 mL.

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/145/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 August 2000
Date of latest renewal: 28 August 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Roche Diagnostics GmbH
Pharma Biotech Penzberg
Nonnenwald 2
D-82377 Penzberg
Germany

Genentech Inc.
1000 New Horizons Way
Vacaville, CA 95688
USA

Roche Singapore Technical Operations Pte. Ltd.
10 Tuas Bay Link
637394 Singapore
Singapore

Lonza Biologics Tuas Pte Ltd
35 Tuas South Ave. 6
637377 Singapore
Singapore

Lonza Portsmouth
101 International Dr.
Portsmouth, NH 03801
USA

Name and address of the manufacturer(s) responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

· **Periodic Safety Update Reports**

The 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 pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Herceptin 150 mg powder for concentrate for solution for infusion

Trastuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

The vial contains 150 mg trastuzumab. After reconstitution 1 ml concentrate contains 21 mg of trastuzumab

3. LIST OF EXCIPIENTS

L-histidine hydrochloride monohydrate, L-histidine, polysorbate 20, a,a-trehalose dihydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only after reconstitution and dilution
Read the package leaflet before 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

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC – 8ºC).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1//00/145/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Herceptin 150 mg powder for concentrate
Trastuzumab
For intravenous use only

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Herceptin 600 mg solution for injection in vial
Trastuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 600 mg/5 mL trastuzumab.

3. LIST OF EXCIPIENTS

Recombinant human hyaluronidase (rHuPH20)
L-histidine
L-histidine hydrochloride monohydrate
α,α-trehalose dihydrate
L-methionine
Polysorbate 20
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use only.
Read the package leaflet before 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

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC – 8ºC).
Keep the vial in the outer carton in order to protect from light.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/145/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN
.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Herceptin 600 mg solution for injection
Trastuzumab
For subcutaneous use only

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

600 mg/5 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Herceptin 150 mg powder for concentrate for solution for infusion
Trastuzumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. What Herceptin is and what it is used for
2. What you need to know before you are given Herceptin
3. How Herceptin is given
4. Possible side effects
5. How to store Herceptin
6. Contents of the pack and other information

1. What Herceptin is and what it is used for

Herceptin contains the active substance trastuzumab, which is a monoclonal antibody. Monoclonal antibodies attach to specific proteins or antigens. Trastuzumab is designed to bind selectively to an antigen called human epidermal growth factor receptor 2 (HER2). HER2 is found in large amounts on the surface of some cancer cells where it stimulates their growth. When Herceptin binds to HER2 it stops the growth of such cells and causes them to die.

Your doctor may prescribe Herceptin for the treatment of breast and gastric cancer when:
- You have early breast cancer, with high levels of a protein called HER2.
- You have metastatic breast cancer (breast cancer that has spread beyond the original tumour) with high levels of HER2. Herceptin may be prescribed in combination with the chemotherapy medicine paclitaxel or docetaxel as first treatment for metastatic breast cancer or it may be prescribed alone if other treatments have proved unsuccessful. It is also used in combination with medicines called aromatase inhibitors with patients with high levels of HER2 and hormone receptor-positive metastatic breast cancer (cancer that is sensitive to the presence of female sex hormones).
- You have metastatic gastric cancer with high levels of HER2, when it is in combination with the other cancer medicines capecitabine or 5-flououracil and cisplatin.

2. What you need to know before you are given Herceptin

Do not use Herceptin if:
- you are allergic to trastuzumab, to murine (mouse) proteins, or to any of the other ingredients of this medicine (listed in section 6).
- you have severe breathing problems at rest due to your cancer or if you need oxygen treatment.

Warnings and precautions

Your doctor will closely supervise your therapy.

Heart checks
Treatment with Herceptin alone or with a taxane may affect the heart, especially if you have ever used an anthracycline (taxanes and anthracyclines are two other kinds of medicine used to treat cancer). The effects may be moderate to severe and could cause death. Therefore, your heart function will be checked before, during (every three months) and after (up to two to five years) treatment with Herceptin. If you develop any signs of heart failure (inadequate pumping of blood by the heart), your heart function may be checked more frequently (every six to eight weeks), you may receive treatment for heart failure or you may have to stop Herceptin treatment.

Talk to your doctor, pharmacist or nurse before you are given Herceptin if:

- you have had heart failure, coronary artery disease, heart valve disease (heart murmurs), high blood pressure, taken any high blood pressure medicine or are currently taking any high blood pressure medicine.

- you have ever had or are currently using a medicine called doxorubicin or epirubicin (medicines used to treat cancer). These medicines (or any other anthracyclines) can damage heart muscle and increase the risk of heart problems with Herceptin.

- you suffer from breathlessness., especially if you are currently using a taxane. Herceptin can cause breathing difficulties, especially when it is first given. This could be more serious if you are already breathless. Very rarely, patients with severe breathing difficulties before treatment have died when they were given Herceptin.

- you have ever had any other treatment for cancer.

If you receive Herceptin with any other medicine to treat cancer, such as paclitaxel, docetaxel, an aromatase inhibitor, capecitabine, 5-fluorouracil, or cisplatin you should also read the patient information leaflets for these products.

Children and adolescents
Herceptin is not recommended for anyone under the age of 18 years.

Other medicines and Herceptin
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or may take any other medicines.

It may take up to 7 months for Herceptin to be removed from the body. Therefore you should tell your doctor, pharmacist or nurse that you have had Herceptin if you start any new medicine in the 7 months after stopping treatment.

Pregnancy
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.
- You should use effective contraception during treatment with Herceptin and for at least 7 months after treatment has ended.
- Your doctor will advise you of the risks and benefits of taking Herceptin during pregnancy. In rare cases, a reduction in the amount of (amniotic) fluid that surrounds the developing baby within the womb has been observed in pregnant women receiving Herceptin. This condition may be harmful to your baby in the womb and has been associated with the lungs not developing fully resulting in foetal death.

Breast-feeding
Do not breast-feed your baby during Herceptin therapy and for 7 months after the last dose of Herceptin as Herceptin may pass to your baby through your breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Herceptin may affect your ability to drive a car or operate machines.If during treatment you experience symptoms, such as dizziness, sleepiness, chills or fever, you should not drive or use machines until these symptoms disappear.

Sodium
Herceptin contains less than 1 mmol of sodium per dose, i.e. it is essentially sodium-free.

3. How Herceptin is given

Before starting the treatment your doctor will determine the amount of HER2 in your tumour. Only patients with a large amount of HER2 will be treated with Herceptin. Herceptin should only be given by a doctor or nurse. Your doctor will prescribe a dose and treatment regimen that is right for ***you***. The dose of Herceptin depends on your body weight.

Two different types (formulations) of Herceptin exist:
- one is given as an infusion into a vein (intravenous infusion)
- the other is given as an injection under the skin (subcutaneous injection).

It is important to check the product labels to ensure that the correct formulation is being given as prescribed. Herceptin intravenous formulation is not for subcutaneous use and should be given as an intravenous infusion only.
Your doctor may consider switching your Herceptin intravenous treatment to Herceptin subcutaneous treatment (and vice versa) if considered appropriate for you.

Herceptin intravenous formulation is given as an intravenous infusion (“drip”) directly into your veins. The first dose of your treatment is given over 90 minutes and you will be observed by a health professional while it is being given in case you have any side effects. If the first dose is well tolerated the next doses may be given over 30 minutes (see section 2 under “Warnings and precautions”). The number of infusions you receive will depend on how you respond to the treatment. Your doctor will discuss this with you.

In order to prevent medication errors it is important to check the vial labels to ensure that the medicine being prepared and given is Herceptin (trastuzumab) and not trastuzumab emtansine.

For early breast cancer, metastatic breast cancer and metastatic gastric cancer, Herceptin is given every 3 weeks. Herceptin may also be given once a week for metastatic breast cancer.

If you stop using Herceptin
Do not stop using this medicine without talking to your doctor first. All doses should be taken at the right time every week or every three weeks (depending on your dosing schedule). This helps your medicine work as well as it can.

It may take up to 7 months for Herceptin to be removed from your body. Therefore your doctor may decide to continue to check your heart functions, even after you finish treatment.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, Herceptin can cause side effects, although not everybody gets them. Some of these side effects may be serious and may lead to hospitalisation.

During a Herceptin infusion, chills, fever and other flu like symptoms may occur. These are very common (may affect more than 1 in 10 people). Other infusion-related symptoms are: feeling sick

(nausea), vomiting, pain, increased muscle tension and shaking, headache, dizziness, breathing difficulties, high or low blood pressure, heart rhythm disturbances (palpitations, heart fluttering or irregular heart beat), swelling of the face and lips, rash and feeling tired. Some of these symptoms can be serious and some patients have died (see section 2 under “Warnings and precautions”).

These effects mainly occur with the first intravenous infusion (“drip” into your vein) and during the first few hours after the start of the infusion. They are usually temporary. You will be observed by a health care professional during the infusion and for at least six hours after the start of the first infusion and for two hours after the start of other infusions. If you develop a reaction, they will slow down or stop the infusion and may give you treatment to counteract the side effects. The infusion may be continued after the symptoms improve.

Occasionally, symptoms start later than six hours after the infusion begins. If this happens to you, contact your doctor immediately. Sometimes, symptoms may improve and then get worse later.

Serious side effects
Other side effects can occur at any time during treatment with Herceptin, not just related to an infusion. **Tell a doctor or nurse straight away, if you notice any of the following side effects:**

- Heart problems can sometimes occur during treatment and occasionally after treatment has stopped and can be serious. They include weakening of the heart muscle possibly leading to heart failure, inflammation of the lining around the heart and heart rhythm disturbances. This can lead to symptoms such as breathlessness (including breathlessness at night), cough, fluid retention (swelling) in the legs or arms, palpitations (heart fluttering or irregular heart beat) (see section 2. Heart checks).

  Your doctor will monitor your heart regularly during and after treatment but you should tell your doctor immediately if you notice any of the above symptoms.

- Tumour lysis syndrome (a group of metabolic complications occurring after cancer treatment characterized by high blood levels of potassium and phosphate, and low blood levels of calcium). Symptoms may include kidney problems (weakness, shortness of breath, fatigue and confusion), heart problems (fluttering of the heart or a faster or slower heartbeat), seizures, vomiting or diarrhoea and tingling in the mouth, hands or feet

If you experience any of the above symptoms when your treatment with Herceptin has finished, you should see your doctor and tell them that you have previously been treated with Herceptin.

Very common side effects of Herceptin: may affect more than 1 in 10 people

- infections
- diarrhoea
- constipation
- heartburn (dyspepsia)
- fatigue
- skin rashes
- chest pain
- abdominal pain
- joint pain
- low counts of red blood cells and white blood cells (which help fight infection) sometimes with fever
- muscle pain
- conjunctivitis
- watery eyes
- nose bleeds
- runny nose

- hair loss
- tremor
- hot flush
- dizziness
- nail disorders
- weight loss
- loss of appetite
- inability to sleep (insomnia)
- altered taste
- low platelet count
- bruising
- numbness or tingling of the fingers and toes
- redness, swelling or sores in your mouth and/or throat
- pain, swelling, redness or tingling of hands and/or feet
- breathlessness
- headache
- cough
- vomiting
- nausea

Common side effects of Herceptin: may affect up to 1 in 10 people

- allergic reactions
- throat infections
- bladder and skin infections
-
- inflammation of the breast
- inflammation of the liver
- kidney disorders
- increased muscle tone or tension (hypertonia)
- pain in the arms and/or legs
- itchy rash
- sleepiness (somnolence)
- haemorrhoids
- itchiness
- dry mouth and skin
- dry eyes
- sweating
- feeling weak and unwell
- anxiety
- depression
- asthma
- infection of lungs
- lung disorders
- back pain
- neck pain
- bone pain
- acne
- leg cramps

Uncommon side effects of Herceptin: may affect up to 1 in 100 people:

- deafness
- bumpy rash· wheezing
- inflammation or scarring of the lungs

Rare side effects of Herceptin: may affect up to 1 in 1000 people

- jaundice

- anaphylactic reactions

Other side effects that have been reported with Herceptin use: frequency cannot be estimated from the available data

- abnormal or impaired blood clotting

- high potassium levels
- swelling or bleeding at the back of the eyes
- shock
- abnormal heart rhythm
- respiratory distress
- respiratory failure
- acute accumulation of fluid in the lungs
- acute narrowing of the airways
- abnormally low oxygen levels in the blood
- difficulty in breathing when lying flat
- liver damage
- swelling of the face, lips and throat
- kidney failure
- abnormally low levels of fluid around baby in womb
- failure of the lungs of the baby to develop in the womb
- abnormal development of the kidneys of the baby in the womb

Some of the side-effects you experience may be due to your underlying cancer. If you receive Herceptin in combination with chemotherapy, some of them may also be due to the chemotherapy.

If you get any side effects, talk to your doctor, pharmacist or nurse.

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 Herceptin

Herceptin will be stored by the health professionals at the hospital or clinic.

- 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 outer carton and on the vial label after EXP. The expiry date refers to the last day of that month.
- The unopened vial should be stored in a refrigerator (2°C – 8°C).
- Do not freeze the reconstituted solution.
- Infusion solutions should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, and would not normally be longer than 24 hours at 2°C – 8°C.
- Do not use Herceptin if you notice any particulate matter or discoloration prior to administration.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Herceptin contains

- The active substance is trastuzumab. Each vial contains 150 mg trastuzumab that has to be dissolved in 7.2 mL of water for injection. The resulting solution contains approximately 21 mg/mL trastuzumab.

- The other ingredient(s) are L-histidine hydrochloride monohydrate, L-histidine, α,α-trehalose dihydrate, polysorbate 20.

What Herceptin looks like and contents of the pack

Herceptin is a powder for concentrate for solution for intravenous infusion, which is supplied in a glass vial with a rubber stopper containing 150 mg of trastuzumab. The powder is a white to pale yellow pellet. Each carton contains 1 vial of powder.

Marketing Authorisation Holder

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
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Manufacturer
Roche Pharma AG
Emil-Barell-Strasse 1
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for medical or healthcare professionals only

Herceptin IV is provided in sterile, preservative-free, non-pyrogenic, single use vials.

Always keep this medicine in the closed original pack at a temperature of 2ºC – 8 ºC in a refrigerator.

Appropriate aseptic technique should be used for reconstitution and dilution procedures. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed.

A vial of Herceptin aseptically reconstituted with sterile water for injections (not supplied) is chemically and physically stable for 48 hours at 2ºC – 8 ºC after reconstitution and must not be frozen.

After aseptic dilution in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 9 mg/mL (0.9 %) solution for injection, chemical and physical stability of Herceptin has been demonstrated for up to 30 days at 2 ºC – 8ºC, and 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution and Herceptin infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, and would not normally be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place under controlled and validated aseptic conditions.

Aseptic preparation, handling and storage:

Aseptic handling must be ensured when preparing the infusion. Preparation should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.
- followed by adequate storage of the prepared solution for intravenous infusion to ensure maintenance of the aseptic conditions

Each vial of Herceptin is reconstituted with 7.2 mL of water for injections (not supplied). Use of other reconstitution solvents should be avoided. This yields a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab. A volume overage of 4 % ensures that the labelled dose of 150 mg can be withdrawn from each vial.

Herceptin should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted Herceptin may result in problems with the amount of Herceptin that can be withdrawn from the vial.

Instructions for aseptic reconstitution:

1) Using a sterile syringe, slowly inject 7.2 mL of water for injections in the vial containing the lyophilised Herceptin, directing the stream into the lyophilised cake.
2) Swirl vial gently to aid reconstitution. DO NOT SHAKE!

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Herceptin results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

Instructions for aseptic dilution of the reconstituted solution

Determine the volume of the solution required:

- based on a loading dose of 4 mg trastuzumab/kg body weight, or a subsequent weekly dose of 2 mg trastuzumab/kg body weight:

Volume (mL) = **Body weight** (kg) x **dose** (**4** mg/kg for loading or **2** mg/kg for maintenance)
21 (mg/mL, concentration of reconstituted solution)

- based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent 3-weekly dose of 6 mg trastuzumab/kg body weight:

Volume (mL) = **Body weight** (kg) x **dose** (**8** mg/kg for loading or **6** mg/kg for maintenance)
21 (mg/mL, concentration of reconstituted solution)

The appropriate amount of solution should be withdrawn from the vial and added to a polyvinylchloride, polyethylene or polypropylene infusion bag containing 250 mL of 0.9 % sodium chloride solution. Do not use with glucose-containing solutions. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Herceptin 600 mg solution for injection in vial
Trastuzumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Herceptin is and what it is used for
2. What you need to know before you are given Herceptin
3. How Herceptin is given
4. Possible side effects
5. How to store Herceptin
6. Contents of the pack and other information

1. What Herceptin is and what it is used for

Herceptin contains the active substance trastuzumab, which is a monoclonal antibody. Monoclonal antibodies attach to specific proteins or antigens. Trastuzumab is designed to bind selectively to an antigen called human epidermal growth factor receptor 2 (HER2). HER2 is found in large amounts on the surface of some cancer cells where it stimulates their growth. When Herceptin binds to HER2 it stops the growth of such cells and causes them to die.

Your doctor may prescribe Herceptin for the treatment of breast cancer when:
- You have early breast cancer, with high levels of a protein called HER2.
- You have metastatic breast cancer (breast cancer that has spread beyond the original tumour) with high levels of HER2. Herceptin may be prescribed in combination with the chemotherapy medicines paclitaxel or docetaxel as first treatment for metastatic breast cancer or it may be prescribed alone if other treatments have proved unsuccessful. It is also used in combination with medicines called aromatase inhibitors with patients with high levels of HER2 and hormone receptor-positive metastatic breast cancer (cancer that is sensitive to the presence of female sex hormones).

2. What you need to know before you are given Herceptin

Do not use Herceptin if:
- you are allergic to trastuzumab (the active substance of Herceptin), murine (mouse) proteins, or any of the other ingredients of this medicine (listed in section 6).
- you have severe breathing problems at rest due to your cancer or if you need oxygen treatment.

Warnings and precautions
Your doctor will closely supervise your therapy.

Heart checks
Treatment with Herceptin alone or with a taxane may affect the heart, especially if you have ever used an anthracycline (taxanes and anthracyclines are two other kinds of medicine used to treat cancer). The effects may be moderate to severe and could cause death. Therefore, your heart function will be checked before, during (every three months) and after (up to two to five years) treatment with Herceptin. If you develop any signs of heart failure (i.e. inadequate pumping of blood by the heart),

your heart function may be checked more frequently (every six to eight weeks), you may receive treatment for heart failure or you may have to stop Herceptin treatment.

Talk to your doctor, pharmacist or nurse before you are given Herceptin if:

- you have had heart failure, coronary artery disease, heart valve disease (heart murmurs), high blood pressure, taken any high blood pressure medicine or are currently taking any high blood pressure medicine.
- you have ever had or are currently using a medicine called doxorubicin or epirubicin (medicines used to treat cancer). These medicines (or any other anthracyclines) can damage heart muscle and increase the risk of heart problems with Herceptin.
- you suffer from breathlessness, especially if you are currently using a taxane. Herceptin can cause breathing difficulties, especially when it is first given. This could be more serious if you are already breathless. Very rarely, patients with severe breathing difficulties before treatment have died when they were given Herceptin.
- you have ever had any other treatment for cancer.

If you receive Herceptin with any other medicine to treat cancer, such as paclitaxel, docetaxel, an aromatase inhibitor, carboplatin or cisplatin you should also read the patient information leaflets for these products.

Children and adolescents
Herceptin is not recommended for anyone under the age of 18 years.

Other medicines and Herceptin
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

It may take up to 7 months for Herceptin to be removed from the body. Therefore you should tell your doctor, pharmacist or nurse that you have had Herceptin if you start any new medicine in the 7 months after stopping treatment.

Pregnancy

- If you are pregnant, think you may be pregnant or are planning to have a baby, you must tell your doctor, pharmacist or nurse before taking this medicine.
- You should use effective contraception during treatment with Herceptin and for at least 7 months after treatment has ended.

Your doctor will advise you of the risks and benefits of taking Herceptin during pregnancy. In rare cases, a reduction in the amount of (amniotic) fluid that surrounds the developing baby within the womb has been observed in pregnant women receiving Herceptin. This condition may be harmful to your baby in the womb and has been associated with the lungs not developing fully resulting in foetal death.

Breast-feeding
Do not breast-feed your baby during Herceptin therapy and for 7 months after the last dose of Herceptin as Herceptin may pass to your baby through your breast milk.

Ask your doctor, pharmacist or nurse for advice before taking any medicine.

Driving and using machines
Herceptin may affect your ability to drive a car or operate machines. If during treatment, you experience symptoms, such as dizziness, sleepiness, chills or fever, you should not drive or use machines until these symptoms disappear.

Sodium
Herceptin contains less than 1 mmol of sodium per dose, i.e. it is essentially sodium-free.

3. How Herceptin is given

Before starting the treatment your doctor will determine the amount of HER2 in your tumour. Only patients with a large amount of HER2 will be treated with Herceptin. Herceptin should only be given by a doctor or nurse.

Two different types (formulations) of Herceptin exist:
- one is given as an infusion into a vein (intravenous infusion)
- the other is given as an injection under the skin (subcutaneous injection).

It is important to check the product labels to ensure that the correct formulation is being given as prescribed. Herceptin subcutaneous fixed dose formulation is not for intravenous use and should be given as a subcutaneous injection only.

Your doctor may consider switching your Herceptin intravenous treatment to Herceptin subcutaneous treatment (and vice versa) if considered appropriate for you.

In order to prevent medication errors it is also important to check the vial labels to ensure that the medicine being prepared and given is Herceptin (trastuzumab) and not trastuzumab emtansine.
The recommended dose is 600 mg. Herceptin is given as a subcutaneous injection (under the skin) over 2 to 5 minutes every three weeks.

The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm away from an old site. No injection should be given into areas where the skin is red, bruised, tender or hard.
If other medicines for subcutaneous use are used during the treatment course with Herceptin, a different injection site should be used.

Herceptin should not be mixed or diluted with other products.

If you stop using Herceptin
Do not stop using this medicine without talking to your doctor first. All doses should be taken at the right time every three weeks. This helps your medicine work as well as it can.

It may take up to 7 months for Herceptin to be removed from your body. Therefore your doctor may decide to continue to check your heart functions, even after you finish treatment.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these side effects may be serious and may lead to hospitalisation.

During treatment with Herceptin, chills, fever and other flu like symptoms may occur. These are very common (may affect more than 1 in 10 people). Other symptoms are: feeling sick (nausea), vomiting, pain, increased muscle tension and shaking, headache, dizziness, breathing difficulties, high or low blood pressure, heart rhythm disturbances (palpitations, heart fluttering or irregular heart beat), swelling of the face and lips, rash and feeling tired. Some of these symptoms can be serious and some patients have died (see the section “Warnings and precautions”).

You will be observed by a healthcare professional during the administration and for six hours after the start of the first administration and for two hours after the start of other administrations.

Serious side effects
Other side effects can occur at any time during treatment with Herceptin. **Tell a doctor or nurse straight away, if you notice any of the following side effects:**

- Heart problems can sometimes occur during treatment and occasionally after treatment has stopped and can be serious. They include weakening of the heart muscle possibly leading to heart failure, inflammation of the lining around the heart and heart rhythm disturbances. This can lead to symptoms such as breathlessness (including breathlessness at night), cough, fluid retention (swelling) in the legs or arms, palpitations (heart fluttering or irregular heart beat) (see section 2. Heart checks).

Your doctor will monitor your heart regularly during and after treatment but you should tell your doctor immediately if you notice any of the above symptoms.

- Tumour lysis syndrome (a group of metabolic complications occurring after cancer treatment characterized by high blood levels of potassium and phosphate, and low blood levels of calcium). Symptoms may include kidney problems (weakness, shortness of breath, fatigue and confusion), heart problems (fluttering of the heart or a faster or slower heartbeat), seizures, vomiting or diarrhoea and tingling in the mouth, hands or feet

If you experience any of the above symptoms when your treatment with Herceptin has finished, you should see your doctor and tell them that you have previously been treated with Herceptin.

Two different types (formulations) of Herceptin exist:
- one is given as an infusion into a vein over 30 to 90 minutes
- the other is given as a subcutaneous injection over 2 to 5 minutes.

In the clinical study comparing these two formulations, infections and cardiac events leading to hospitalisation were more frequent with the subcutaneous formulation. There were also more local reactions at the site of injection and more increases in blood pressure. Other side effects were similar.

Very common side effects of Herceptin: may affect more than 1 in 10 people

- infections
- diarrhoea
- constipation
- heartburn (dyspepsia)
- fatigue
- skin rashes
- chest pain
- abdominal pain
- joint pain
- low counts of red blood cells and white blood cells (which help fight infection) sometimes with fever
- muscle pain
- conjunctivitis
- watery eyes
- nose bleeds
- runny nose
- hair loss
- tremor
- hot flush
- dizziness
- nail disorders
- weight loss
- loss of appetite

- inability to sleep (insomnia)
- altered taste
- low platelet count
- bruising
- numbness or tingling of the fingers and toes
- redness, swelling or sores in your mouth and/or throat
- pain, swelling, redness or tingling of hands and/or feet
- breathlessness
- headache
- cough
- vomiting
- nausea

Common side effects of Herceptin: may affect up to 1 in 10 people

- allergic reactions
- throat infections
- bladder and skin infections
- inflammation of the breast
- inflammation of the liver
- kidney disorders
- increased muscle tone or tension (hypertonia)
- pain in the arms and/or legs
- itchy rash
- sleepiness (somnolence)
- haemorrhoids
- itchiness
- dry mouth and skin
- dry eyes
- sweating
- feeling weak and unwell
- anxiety
- depression
- asthma
- infection of lungs
- lung disorders
- back pain
- neck pain
- bone pain
- acne
- leg cramps

Uncommon side effects of Herceptin: may affect up to 1 in 100 people

- deafness
- bumpy rash
- wheezing
- inflammation or scarring of the lungs

Rare side effects of Herceptin: may affect up to 1 in 1,000 people

- jaundice
- anaphylactic reactions

Other side effects that have been reported with Herceptin use: frequency cannot be estimated from the available data

- abnormal or impaired blood clotting
- high potassium levels
- swelling or bleeding at the back of the eyes
- shock
- abnormal heart rhythm
- respiratory distress

- respiratory failure
- acute accumulation of fluid in the lungs
- acute narrowing of the airways
- abnormally low oxygen levels in the blood
- difficulty in breathing when lying flat
- liver damage
- swelling of the face, lips and throat
- kidney failure
- abnormally low levels of fluid around baby in womb
- failure of the lungs of the baby to develop in the womb
- abnormal development of the kidneys of the baby in the womb

Some of the side effects you experience may be due to your underlying breast cancer. If you receive Herceptin in combination with chemotherapy, some of them may also be due to the chemotherapy.

If you get any side effects, talk to your doctor, pharmacist or nurse.

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 Herceptin

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 outer carton and on the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Keep the vial in the outer carton to protect from light.

Do not freeze.

Upon opening of the vial, the solution should be used immediately.

Do not use this medicine if you notice any particulate matter or discoloration prior to administration.

Do not throw away any medicines via wastewater. 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 Herceptin contains

- The active substance is trastuzumab. One vial of 5 mL contains 600 mg of trastuzumab.

- The other ingredients are recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, L-methionine, polysorbate 20, water for injections.

What Herceptin looks like and contents of the pack
Herceptin is a solution for injection that is supplied in a glass vial with a butyl rubber stopper containing 5 mL (600 mg) of trastuzumab. The solution is clear to opalescent and colourless to yellowish.

Each carton contains one vial.

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Manufacturer

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

1.6.5 企業中核データシート（CDS）

CORE DATA SHEET

HERCEPTIN®
Trastuzumab

1

2ページから44ページは削除

1.7 同種同効品一覧

本申請品目の効能及び効果は、「HER2 陽性の根治切除不能な進行・再発の唾液腺癌」である。本申請における対象疾患である再発・転移唾液腺癌に対する標準療法は存在していないと考えられており、HER2 陽性に対してはトラスツズマブを始めとする抗 HER2 薬の有効性が示唆されている。しかしながら、現時点で唾液腺癌に対する適応で薬事承認されている抗 HER2 薬は存在していない。

以上の背景より、本邦では承認された競合品は存在しないと考える。

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1.8　添付文書（案）

1.8.1　効能又は効果、用法及び用量の設定理由

1.8.1.1　効能又は効果及びその設定理由

1.8.1.1.1　効能又は効果

〇HER2 過剰発現が確認された乳癌

〇HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌

〇HER2 過剰発現が確認された治癒切除不能な進行・再発の唾液腺癌

注）追加箇所に下線を付した。以下同様。

設定理由

本薬は、HER2 蛋白の細胞外領域に特異的に結合し、HER2 シグナル伝達阻害及び抗体依存性細胞障害作用により抗腫瘍効果を示すと考えられており、HER2 過剰発現が確認された乳癌及び HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌に対する適応で承認されている。

HER2 陽性の切除不能再発・転移唾液腺癌を対象に国内で実施された医師主導治験（HUON-003-01 試験）において、下表に示すように本剤とドセタキセルの併用により臨床的に意義のある奏効率（95%信頼区間）60.0（32.3～83.7）%が得られ（表）、安全性においてはトラスツズマブ及びドセタキセルの既知の安全性プロファイルと一致しており忍容可能と考えられたことから、本申請における効能又は効果を「HER2 過剰発現が確認された治癒切除不能な進行・再発の唾液腺癌」と設定した。

表　中央画像評価委員会判定の最良総合効果に基づく奏効率（FAS）

最良総合効果	結果
CR	1
PR	8
SD	5
PD	0
NE	1
奏効	9
非奏効	6
奏効率 (95%**信頼区間**) (%)	60.0 (32.3~83.7)

CR＝完全奏効；FAS=有効性解析対象集団；NE=評価不能；PD=進行；PR=部分奏効；SD=安定；奏効=CR+PR
奏効率の95%信頼区間下限が閾値である25%を上回れば、併用療法の効果が立証されたとした。
引用：治験総括報告書 表11.1-1

1.8.1.1.2　審査の結果を反映した効能又は効果

審査の過程において、以下の記載になった。

効能又は効果
○ HER2 過剰発現が確認された乳癌
○ HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌
○ HER2 陽性の根治切除不能な進行・再発の唾液腺癌

1.8.1.2　効能又は効果に関連する注意とその設定理由

1.8.1.2.1　効能又は効果に関連する注意

〈効能共通〉
HER2 過剰発現の検査は、承認された体外診断用医薬品又は医療機器を用いて、十分な経験を有する病理医又は検査施設において実施すること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である。

https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

〈HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌〉

本剤による術後補助化学療法の有効性及び安全性は確立していない。

接合部領域における原発部位、組織型等に関して「17. 臨床成績」 の項の内容を熟知し、適応患者の選択を行うこと。

〈HER2 過剰発現が確認された治癒切除不能な進行・再発の唾液腺癌〉

本剤による術後補助化学療法の有効性及び安全性は確立していない。

設定理由

コンパニオン診断を必要とする医薬品の記載整備に準じて追記した。診断薬側も承認事項一部変更申請を行う予定である。本剤の唾液腺癌術後補助化学療法の有効性及び安全性に関するエビデンスはないため、その旨追記した。

1.8.1.2.2　審査の結果を反映した効能又は効果に関連する注意

審査の過程において、以下の記載になった。

効能又は効果に関連する注意
〈HER2 過剰発現が確認された乳癌〉
5.1 HER2 過剰発現の検査は、十分な経験を有する病理医又は検査施設において実施すること。
〈HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌〉
5.2 HER2 過剰発現の検査は、十分な経験を有する病理医又は検査施設において実施すること。
5.3 本剤による術後補助療法の有効性及び安全性は確立していない。
5.4 接合部領域における原発部位、組織型等に関して「17. 臨床成績」の項の内容を熟知し、適応患者の選択を行うこと。
［17.1.10 参照］
〈HER2 陽性の根治切除不能な進行・再発の唾液腺癌〉
5.5 十分な経験を有する病理医又は検査施設における検査により、HER2 陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。

なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である。
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

1.8.1.3　用法及び用量及びその設定理由

1.8.1.3.1　用法及び用量

HER2 過剰発現が確認された乳癌には A 法又は B 法を使用する。

HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌には他の抗悪性腫瘍剤との併用で B 法を使用する。

HER2 過剰発現が確認された治癒切除不能な進行・再発の唾液腺癌には他の抗悪性腫瘍剤との併用で B 法を使用する。

A 法：通常、成人に対して 1 日 1 回、トラスツズマブ（遺伝子組換え）として初回投与時には 4mg/kg(体重)を、2 回目以降は 2mg/kg を 90 分以上かけて 1 週間間隔で点滴静注する。

B 法：通常、成人に対して 1 日 1 回、トラスツズマブ（遺伝子組換え）として初回投与時には 8mg/kg(体重)を、2 回目以降は 6mg/kg を 90 分以上かけて 3 週間間隔で点滴静注する。なお､初回投与の忍容性が良好であれば､2 回目以降の投与時間は 30 分間まで短縮できる。

設定理由

HUON-003-01 試験では既承認の用法・用量（B 法）に従って本剤の投与が行われたことから、記載を追加した。

1.8.1.3.2　審査の結果を反映した用法及び用量

審査の過程において、以下の記載になった。

用法及び用量
HER2 過剰発現が確認された乳癌には A 法又は B 法を使用する。
HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌には他の抗悪性腫瘍剤との併用で B 法を使用する。
HER2 陽性の根治切除不能な進行・再発の唾液腺癌にはドセタキセル製剤との併用で B 法を使用する。
A 法：通常、成人に対して 1 日 1 回、トラスツズマブ（遺伝子組換え）として初回投与時には 4mg/kg（体重）を、2 回目以降は 2mg/kg を 90 分以上かけて 1 週間間隔で点滴静注する。
B 法：通常、成人に対して 1 日 1 回、トラスツズマブ（遺伝子組換え）として初回投与時には 8mg/kg（体重）を、2 回目以降は 6mg/kg を 90 分以上かけて 3 週間間隔で点滴静注する。
なお、初回投与の忍容性が良好であれば、2 回目以降の投与時間は 30 分間まで短縮できる。

1.8.1.4　用法及び用量に関連する注意とその設定理由

1.8.1.4.1　用法及び用量に関連する注意

〈効能共通〉

本剤を投与する場合に、何らかの理由により予定された投与が遅れた際には、以下のとおり投与することが望ましい。

投与予定日より 1 週間以内の遅れで投与する際は、A 法では 2mg/kg を、B 法では 6mg/kg を投与する。

投与予定日より 1 週間を超えた後に投与する際は、改めて初回 投与量（A 法では 4mg/kg、B 法では 8mg/kg）で投与を行う。なお、次回以降は A 法では 2mg/kg を 1 週間間隔で、B 法では 6mg/kg を 3 週間間隔で投与する。

〈HER2 過剰発現が確認された乳癌〉

術後補助化学療法においては、以下の点に注意すること。

1 年を超える投与の有効性及び安全性は確立していない。

本剤は「17.臨床成績」の項を熟知した上で投与すること。

1.8.1.4.2　審査の結果を反映した用法及び用量に関連する注意

審査の過程において、以下の記載になった。

用法及び用量に関連する注意
〈効能共通〉
7.1 本剤を投与する場合に、何らかの理由により予定された投与が遅れた際には、以下のとおり投与することが望ましい。
7.1.1 投与予定日より 1 週間以内の遅れで投与する際は、A 法では 2mg/kg を、B 法では 6mg/kg を投与する。
7.1.2 投与予定日より 1 週間を超えた後に投与する際は、改めて初回投与量（A 法では 4mg/kg、B 法では 8mg/kg）で投与を行う。なお、次回以降は A 法では 2mg/kg を 1 週間間隔で、B 法では 6mg/kg を 3 週間間隔で投与する。
〈HER2 過剰発現が確認された乳癌〉
7.2 術後薬物療法においては、以下の点に注意すること。
7.2.1 1 年を超える投与の有効性及び安全性は確立していない。
7.2.2 本剤は「17.臨床成績」の項を熟知した上で投与すること。［17.1.9 参照］
〈HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌〉
7.3 本剤は、他の抗悪性腫瘍剤との併用により開始すること。本剤と併用する抗悪性腫瘍剤は、「17.臨床成績」の項の内容を熟知した上で、選択すること。［17.1.10 参照］

1.8.2　使用上の注意の設定根拠

使用上の注意（案）	設定根拠
1.警告 1.1　本剤を含むがん化学療法は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤が適切と判断される症例についてのみ実施すること。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。 1.2　心不全等の重篤な心障害があらわれ、死亡に至った例も報告されているので、必ず本剤投与開始前には、患者の心機能を確認すること。また、本剤投与中は適宜心機能検査（心エコー等）を行い患者の状態（左室駆出率（LVEF）の変動を含む）を十分に観察すること。特に以下の患者については、心機能検査（心エコー等）を頻回に行うこと。［8.1、9.1.1-9.1.7、11.1.1参照］ ・アントラサイクリン系薬剤を投与中の患者又はその前治療歴のある患者 ・胸部へ放射線を照射中の患者 ・心不全症状のある患者 ・冠動脈疾患（心筋梗塞、狭心症等）の患者又はその既往歴のある患者 ・高血圧症の患者又はその既往歴のある患者 1.3 本剤投与中又は本剤投与開始後24時間以内に多くあらわれるInfusion reactionのうち、アナフィラキシー、肺障害等の重篤な副作用（気管支痙攣、重度の血圧低下、急性呼吸促迫症候群等）が発現し死亡に至った例が報告されている。これらの副作用は、特に安静時呼吸困難（肺転移、循環器疾患等による）のある患者又はその既往歴のある患者において重篤化しやすいので、患者の状態を十分に観察しながら慎重に投与すること。［9.1.8、11.1.2、11.1.3参照］	変更なし。
2.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	変更なし。
8.重要な基本的注意 ＜効能共通＞ 8.1 心障害があらわれることがあるので、本剤投与開始前には、必ず患者の心機能を確認すること。本剤投与中は心症状の発現状況・重篤度等に応じて適宜心機能検査（心エコー等）を行い、患者の状態（左室駆出率（LVEF）の変動を含む）を十分に観察し、休薬、投与再開、あるいは中止を判断すること。［1.2、9.1.1-9.1.7、11.1.1参照］ 8.2 Infusion reactionの発現回避等を目的とした前投薬（抗ヒスタミン剤、副腎皮質ホルモン剤等）に関する有用性は確認されていない。 8.3 腫瘍崩壊症候群があらわれることがあるので、血清中電解質濃度及び腎機能検査を行うなど、患者の状態を十分に観察すること。［11.1.9参照］ 8.4 本剤の使用にあたっては、本剤と一般名が類似しているトラスツズマブ エムタンシン及びトラスツズマブ　デルクステカンとの取り違えに注意すること。 ＜HER2過剰発現が確認された乳癌＞ 8.5 術前薬物療法（A法、B法）、術後薬物療法のA法及び転移性乳癌のB法に本剤を使用する際には、関連文献（「医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書」[1)-3)] 等）を熟読すること。	＜効能共通＞、＜HER2過剰発現が確認された乳癌＞に分けて記載した。 8.1～8.5 記載内容に変更はないが、見出し項目の追加により、8.4と8.5の順番を入れ替えた。また、8.5の記載整備を行った。
9.特定の背景を有する患者に関する注意 9.1 合併症・既往歴等のある患者 9.1.1 重篤な心障害のある患者	変更なし。

<table>
<tr><th>使用上の注意（案）</th><th>設定根拠</th></tr>
<tr><td>治療上やむを得ないと判断される場合を除き、投与しないこと。[1.2、8.1、11.1.1参照]
9.1.2 アントラサイクリン系薬剤の前治療歴のある患者
心不全等の心障害があらわれやすい。[1.2、8.1、11.1.1参照]
9.1.3 胸部へ放射線を照射中の患者
胸部への放射線照射との併用時には、放射線の適切な治療計画を設定した上で、心障害の発現に留意すること。心不全等の心障害があらわれやすい。[1.2、8.1、11.1.1参照]
9.1.4 心不全症状のある患者又はその既往歴のある患者
症状が悪化するおそれがある。[1.2、8.1、11.1.1参照]
9.1.5 左室駆出率（LVEF）が低下している患者、コントロール不能な不整脈のある患者、臨床上重大な心臓弁膜症のある患者
症状が悪化するおそれがある。[1.2、8.1、11.1.1参照]
9.1.6 冠動脈疾患（心筋梗塞、狭心症等）の患者又はその既往歴のある患者
症状が悪化するおそれがある。又は心不全等の心障害があらわれやすい。[1.2、8.1、11.1.1参照]
9.1.7 高血圧症の患者又はその既往歴のある患者
心不全等の心障害があらわれやすい。[1.2、8.1、11.1.1参照]
9.1.8 安静時呼吸困難（肺転移、循環器疾患等による）のある患者又はその既往歴のある患者
Infusion reaction が重篤化しやすい。[1.3、11.1.2、11.1.3参照]
9.4 生殖能を有する者
妊娠する可能性のある女性には、本剤投与中及び投与終了後最低 7 カ月間は、適切な避妊法を用いるよう指導すること。[9.5 参照]
9.5 妊婦
妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤を投与した妊婦に羊水過少が起きたとの報告がある。また、羊水過少を発現した症例で、胎児・新生児の腎不全、胎児発育遅延、新生児呼吸窮迫症候群、胎児の肺形成不全等が認められ死亡に至った例も報告されている。動物実験（サル）において、胎盤通過（1、5、25mg/kg 反復投与）が報告されている[4]が、胎児への影響は報告されていない。[9.4 参照]
9.6 授乳婦
治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。ヒトでの乳汁移行に関するデータはないが、ヒト IgG は母乳中に移行することが報告されている。また、動物実験（サル）において、乳汁への移行（25mg/kg 反復投与）が報告されている[5]。
9.7 小児等
小児等を対象とした臨床試験は実施していない。
9.8 高齢者
特に心機能、肝・腎機能検査、血液検査を行うなど患者の状態を観察しながら慎重に投与すること。高齢者では生理機能が低下している。</td><td></td></tr>
<tr><td>10.相互作用
10.2 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>アントラサイクリン系薬剤</td><td>心障害の発現頻度が上昇することが報告されているので、特に注意すること。</td><td>心障害のリスクを増強させるおそれがある。</td></tr>
</table></td><td>変更なし。</td></tr>
</table>

使用上の注意（案）	設定根拠
11.副作用 次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。 11.1　重大な副作用 11.1.1 心障害 心不全（4.5%）（症候：呼吸困難、起座呼吸、咳嗽等、症状・異常：S3 ギャロップ、駆出率低下、末梢性浮腫等）、心原性ショック（頻度不明）、肺浮腫（頻度不明）、心嚢液貯留（0.1%）、心筋症（0.4%）、心膜炎（頻度不明）、不整脈（1.4%）、徐脈（0.1%）等が報告されている。異常が認められた場合には、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継続を検討し、適切な処置を行うこと。ただし、症状が重篤な場合には、投与を中止し、適切な処置を行うこと。［1.2、8.1、9.1.1-9.1.7 参照］ 11.1.2 Infusion reaction（頻度不明） 本剤投与中又は投与開始後 24 時間以内に多くあらわれる Infusion reaction（症状：発熱、悪寒、悪心、嘔吐、疼痛、頭痛、咳嗽、めまい、発疹、無力症等）が約 40%の患者において報告されている（HER2 過剰発現が確認された転移性乳癌の承認時）。これらの症状は、通常軽度～中等度で主に本剤の初回投与時にあらわれやすい。また、Infusion reaction のうち、ショック、アナフィラキシー、肺障害等の重篤な副作用（気管支痙攣、重度の血圧低下、急性呼吸促迫症候群、頻脈、顔面浮腫、眩暈、耳鳴、呼吸困難、喘息、喘鳴、血管浮腫、咽頭浮腫、呼吸不全、非心原性肺浮腫、胸水、低酸素症等）が発現し死亡に至った例が報告されている。本剤投与中にこれらの異常が認められた場合には直ちに投与を中止すること。なお、このような症状があらわれた患者において再投与の可否を判断する基準は確立していない。 異常が認められた場合には、適切な処置（酸素吸入、β-アゴニスト・副腎皮質ホルモン剤、解熱鎮痛剤、抗ヒスタミン剤の投与等）を行うとともに症状が回復するまで患者の状態を十分に観察すること。［1.3、9.1.8、11.1.3 参照］ 11.1.3 間質性肺炎・肺障害 間質性肺炎（0.2%）、肺線維症（頻度不明）、肺炎（アレルギー性肺炎等を含む）（0.3%）、急性呼吸促迫症候群（0.1%未満）等の肺障害があらわれることがある。［1.3、9.1.8、11.1.2 参照］ 11.1.4 白血球減少（4.4%）、好中球減少（6.9%）、血小板減少（1.9%）、貧血（3.7%） 11.1.5 肝不全（0.1%未満）、黄疸（0.1%）、肝炎（0.1%）、肝障害（0.5%） 11.1.6 腎障害 腎不全（0.2%）、腎障害（1.0%）があらわれることがある。 11.1.7 昏睡（頻度不明）、脳血管障害（0.2%）、脳浮腫（頻度不明） 11.1.8 敗血症（0.2%） 11.1.9 腫瘍崩壊症候群（頻度不明） 異常が認められた場合には投与を中止し、適切な処置（生理食塩液、高尿酸血症治療剤等の投与、透析等）を行うとともに、症状が回復するまで患者の状態を十分に観察すること。［8.3 参照］ 注）発現頻度は HER2 過剰発現の腫瘍に対する海外臨床試験［H0407g 試験、H0452g 試験、H0453g 試験］、HER2 過剰発現の転移性乳癌に対する海外臨床試験［H0551g 試験、H0552g 試験、H0648g 試験、H0649g 試験、H0650g 試験、H0659g 試験、H0693g 試験］、HER2 過剰発現の進行・再発乳癌に対する国内臨床試験［MKC-454-02 試験］、HER2 過剰発現の転移性乳癌に対する製造販売後臨床試験、HER2 過剰発現の転移性乳癌に対する使用成績調査、HER2 過剰発現が確認された乳癌（術後薬物療法）に対する国際共同試験［HERA 試験］、HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌に対する国際共同試験［ToGA 試験］及び HER2 陽性の根治切除不能な進行・再発の唾液	11.1 HER2陽性の根治切除不能な進行・再発の唾液腺癌に対する国内臨床試験［HUON-003-01試験］のデータを含めて集計を行ったため、注釈に本試験を追記した。 11.1.3、11.1.4 HER2陽性の根治切除不能な進行・再発の唾液腺癌に対する国内臨床試験［HUON-003-01試験］の副作用データを含めて集計し、頻度の変更があった副作用の頻度を更新した。 11.2.1、11.2.2、11.2.3 変更なし 11.2.4の追加 HER2陽性の根治切除不能な進行・再発の唾液腺癌に対する国内臨床試験［HUON-003-01試験］の副作用の発現頻度表を作成した。

使用上の注意（案）	設定根拠

腺癌に対する国内臨床試験［HUON-003-01 試験］含む。

11.2 その他の副作用

11.2.1 HER2 過剰発現が確認された転移性乳癌

	10%以上	2～10%未満	2%未満	頻度不明
精神神経系		頭痛、めまい、味覚異常、感覚鈍麻、ニューロパチー	錯感覚、不眠症、不安、うつ病、傾眠、筋緊張亢進	運動失調、不全麻痺、しびれ（感）、思考異常
消化器	悪心・嘔吐（16.8%）	下痢、食欲不振、口内炎、便秘、腹痛	上腹部痛、消化不良、腸炎	
循環器			低血圧、頻脈、潮紅、高血圧、動悸、熱感	血管拡張
呼吸器		呼吸困難、咳嗽、鼻出血	胸水、喘息	
血液				プロトロンビン減少
皮膚		発疹、脱毛症、爪の障害、瘙痒症	紅斑、皮膚乾燥、蕁麻疹、皮膚炎、斑状丘疹状皮疹、発汗、痤瘡	
肝臓			AST 増加、ALT 増加	
眼			流涙増加、結膜炎、視力障害	
その他	発熱（31.5%）、悪寒（20.0%）、疲労（10.5%）	倦怠感、関節痛、疼痛、浮腫、背部痛、無力症、筋肉痛、胸痛、末梢性浮腫、四肢痛	上気道感染（鼻炎、鼻咽頭炎、咽頭炎、副鼻腔炎等）、胸部不快感、骨痛、頚部痛、尿路感染症、難聴、感染症	

注）発現頻度は HER2 過剰発現の腫瘍に対する海外臨床試験［H0407g 試験、H0452g 試験、H0453g 試験］、HER2 過剰発現の転移性乳癌に対する海外臨床試験［H0551g 試験、H0552g 試験、H0648g 試験、H0649g 試験、H0650g 試験、H0659g 試験、H0693g 試験］、HER2 過剰発現の進行・再発乳癌に対する国内臨床試験［MKC-454-02 試験］、HER2 過剰発現の転移性乳癌に対する製造販売後臨床試験及び HER2 過剰発現の転移性乳癌に対する使用成績調査を含む。

11.2.2 HER2 過剰発現が確認された乳癌における術後薬物療法

	1%以上	0.2～1%未満	0.2%未満	頻度不明
精神神経系	頭痛	めまい、錯感覚、振戦、嗜眠、不眠症、味覚異常、不		感覚鈍麻、ニューロパチー

使用上の注意（案）	設定根拠

		安、うつ病、回転性眩暈		
消化器	悪心、下痢、嘔吐	口内炎、腹痛、消化不良	上腹部痛、便秘、胃炎	口内乾燥、口腔内潰瘍形成、鼓腸
循環器	動悸	高血圧、頻脈、熱感	リンパ浮腫	ほてり、低血圧、潮紅
呼吸器	呼吸困難	鼻漏、鼻出血	咽喉頭疼痛、咳嗽、副鼻腔炎、気管支炎	鼻乾燥、鼻潰瘍、鼻部不快感
皮膚	爪の障害、発疹、瘙痒症	紅斑、痤瘡		爪破損、皮膚乾燥、皮膚亀裂
腎臓			排尿困難	
その他	無力症、悪寒、発熱、疲労、関節痛、筋肉痛、インフルエンザ様疾患、上気道感染（鼻炎、鼻咽頭炎、咽頭炎等）	末梢性浮腫、背部痛、筋痙縮、胸部不快感、粘膜の炎症、倦怠感、骨痛、胸痛、インフルエンザ	浮腫、筋骨格痛、膀胱炎、尿路感染症、丹毒	帯状疱疹、乳房痛、蜂巣炎、四肢痛、流涙増加、体重増加、冷感、疼痛、粘膜乾燥、霧視、筋骨格硬直

11.2.3 HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌

	10%以上	2～10%未満	2%未満
精神神経系	ニューロパチー	味覚異常、浮動性めまい、不眠症、錯感覚	頭痛、嗜眠
消化器	悪心、嘔吐、食欲不振、下痢、口内炎、便秘	腹痛、上腹部痛	消化不良、口内乾燥、嚥下障害
循環器		高血圧	動悸、潮紅、起立性低血圧
呼吸器		しゃっくり、鼻出血	咳嗽、呼吸困難
血液		ヘモグロビン減少	
皮膚	手掌・足底発赤知覚不全症候群	色素沈着障害、脱毛症、爪の障害、発疹、皮膚乾燥	瘙痒症
腎臓		腎クレアチニン・クリアランス減少、中毒性ネフロパシー	
その他	疲労、無力症、粘膜の炎症、体重減少	発熱、悪寒、脱水、低カリウム血症、低ナトリウム血症、上気道感染、難聴、浮腫、末梢性浮	倦怠感、低アルブミン血症、体重増加

使用上の注意（案）	設定根拠

		腫、高クレアチニン血症、口腔カンジダ症、耳鳴、過敏症	

11.2.4 HER2陽性の根治切除不能な進行・再発の唾液腺癌

	30%以上	20～30%未満	20%未満
消化器			口内炎、上腹部痛、嘔吐、食欲不振
呼吸器		胸水	気管支炎、呼吸困難
皮膚			爪甲剥離症、皮膚乾燥、脱毛症
肝臓		ALT 増加	
眼			流涙増加
血液			リンパ球数減少
その他	倦怠感、末梢性浮腫、低アルブミン血症		体重増加、顔面浮腫、発熱、低カルシウム血症、血中乳酸脱水素酵素増加

14. 適用上の注意
14.1 薬剤調製時の注意
14.1.1 本剤の調製時には、下記の体重あたりの換算式により、投与に必要な抜き取り量を算出すること。
・ A 法：
初回　抜き取り量（mL）＝体重（kg）×4（mg/kg）／21（mg/mL）
2回目以降　抜き取り量（mL）＝体重（kg）×2（mg/kg）／21（mg/mL）
・ B 法：
初回　抜き取り量（mL）＝体重（kg）×8（mg/kg）／21（mg/mL）
2回目以降　抜き取り量（mL）＝体重（kg）×6（mg/kg）／21（mg/mL）
14.1.2 調製時には、日局注射用水、日局生理食塩液以外は使用しないこと。
14.1.3 ブドウ糖溶液と混合した場合、蛋白凝集が起こるため、添付の日局注射用水（注射用60：3.0mL、注射用150：7.2mL）により溶解してトラスツズマブ（遺伝子組換え）21mg/mL の濃度とした後、必要量を注射筒で抜き取り、直ちに日局生理食塩液250mL に希釈すること。
14.1.4 本剤はポリソルベートを含有しており、泡立ちやすいため、溶解時は静かに転倒混和し、ほぼ泡が消えるまで数分間放置する。
14.1.5 用時調製し、調製後は速やかに使用すること。また、残液は廃棄すること。
14.2 薬剤投与時の注意
14.2.1 本剤と5%ブドウ糖溶液を混合した場合、蛋白凝集が起こるため、ブドウ糖溶液との混合を避け、本剤とブドウ糖溶液の同じ点滴ラインを用いた同時投与は行わないこと。
14.2.2 他剤との混注をしないこと。

変更なし。

使用上の注意（案）	設定根拠
15.その他の注意 15.1 臨床使用に基づく情報 15.1.1 本剤投与により抗トラスツズマブ抗体が出現したとの報告（921例中1例）があるが、当該症例において副作用は認められなかった。 15.1.2 本剤と他の抗悪性腫瘍剤を併用した患者に、急性白血病、骨髄異形成症候群（MDS）が発生したとの報告がある。 15.1.3 無作為化比較試験にて、骨髄抑制を有する他の抗悪性腫瘍剤に本剤を併用した場合、その抗悪性腫瘍剤単独と比較し発熱性好中球減少の発現率が上昇したとの報告がある。	変更なし。

最新の添付文書を参照すること

20**年**月改訂（第*版）

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貯　　法：2～8℃保存

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注 1）HER2：Human Epidermal Growth Factor Receptor Type 2（ヒト上皮増殖因子受容体 2 型、別称：c-erbB-2）

注 2）注意－医師等の処方箋により使用すること

抗HER2[注1)] ヒト化モノクローナル抗体　抗悪性腫瘍剤

トラスツズマブ（遺伝子組換え）製剤

生物由来製品、処方箋医薬品[注2)]

ハーセプチン®注射用60

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	注射用 60	注射用 150
承認番号	21600AMY00065	21300AMY00128
販売開始	2004 年 8 月	2001 年 6 月

CHUGAI

Roche ロシュ グループ

1. 警告

1.1 本剤を含むがん化学療法は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤が適切と判断される症例についてのみ実施すること。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。

1.2 心不全等の重篤な心障害があらわれ、死亡に至った例も報告されているので、必ず本剤投与開始前には、患者の心機能を確認すること。また、本剤投与中は適宜心機能検査（心エコー等）を行い患者の状態（左室駆出率（LVEF）の変動を含む）を十分に観察すること。特に以下の患者については、心機能検査（心エコー等）を頻回に行うこと。[8.1、9.1.1-9.1.7、11.1.1 参照]

- アントラサイクリン系薬剤を投与中の患者又はその前治療歴のある患者
- 胸部へ放射線を照射中の患者
- 心不全症状のある患者
- 冠動脈疾患（心筋梗塞、狭心症等）の患者又はその既往歴のある患者
- 高血圧症の患者又はその既往歴のある患者

1.3 本剤投与中又は本剤投与開始後 24 時間以内に多くあらわれる Infusion reaction のうち、アナフィラキシー、肺障害等の重篤な副作用（気管支痙攣、重度の血圧低下、急性呼吸促迫症候群等）が発現し死亡に至った例が報告されている。これらの副作用は、特に安静時呼吸困難（肺転移、循環器疾患等による）のある患者又はその既往歴のある患者において重篤化しやすいので、患者の状態を十分に観察しながら慎重に投与すること。[9.1.8 、11.1.2、11.1.3 参照]

2. 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

3. 組成・性状

3.1 組成

販売名	ハーセプチン注射用 60	ハーセプチン注射用 150
有効成分	1 バイアル中	1 バイアル中
	トラスツズマブ（遺伝子組換え）注）60mg	トラスツズマブ（遺伝子組換え）注）150mg
添加剤	1 バイアル中 トレハロース水和物 54.48mg L-ヒスチジン塩酸塩水和物 1.34mg L-ヒスチジン 0.86mg ポリソルベート 20 0.24mg	1 バイアル中 トレハロース水和物 136.2mg L-ヒスチジン塩酸塩水和物 3.36mg L-ヒスチジン 2.16mg ポリソルベート 20 0.6mg

注）本剤は、チャイニーズハムスター卵巣細胞を用いて製造される。製造工程の培地成分としてブタ由来成分（ペプトン）を使用している。

3.2 製剤の性状

販売名	ハーセプチン注射用 60	ハーセプチン注射用 150
剤形	注射剤（バイアル）	
性状	白色～微黄色の塊	
溶解液	日局注射用水 3.0mL	日局注射用水 7.2mL
浸透圧比（生理食塩液に対する比）	1.0（日局注射用水及び日局生理食塩液にて調製後）	
日局注射用水に溶解後の性状は下記のとおり		
溶状	澄明又はわずかに乳白光を呈する、無色～微黄色の液である。	
pH	5.8～6.4	
浸透圧	55～70mOsm/kg	

4. 効能又は効果

○ HER2 過剰発現が確認された乳癌

○ HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌

○ HER2 陽性の根治切除不能な進行・再発の唾液腺癌

5. 効能又は効果に関連する注意

〈HER2 過剰発現が確認された乳癌〉

5.1 HER2 過剰発現の検査は、十分な経験を有する病理医又は検査施設において実施すること。

〈HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌〉

5.2 HER2 過剰発現の検査は、十分な経験を有する病理医又は検査施設において実施すること。

5.3 本剤による術後補助療法の有効性及び安全性は確立していない。

5.4 接合部領域における原発部位、組織型等に関して「17. 臨床成績」の項の内容を熟知し、適応患者の選択を行うこと。［17.1.10 参照］

〈HER2 陽性の根治切除不能な進行・再発の唾液腺癌〉

5.5 十分な経験を有する病理医又は検査施設における検査により、HER2 陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である。
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

6. 用法及び用量

HER2 過剰発現が確認された乳癌には A 法又は B 法を使用する。

HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌には他の抗悪性腫瘍剤との併用で B 法を使用する。

HER2 陽性の根治切除不能な進行・再発の唾液腺癌にはドセタキセル製剤との併用で B 法を使用する。

A 法：通常、成人に対して 1 日 1 回、トラスツズマブ（遺伝子組換え）として初回投与時には 4mg/kg（体重）を、2 回目以降は 2mg/kg を 90 分以上かけて 1 週間間隔で点滴静注する。

B 法：通常、成人に対して 1 日 1 回、トラスツズマブ（遺伝子組換え）として初回投与時には 8mg/kg（体重）を、2 回目以降は 6mg/kg を 90 分以上かけて 3 週間間隔で点滴静注する。

なお、初回投与の忍容性が良好であれば、2 回目以降の投与時間は 30 分間まで短縮できる。

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 本剤を投与する場合に、何らかの理由により予定された投与が遅れた際には、以下のとおり投与することが望ましい。

7.1.1 投与予定日より 1 週間以内の遅れで投与する際は、A 法では 2mg/kg を、B 法では 6mg/kg を投与する。

7.1.2 投与予定日より 1 週間を超えた後に投与する際は、改めて初回投与量（A 法では 4mg/kg、B 法では 8mg/kg）で投与を行う。なお、次回以降は A 法では 2mg/kg を 1 週間間隔で、B 法では 6mg/kg を 3 週間間隔で投与する。

〈HER2 過剰発現が確認された乳癌〉

7.2 術後薬物療法においては、以下の点に注意すること。

7.2.1 1 年を超える投与の有効性及び安全性は確立していない。

7.2.2 本剤は「17.臨床成績」の項を熟知した上で投与すること。［17.1.9 参照］

〈HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌〉

7.3 本剤は、他の抗悪性腫瘍剤との併用により開始すること。本剤と併用する抗悪性腫瘍剤は、「17.臨床成績」の項の内容を熟知した上で、選択すること。［17.1.10 参照］

8. 重要な基本的注意

〈効能共通〉

8.1 心障害があらわれることがあるので、本剤投与開始前には、必ず患者の心機能を確認すること。本剤投与中は心症状の発現状況・重篤度等に応じて適宜心機能検査（心エコー等）を行い、患者の状態（左室駆出率（LVEF）の変動を含む）を十分に観察し、休薬、投与再開、あるいは中止を判断すること。［1.2、9.1.1-9.1.7、11.1.1 参照］

8.2 Infusion reaction の発現回避等を目的とした前投薬（抗ヒスタミン剤、副腎皮質ホルモン剤等）に関する有用性は確認されていない。

8.3 腫瘍崩壊症候群があらわれることがあるので、血清中電解質濃度及び腎機能検査を行うなど、患者の状態を十分に観察すること。［11.1.9 参照］

8.4 本剤の使用にあたっては、本剤と一般名が類似しているトラスツズマブ　エムタンシン及びトラスツズマブ　デルクステカンとの取り違えに注意すること。

〈HER2 過剰発現が確認された乳癌〉

8.5 術前薬物療法（A 法、B 法）、術後薬物療法の A 法及び転移性乳癌の B 法に本剤を使用する際には、関連文献（「医療上の必要性の高い未承認薬・適応外薬検討会議　公知申請への該当性に係る報告書」1)-3)等）を熟読すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 重篤な心障害のある患者

治療上やむを得ないと判断される場合を除き、投与しないこと。［1.2、8.1、11.1.1 参照］

9.1.2 アントラサイクリン系薬剤の前治療歴のある患者

心不全等の心障害があらわれやすい。［1.2、8.1、11.1.1 参照］

9.1.3 胸部へ放射線を照射中の患者

胸部への放射線照射との併用時には、放射線の適切な治療計画を設定した上で、心障害の発現に留意すること。心不全等の心障害があらわれやすい。［1.2、8.1、11.1.1 参照］

9.1.4 心不全症状のある患者又はその既往歴のある患者

症状が悪化するおそれがある。［1.2、8.1、11.1.1 参照］

9.1.5 左室駆出率（LVEF）が低下している患者、コントロール不能な不整脈のある患者、臨床上重大な心臓弁膜症のある患者

症状が悪化するおそれがある。［1.2、8.1、11.1.1 参照］

9.1.6 冠動脈疾患（心筋梗塞、狭心症等）の患者又はその既往歴のある患者

症状が悪化するおそれがある。又は心不全等の心障害があらわれやすい。［1.2、8.1、11.1.1 参照］

9.1.7 高血圧症の患者又はその既往歴のある患者

心不全等の心障害があらわれやすい。［1.2、8.1、11.1.1 参照］

9.1.8 安静時呼吸困難（肺転移、循環器疾患等による）のある患者又はその既往歴のある患者

Infusion reaction が重篤化しやすい。［1.3、11.1.2、11.1.3 参照］

9.4 生殖能を有する者

妊娠する可能性のある女性には、本剤投与中及び投与終了後最低 7 カ月間は、適切な避妊法を用いるよう指導すること。［9.5 参照］

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤を投与した妊婦に羊水過少が起きたとの報告がある。また、羊水過少を発現した症例で、胎児・新生児の腎不全、胎児発育遅延、新生児呼吸窮迫症候群、胎児の肺形成不全等が認められ死亡に至った例も報告されている。動物実験（サル）において、胎盤通過（1、5、25mg/kg 反復投与）が報告されている[4]が、胎児への影響は報告されていない。［9.4 参照］

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。ヒトでの乳汁移行に関するデータはないが、ヒト IgG は母乳中に移行することが報告されている。ま

た、動物実験（サル）において、乳汁への移行（25mg/kg 反復投与）が報告されている[5]。

9.7 小児等

小児等を対象とした臨床試験は実施していない。

9.8 高齢者

特に心機能、肝・腎機能検査、血液検査を行うなど患者の状態を観察しながら慎重に投与すること。高齢者では生理機能が低下している。

10. 相互作用

10.2 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
アントラサイクリン系薬剤	心障害の発現頻度が上昇することが報告されているので、特に注意すること。	心障害のリスクを増強させるおそれがある。

11. 副作用

次の副作用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は投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 心障害

心不全（4.5%）（症候：呼吸困難、起座呼吸、咳嗽等、症状・異常：S3 ギャロップ、駆出率低下、末梢性浮腫等）、心原性ショック（頻度不明）、肺浮腫（頻度不明）、心嚢液貯留（0.1%）、心筋症（0.4%）、心膜炎（頻度不明）、不整脈（1.4%）、徐脈（0.1%）等が報告されている。

異常が認められた場合には、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継続を検討し、適切な処置を行うこと。

ただし、症状が重篤な場合には、投与を中止し、適切な処置を行うこと。［1.2、8.1、9.1.1-9.1.7 参照］

11.1.2 Infusion reaction（頻度不明）

本剤投与中又は投与開始後 24 時間以内に多くあらわれる Infusion reaction（症状：発熱、悪寒、悪心、嘔吐、疼痛、頭痛、咳嗽、めまい、発疹、無力症等）が約 40%の患者において報告されている（HER2 過剰発現が確認された転移性乳癌の承認時）。これらの症状は、通常軽度～中等度で主に本剤の初回投与時にあらわれやすい。

また、Infusion reaction のうち、ショック、アナフィラキシー、肺障害等の重篤な副作用（気管支痙攣、重度の血圧低下、急性呼吸促迫症候群、頻脈、顔面浮腫、眩暈、耳鳴、呼吸困難、喘息、喘鳴、血管浮腫、咽頭浮腫、呼吸不全、非心原性肺浮腫、胸水、低酸素症等）が発現し死亡に至った例が報告されている。本剤投与中にこれらの異常が認められた場合には直ちに投与を中止すること。なお、このような症状があらわれた患者において再投与の可否を判断する基準は確立していない。

異常が認められた場合には、適切な処置（酸素吸入、β-アゴニスト・副腎皮質ホルモン剤、解熱鎮痛剤、抗ヒスタミン剤の投与等）を行うとともに症状が回復するまで患者の状態を十分に観察すること。［1.3、9.1.8、11.1.3 参照］

11.1.3 間質性肺炎・肺障害

間質性肺炎（0.2%）、肺線維症（頻度不明）、肺炎（アレルギー性肺炎等を含む）（0.3%）、急性呼吸促迫症候群（0.1%未満）等の肺障害があらわれることがある。［1.3、9.1.8、11.1.3 参照］

11.1.4 白血球減少（4.4%）、好中球減少（6.9%）、血小板減少（1.9%）、貧血（3.7%）

11.1.5 肝不全（0.1%未満）、黄疸（0.1%）、肝炎（0.1%）、肝障害（0.5%）

11.1.6 腎障害

腎不全（0.2%）、腎障害（1.0%）があらわれることがある。

11.1.7 昏睡（頻度不明）、脳血管障害（0.2%）、脳浮腫（頻度不明）

11.1.8 敗血症（0.2%）

11.1.9 腫瘍崩壊症候群（頻度不明）

異常が認められた場合には投与を中止し、適切な処置（生理食塩液、高尿酸血症治療剤等の投与、透析等）を行うとともに、症状が回復するまで患者の状態を十分に観察すること。［8.3 参照］

注）発現頻度は HER2 過剰発現の腫瘍に対する海外臨床試験［H0407g 試験、H0452g 試験、H0453g 試験］、HER2 過剰発現の転移性乳癌に対する海外臨床試験［H0551g 試験、H0552g 試験、H0648g 試験、H0649g 試験、H0650g 試験、H0659g 試験、H0693g 試験］、HER2 過剰発現の進行・再発乳癌に対する国内臨床試験［MKC-454-02 試験］、HER2 過剰発現の転移性乳癌に対する製造販売後臨床試験、HER2 過剰発現の転移性乳癌に対する使用成績調査、HER2 過剰発現が確認された乳癌（術後薬物療法）に対する国際共同試験［HERA 試験］、HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌に対する国際共同試験［ToGA 試験］及び HER2 陽性の根治切除不能な進行・再発の唾液腺癌に対する国内臨床試験［HUON-003-01 試験］を含む。

11.2 その他の副作用

11.2.1 HER2 過剰発現が確認された転移性乳癌

	10%以上	2～10%未満	2%未満	頻度不明
精神神経系		頭痛、めまい、味覚異常、感覚鈍麻、ニューロパチー	錯感覚、不眠症、不安、うつ病、傾眠、筋緊張亢進	運動失調、不全麻痺、しびれ（感）、思考異常
消化器	悪心・嘔吐（16.8%）	下痢、食欲不振、口内炎、便秘、腹痛	上腹部痛、消化不良、腸炎	
循環器			低血圧、頻脈、潮紅、高血圧、動悸、熱感	血管拡張
呼吸器		呼吸困難、咳嗽、鼻出血	胸水、喘息	
血液				プロトロンビン減少
皮膚		発疹、脱毛症、爪の障害、瘙痒症	紅斑、皮膚乾燥、蕁麻疹、皮膚炎、斑状丘疹状皮疹、発汗、痤瘡	
肝臓			AST 増加、ALT 増加	
眼			流涙増加、結膜	

			炎、視力障害	
その他	発熱（31.5%）、悪寒（20.0%）、疲労（10.5%）	倦怠感、関節痛、疼痛、浮腫、背部痛、無力症、筋肉痛、胸痛、末梢性浮腫、四肢痛	上気道感染（鼻炎、鼻咽頭炎、咽頭炎、副鼻腔炎等）、胸部不快感、骨痛、頚部痛、尿路感染症、難聴、感染症	

注）発現頻度はHER2過剰発現の腫瘍に対する海外臨床試験［H0407g試験、H0452g試験、H0453g試験］、HER2過剰発現の転移性乳癌に対する海外臨床試験［H0551g試験、H0552g試験、H0648g試験、H0649g試験、H0650g試験、H0659g試験、H0693g試験］、HER2過剰発現の進行・再発乳癌に対する国内臨床試験［MKC-454-02試験］、HER2過剰発現の転移性乳癌に対する製造販売後臨床試験及びHER2過剰発現の転移性乳癌に対する使用成績調査を含む。

11.2.2 HER2 過剰発現が確認された乳癌における術後薬物療法

	1%以上	0.2～1%未満	0.2%未満	頻度不明
精神神経系	頭痛	めまい、錯感覚、振戦、嗜眠、不眠症、味覚異常、不安、うつ病、回転性眩暈		感覚鈍麻、ニューロパチー
消化器	悪心、下痢、嘔吐	口内炎、腹痛、消化不良	上腹部痛、便秘、胃炎	口内乾燥、口腔内潰瘍形成、鼓腸
循環器	動悸	高血圧、頻脈、熱感	リンパ浮腫	ほてり、低血圧、潮紅
呼吸器	呼吸困難	鼻漏、鼻出血	咽喉頭疼痛、咳嗽、副鼻腔炎、気管支炎	鼻乾燥、鼻潰瘍、鼻部不快感
皮膚	爪の障害、発疹、瘙痒症	紅斑、痤瘡		爪破損、皮膚乾燥、皮膚亀裂
腎臓			排尿困難	
その他	無力症、悪寒、発熱、疲労、関節痛、筋肉痛、インフルエンザ様疾患、上気道感染（鼻炎、鼻咽頭炎、咽頭炎等）	末梢性浮腫、背部痛、筋痙縮、胸部不快感、粘膜の炎症、倦怠感、骨痛、胸痛、インフルエンザ	浮腫、筋骨格痛、膀胱炎、尿路感染症、丹毒	帯状疱疹、乳房痛、蜂巣炎、四肢痛、流涙増加、体重増加、冷感、疼痛、粘膜乾燥、霧視、筋骨格硬直

11.2.3 HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌

	10%以上	2～10%未満	2%未満
精神神経系	ニューロパチー	味覚異常、浮動性めまい、不眠症、錯感覚	頭痛、嗜眠
消化器	悪心、嘔吐、食欲不振、下痢、口内炎、便秘	腹痛、上腹部痛	消化不良、口内乾燥、嚥下障害
循環器		高血圧	動悸、潮紅、起立性低血圧
呼吸器		しゃっくり、鼻出血	咳嗽、呼吸困難
血液		ヘモグロビン減少	
皮膚	手掌・足底発赤知覚不全症候群	色素沈着障害、脱毛症、爪の障害、発疹、皮膚乾燥	瘙痒症
腎臓		腎クレアチニン・クリアランス減少、中毒性ネフロパシー	
その他	疲労、無力症、粘膜の炎症、体重減少	発熱、悪寒、脱水、低カリウム血症、低ナトリウム血症、上気道感染、難聴、浮腫、末梢性浮腫、高クレアチニン血症、口腔カンジダ症、耳鳴、過敏症	倦怠感、低アルブミン血症、体重増加

11.2.4 HER2 陽性の根治切除不能な進行・再発の唾液腺癌

	30%以上	20～30%未満	20%未満
消化器			口内炎、上腹部痛、嘔吐、食欲不振
呼吸器		胸水	気管支炎、呼吸困難
皮膚			爪甲剥離症、皮膚乾燥、脱毛症
肝臓		ALT増加	
眼			流涙増加
血液			リンパ球数減少
その他	倦怠感、末梢性浮腫、低アルブミン血症		体重増加、顔面浮腫、発熱、低カルシウム血症、血中乳酸脱水素酵素増加

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 本剤の調製時には、下記の体重あたりの換算式により、投与に必要な抜き取り量を算出すること。

・ A 法:
初回　抜き取り量(mL)＝体重(kg)×4(mg/kg)／21(mg/mL)
2 回目以降　抜き取り量(mL)＝体重(kg)×2(mg/kg)／21(mg/mL)

・ B 法:
初回　抜き取り量(mL)＝体重(kg)×8(mg/kg)／21(mg/mL)
2 回目以降　抜き取り量(mL)＝体重(kg)×6(mg/kg)／21(mg/mL)

14.1.2 調製時には、日局注射用水、日局生理食塩液以外は使用しないこと。

14.1.3 ブドウ糖溶液と混合した場合、蛋白凝集が起こるため、添付の日局注射用水(注射用 60:3.0mL、注射用 150:7.2mL)により溶解してトラスツズマブ(遺伝子組換え)21mg/mL の濃度とした後、必要量を注射筒で抜き取り、直ちに日局生理食塩液 250mL に希釈すること。

14.1.4 本剤はポリソルベートを含有しており、泡立ちやすいため、溶解時は静かに転倒混和し、ほぼ泡が消えるまで数分間放置する。

14.1.5 用時調製し、調製後は速やかに使用すること。また、残液は廃棄すること。

14.2 薬剤投与時の注意

14.2.1 本剤と 5%ブドウ糖溶液を混合した場合、蛋白凝集が起こるため、ブドウ糖溶液との混合を避け、本剤とブドウ糖溶液の同じ点滴ラインを用いた同時投与は行わないこと。

14.2.2 他剤との混注をしないこと。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 本剤投与により抗トラスツズマブ抗体が出現したとの報告(921 例中 1 例)があるが、当該症例において副作用は認められなかった。

15.1.2 本剤と他の抗悪性腫瘍剤を併用した患者に、急性白血病、骨髄異形成症候群(MDS)が発生したとの報告がある。

15.1.3 無作為化比較試験にて、骨髄抑制を有する他の抗悪性腫瘍剤に本剤を併用した場合、その抗悪性腫瘍剤単独と比較し発熱性好中球減少の発現率が上昇したとの報告がある。

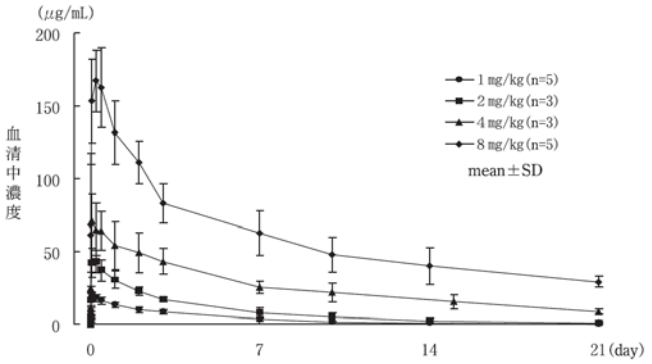
16. 薬物動態

16.1 血中濃度

16.1.1 単回投与時

日本人 HER2 過剰発現乳癌患者 18 例にトラスツズマブとして 1～8mg/kg [注1)]を 90 分間点滴静注したときの血清中濃度は以下のとおりであった。トラスツズマブの血清中からの消失は緩やかで、被験者毎に 1-コンパートメントモデルを当てはめて算出した半減期は投与量の増加とともに延長し、投与量 1mg/kg [注1)]では 2.4 日、8mg/kg では 5.5 日であった。最高血清中濃度(C_{max})は用量比例的な増加傾向を示し、クリアランス(CL)は投与量の増加に伴って低下した。分布容積(V_d)では、投与量の増加に伴う変化は認められず、ほぼ血漿容量に相当した [6)]。

単回投与後の血清中トラスツズマブ濃度推移



単回投与時のトラスツズマブの薬物動態パラメータ

投与量(mg/kg)	症例数	C_{max}(μg/mL)	AUC_{inf}(μg・day/mL)	$t_{1/2}$(day)	CL(mL/day/kg)	V_d(mL/kg)
1	5	19±2.8	66±15	2.4±0.4	16±3.8	55±7.5
2	3	43±8.5	154±16	2.6±0.7	13±1.4	49±12
4	3	72±17	544±68	5.9±1.5	7.4±1.0	63±15
8	5	177±19	1,261±330	5.5±1.5	6.8±2.4	51±6.5

mean±SD

注 1)承認された用法・用量は初回投与時 4mg/kg、2 回目以降 2mg/kg を週 1 回投与(A 法)及び初回投与時 8mg/kg、2 回目以降 6mg/kg を 3 週間 1 回投与(B 法)である。

16.1.2 反復投与時

(1) 日本人 HER2 過剰発現乳癌患者 18 例にトラスツズマブとして 1～8mg/kg [注1)]を 90 分間点滴静注後 21 日目より、週 1 回 90 分間点滴静注を繰り返したとき、初回投与後 43 日目における最低(C_{min})及び最高血清中濃度(C_{max})は以下のとおりであった [7)]。

反復投与時の最低及び最高血清中トラスツズマブ濃度

投与量(mg/kg)	症例数	C_{min}(μg/mL)	C_{max}(μg/mL)
1	4	6.72±0.869	26.7±3.18
2	2	2.14、24.7	60.1、64.4
4	2	74.9、116	134、220
8	4	200±20.6	327±41.6

1、8mg/kg:mean±SD

(2) HER2 過剰発現乳癌の術後薬物療法において、日本人を含む患者 8 例にトラスツズマブとして初回投与時 8mg/kg、2 回目以降 6mg/kg を 90 分間点滴静注にて 3 週間に 1 回投与した。定常状態に達したサイクル 18 において、モデルに依存しない解析により算出した薬物動態パラメータは、以下のとおりであった [8)]。

反復投与時のトラスツズマブの薬物動態パラメータ

症　例	症例数	C_{min}(μg/mL)	C_{max}(μg/mL)	$AUC_{0\text{-}21d}$(μg・day/mL)	CL_{ss}(L/day)	$t_{1/2}$ [注2)](day)
日本人	3	58.5±21.6	203±19	2067±551	0.171±0.058	16.7±5.3
外国人	5	71.2±23.2	215±5	2289±297	0.188±0.027	16.3±3.8

mean±SD

注 2)最終相の半減期

(3) HER2 過剰発現乳癌患者 213 例に、トラスツズマブとして初回 4mg/kg、2 回目以降 2mg/kg を週 1 回反復点滴静注したとき、shed 抗原（腫瘍から遊離した HER2 細胞外領域）ベースライン濃度が高値である症例のトラスツズマブ最低血清中濃度（C_{min}）は、低値を示す傾向が認められた [9]（外国人データ）。

16.1.3 母集団薬物動態解析

HER2 過剰発現乳癌患者 476 例（ただし 3 例は乳癌以外の患者）にトラスツズマブとして初回 4mg/kg、2 回目以降 2mg/kg を週 1 回 90 分間反復点滴静注（16 例は 10～500mg を単回投与）したときの血清中濃度を用い、population pharmacokinetics 解析を実施した。モデル検討の結果 2-コンパートメントモデルが選択され、半減期（$t_{1/2}$）は 28.5 日（母集団平均、95%信頼区間：25.5～32.8 日）であった [10]（外国人データ）。

Population pharmacokinetics 解析から得られたトラスツズマブの薬物動態パラメータ

C_{min} 注 3) (μg/mL)	C_{max} 注 3) (μg/mL)	AUC 注 3) (mg・day/L)	$t_{1/2}$ (day)	CL (L/day)
66	110	578	28.5	0.225

注 3）A 法で投与した際の定常状態時（約 20 週で到達）の予測値

16.3 分布

HER2 過剰発現の腫瘍を皮下移植したヌードマウスに、^{125}I 標識トラスツズマブ（10mg/kg）を単回静脈内投与したとき、放射能の正常組織への移行性は低かった。腫瘍中の放射能は投与後 24 時間に最高値を示した後、正常組織に比べ高く推移し、血清中濃度とほぼ同様の濃度で漸減した [11]。血清中放射能のほとんどはトラスツズマブであった [12]。

16.5 排泄

16.5.1 HER2 過剰発現乳癌患者

日本人 HER2 過剰発現乳癌患者 18 例にトラスツズマブとして 1～8mg/kg 注 1)を 90 分間点滴静注したとき、投与 24 時間後の未変化体の尿中排泄率は、0.01%以下であった [13]。

16.5.2 正常マウス

正常マウス（ICR 系）に ^{125}I 標識トラスツズマブ（10mg/kg）を単回静脈内投与したとき、投与後 7 日までの放射能の尿中及び糞中排泄率は雄でそれぞれ 31%及び 2%であり、雌でそれぞれ 28%及び 5%であった。投与後 76 日まででは雄でそれぞれ 83%及び 12%であり、雌でそれぞれ 65%及び 29%であった [14]。しかし、尿中にトラスツズマブはほとんど認められなかった [12]。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈HER2 過剰発現が確認された乳癌〉

17.1.1 国内第Ⅰ相臨床試験（MKC-454-02 試験）

HER2 過剰発現の転移性乳癌患者を対象に、本剤を投与した（1～8mg/kg）注 1)。抗腫瘍効果の成績は下表のとおりであった [15]。

副作用は 14/18 例（77.8%）に発現した。主な副作用は、発熱 44.4%、AST 増加 22.2%、嘔吐 16.7%、悪寒 16.7%、倦怠感 16.7%等であった。

HER2 過剰発現乳癌患者に対する抗腫瘍効果

投与量	CR	PR	MR	NC	PD	NE	計
1mg/kg	－	－	－	1	4	1	6
2mg/kg	－	－	1	－	2	－	3
4mg/kg	－	1	－	－	2	－	3
8mg/kg	1	－	2	1	1	1	6
計	2（11.1）	3	2	9	2	18	

NE：Not Evaluate　　症例数（%）

上記 18 例における本剤の投与期間は 1～10 週（中央値：10 週）であった。また、高齢者（65 歳以上）への投与は行われなかった。

注 1）承認された用法・用量は初回投与時 4mg/kg、2 回目以降 2mg/kg を 1 週間間隔で投与（A 法）及び初回投与時 8mg/kg、2 回目以降 6mg/kg を 3 週間間隔で投与（B 法）である。

17.1.2 海外第Ⅱ相臨床試験（H0551g 試験）

HER2 過剰発現の転移性乳癌患者を対象に、本剤を単独投与した（初回 250mg、2 回目以降は 100mg を 7 日毎に 10 週間投与）注 1)。評価可能例 43 例のうち奏効例は 5 例（11.6%）であった [16]。

副作用は 28/46 例（60.9%）に発現した。主な副作用は、さむけ 21.7%、発熱 17.4%、下痢 15.2%等であった。

17.1.3 海外第Ⅱ相臨床試験（H0552g 試験）

HER2 過剰発現の転移性乳癌患者を対象に、本剤をシスプラチンと併用で投与した（初回 250mg、2 回目以降は 100mg を 7 日毎に 8 週間投与）注 1)。評価可能例 37 例のうち奏効例は 9 例（24.3%）であった [17]。

副作用は 22/39 例（56.4%）に発現した。主な副作用は、無力症 28.2%、発熱 18.0%、嘔気 18.0%、さむけ 15.4%、白血球減少症 15.4%等であった。

17.1.4 海外第Ⅲ相臨床試験（H0648g 試験）

HER2 過剰発現の転移性乳癌患者を対象に、本剤を他の化学療法と併用で投与した（初回 4mg/kg、2 回目以降は 2mg/kg を 1 週間間隔で投与）。主要評価項目である病勢進行までの期間の中央値は、アントラサイクリン＋シクロホスファミド（AC）併用群が 9.08 カ月、AC 単独群が 6.48 カ月、パクリタキセル併用群が 6.87 カ月、パクリタキセル単独群が 2.89 カ月であった。

HER2 過剰発現の程度別の病勢進行までの期間の中央値は、AC 併用群では 3＋群が 9.05 カ月、2＋群が 9.11 カ月、パクリタキセル併用群では 3＋群が 7.14 カ月、2＋群が 5.30 カ月であった。奏効例は、AC 併用群が 80/143 例（55.9%）、パクリタキセル併用群が 38/92 例（41.3%）であった [18]。

副作用は AC 併用群では 122/143 例（85.3%）、パクリタキセル併用群では 78/91 例（85.7%）に発現した。主な副作用は AC 併用群では、発熱 28.7%、嘔気 25.9%、無力症 25.2%、さむけ 23.8%、嘔吐 18.9%、下痢 18.2%、疼痛 17.5%、呼吸困難 16.1%等、パクリタキセル併用群では、さむけ 36.3%、無力症 35.2%、発熱 29.7%、嘔気 23.1%、疼痛 22.0%、下痢 19.8%、発疹 17.6%、嘔吐 17.6%等であった。

17.1.5 海外第Ⅲ相臨床試験（H0649g 試験）

前化学療法 1～2 レジメン施行後に再発が認められた HER2 過剰発現の転移性乳癌患者を対象に、本剤を投与した（初回 4mg/kg、2 回目以降は 2mg/kg を 1 週間間隔で投与）。主要評価項目である抗腫瘍効果について、ITT 解析対象集団 222 例のうち奏効例は 34 例（15.3%）、評価可能例 207 例のうち奏効例は 34 例（16.4%）であった。病勢進行までの期間の中央値は 3.1 カ月であった。HER2 過剰発現の程度別の病勢進行までの期間の中央値は、3＋群が 3.3 カ月、2＋群が 1.9 カ月であった [19]。

副作用は 182/213 例（85.4%）に発現した。主な副作用は、発熱 36.6%、さむけ 35.2%、無力症 27.2%、嘔気 21.1%、疼痛 17.8%、頭痛 15.0%等であった。

17.1.6 海外臨床試験（H0650g 試験）

化学療法未治療の HER2 過剰発現の転移性乳癌患者を対象に、本剤を投与した（初回 4mg/kg 又は 8mg/kg、2 回目以降はそれぞれ 2mg/kg 又は 4mg/kg を 1 週間間隔で投与注 1)）。主要評価項目である抗腫瘍効果について、評価可能例の奏効例は、4mg/kg→2mg/kg 群が 7/33 例（21.2%）、8mg/kg→4mg/kg 群が 8/29 例（27.6%）であった [20]。

副作用は 4mg/kg→2mg/kg 群では 40/59 例（67.8%）、8mg/kg→4mg/kg 群では 47/55 例（85.5%）に発現した。主な副

作用は 4mg/kg→2mg/kg 群では、無力症 20.3%、疼痛 20.3%、さむけ 20.3%、発熱 18.6%等、8mg/kg→4mg/kg 群では、さむけ 29.1%、発熱 25.5%、無力症 25.5%、嘔気 18.2%、疼痛 16.4%等であった。

17.1.7 海外臨床試験（H0659g 試験）［H0648g 試験からの継続試験］

海外第III相臨床試験（H0648g 試験）に参加し転移性乳癌の進行が確認された患者を対象に本剤を投与した（放射線療法、化学療法、免疫療法及びホルモン療法との併用可能）。評価可能例 155 例のうち奏効例は 22 例（14.2%）であった[21]。

主な副作用は、無力症 18.4%、さむけ 18.4%、発熱 16.4%、嘔気 15.6%等であった。

17.1.8 海外臨床試験（H0693g 試験）

化学療法を 3 レジメン以上施行後に、再発が認められた HER2 過剰発現の転移性乳癌患者を対象に、本剤を標準的癌化学療法と併用で投与した（初回 4mg/kg、2 回目以降は 2mg/kg を 1 週間間隔で投与）。評価可能例の奏効例は 5/154 例（3.2%）であった[22]。副作用は 240/360 例（66.7%）に発現した。主な副作用は、発熱 26.7%、さむけ 25.8%、無力症 10.6%、嘔気 10.3%等であった。

17.1.9 国際共同第Ⅲ相試験（HERA 試験）

HER2 過剰発現の手術可能乳癌患者で、手術、全身的な術前又は術後薬物療法及び放射線療法（適応となる場合）を完了した患者を対象[注2)]とし、本剤を初回 8mg/kg（体重）、2 回目以降 6mg/kg を 3 週間間隔で 1 年間投与した群又は 2 年間投与した群と、本剤を投与しない対照群とで有効性を比較した。なお、本剤投与群においては、定期的な LVEF 評価に基づき、本剤の投与継続あるいは中止が判断された。

中間解析結果：観察期間中央値 12 カ月時点で中間解析が実施され、本剤 1 年投与群は対照群に比べて、無病生存に関するイベント[注3)]発現率が有意に改善された。なお、本試験における国内からの登録被験者の同時点の解析におけるイベント発現率は、1 年投与群 7.3%（3/41）、対照群 13.0%（6/46）であった[23]。

HERA 試験のうち本剤が投与された 1,678 例において、副作用が 600 例（35.8%）に認められた。主な副作用は、悪寒 75 例（4.5%）、頭痛 61 例（3.6%）、発熱 58 例（3.5%）、悪心 52 例（3.1%）、疲労 51 例（3.0%）、駆出率低下 51 例（3.0%）等であった。そのうち、本試験に参加した国内症例 41 例において、副作用が 23 例（56.1%）に認められ、主な副作用は悪寒 6 例（14.6%）、発熱 5 例（12.2%）、疲労 5 例（12.2%）、頭痛 5 例（12.2%）、爪の障害 5 例（12.2%）等であった。

最終解析結果：観察期間中央値 8 年時点で最終解析が実施された。本剤 1 年投与群は対照群に比べて、無病生存に関するイベント発現率が有意に改善された。本剤 2 年投与群と 1 年投与群の比較は、ランダム化の 12 カ月後に無病かつ生存している被験者に対して実施された。本剤 2 年投与群の無病生存に関するイベント発現率は 23.6%（367/1,553）で、1 年投与群（23.6%［367/1,552］）に比べて有意な改善は認められなかった（HR：0.99、P＝0.86）[24]。

また、安全性については、3,355 例（1 年投与群 1,682 例、2 年投与群 1,673 例）が解析対象とされ、グレード 3 又は 4 の有害事象及び無症候性又は軽度症候性の左室駆出率（LVEF）低下は、1 年投与群に比べて 2 年投与群で発現率が高い傾向が認められた［グレード 3 又は 4 の有害事象：1 年投与群 16.3%（275/1,682 例）、2 年投与群 20.4%（342/1,673 例）、無症候性又は軽度症候性の左室駆出率低下：1 年投与群 4.1%（69/1,682 例）、2 年投与群 7.2%（120/1,673 例）］。

注 2）HERA 試験では、非転移性で根治的手術が可能であった原発性乳癌患者を対象とした。なお、腋窩リンパ節転移陰性で腫瘍径 1cm 以下の患者、化学療法が適応されない患者は対象外であった。

注 3）乳癌の再発（部位を問わない）、対側乳癌、乳癌以外の二次癌（皮膚の基底細胞癌及び扁平上皮癌、子宮頸部上皮内癌を除く）の発症、死亡（死因は問わない）

1 年投与群及び対照群の無病生存に関するイベント発現率の比較

		症例数	イベント[注3)]発現例数（発現率）	ハザード比	P 値
観察期間中央値 12 カ月時点	対照群	1693	219（12.9%）	0.54	＜0.0001
	1 年投与群	1693	127（ 7.5%）		
観察期間中央値 8 年時点	対照群[注4)]	1697[注5)]	570（33.6%）	0.76	＜0.0001
	1 年投与群	1702[注5)]	471（27.7%）		

注 4）対照群には、中間解析結果発表の後、本剤の投与を開始した症例が 52.1%（884/1,697）含まれた。

注 5）観察期間中央値 12 カ月時点における解析のためのカットオフ日より後で試験にランダム化された被験者が少数含まれるため、症例数に相違がある。

〈HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌〉

17.1.10 国際共同第Ⅲ相試験（ToGA 試験）

HER2 過剰発現（IHC 法 3＋又は FISH 法陽性）の進行・再発の胃又は胃食道接合部腺癌患者（化学療法未治療）584 例を対象に、化学療法（カペシタビン＋シスプラチン又はフルオロウラシル＋シスプラチン）と化学療法＋本剤を比較する第III相臨床試験を実施した。本剤は初回 8mg/kg（体重）、2 回目以降 6mg/kg を 3 週間間隔で、化学療法中止後も病勢進行が認められるまで同一の用法・用量で投与を継続した。化学療法は、カペシタビン 1000mg/m^2 の 1 日 2 回 14 日間経口投与又はフルオロウラシル 800mg/m^2 の 5 日間持続静脈内投与[注6)]とシスプラチン 80mg/m^2 の静脈内投与を 3 週間間隔で行った。目標イベント数の 75%時点の中間解析において、化学療法＋本剤は化学療法単独に比べて、主要評価項目である全生存期間において有意な延長が認められた。なお、化学療法の内訳は 584 例中、カペシタビン＋シスプラチンが 511 例、フルオロウラシル＋シスプラチンが 73 例であった。国内では、全例（101 例）においてカペシタビン＋シスプラチンが使用された[25]。

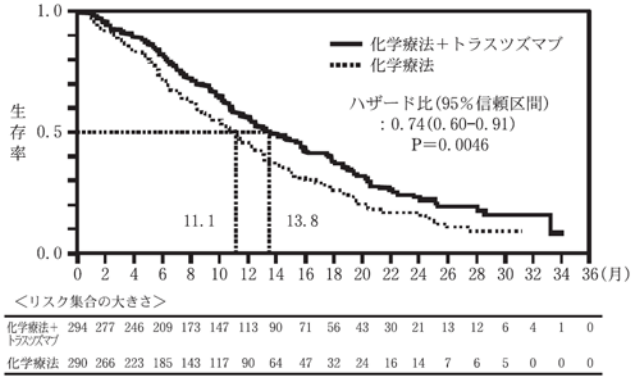
ToGA 試験のうち本剤が投与された 294 例において、副作用が 283 例（96.3%）に認められた。主な副作用は、悪心 186 例（63.3%）、好中球減少症 157 例（53.4%）、嘔吐 129 例（43.9%）、食欲不振 121 例（41.2%）、疲労 87 例（29.6%）、下痢 85 例（28.9%）、手掌・足底発赤知覚不全症候群 72 例（24.5%）、口内炎 66 例（22.4%）等であった。そのうち、本試験に参加した国内症例 51 例において、副作用が 50 例（98.0%）に認められ、主な副作用は食欲不振 43 例（84.3%）、悪心 41 例（80.4%）、腎機能障害 31 例（60.8%）、好中球減少症 30 例（58.8%）、嘔吐 29 例（56.9%）、疲労 29 例（56.9%）、口内炎 26 例（51.0%）、しゃっくり 20 例（39.2%）、手掌・足底発赤知覚不全症候群 19 例（37.3%）、便秘 18 例（35.3%）等であった。

注 6）フルオロウラシルの他の抗悪性腫瘍剤との併用における国内承認用法・用量：フルオロウラシルとして、通常成人 1 日 5～10mg/kg を他の抗悪性腫瘍剤と併用し、単独で使用する場合の方法に準じ、又は間歇的に週 1～2 回用いる。

単独で使用する場合：フルオロウラシルとして、通常成人 1 日 5

～15mg/kg を最初の 5 日間連日 1 日 1 回静脈内に注射又は点滴静注する。以後 5～7.5mg/kg を隔日に 1 日 1 回静脈内に注射又は点滴静注する。なお、年齢、症状により適宜増減する。

全生存期間の Kaplan-Meier 曲線



＜HER2 陽性の根治切除不能な進行・再発の唾液腺癌＞

17.1.11 国内第Ⅱ相試験（HUON-003-01 試験）

HER2 陽性（IHC 法 3＋、又は IHC 法 2＋かつ DISH 法陽性[注 7)]）の根治切除不能な進行・再発の唾液腺癌患者 16 例を対象に、本剤をドセタキセルと併用で投与した。本剤は初回 8mg/kg（体重）、2 回目以降 6mg/kg、ドセタキセルは 70mg/m^2 をいずれも 3 週間間隔で投与し、疾患進行又は治験中止基準に該当しない限り、最大 8 サイクル継続した。主要評価項目である RECIST ver.1.1 に基づく中央判定による奏効率［95%信頼区間］は 60.0%［32.3, 83.7］であった [26]。

副作用は 12/16 例（75.0%）に発現した。主な副作用は、好中球数減少 10 例（62.5%）、貧血 9 例（56.3%）、白血球数減少 9 例（56.3%）、倦怠感 6 例（37.5%）、末梢性浮腫 6 例（37.5%）、低アルブミン血症 5 例（31.3%）、注入に伴う反応 4 例（25.0%）、ALT 増加 4 例（25.0%）、胸水 4 例（25.0%）等であった。

注 7）登録された 16 例全例が IHC 法 3＋であった。

18. 薬効薬理

18.1 作用機序

本薬は HER2 に特異的に結合した後、NK 細胞、単球を作用細胞とした抗体依存性細胞傷害作用（ADCC）により抗腫瘍効果を発揮する [27),28)]。

また、HER2 分子数を低下させることにより細胞増殖シグナルが低減し、その結果本薬が直接的に細胞増殖を抑制するとの機序も考えられる [29)]。

18.2 抗腫瘍効果

HER2 高発現のヌードマウス可移植性ヒト乳癌（MCF7-HER2、BT-474（細胞当たりの HER2 レセプター数＝1.0×10^6））及びヒト胃癌（NCI-N87）に対し抗腫瘍効果が認められた [30-32)]また、NCI-N87 において、他の抗悪性腫瘍剤との併用により、抗腫瘍効果の増強が認められた [33)]。

MCF-7-HER2 に対しては総投与量 3～100mg/kg（3 回投与）の範囲で、NCI-N87 に対しては総投与量 70～280mg/kg（6 回投与）の範囲で用量依存的に増殖抑制効果を示した [30),32)]。一方、BT-474 に対しては、1 日投与量 0.1～30mg/kg（8～10 回投与）の範囲で用量依存的に増殖抑制効果を示し、1mg/kg 以上の高用量投与群では腫瘍の完全退縮も観察された [31)]。

18.3 抗体依存性細胞傷害作用（ADCC）

ヒト Interleukin-2 で処理したヒト末梢血単核球を作用細胞として、$Na^{51}CrO_4$ で予めラベルした下記の標的細胞を作用細胞：標的細胞＝25：1、12.5：1、6.25：1、3.13：1 の比率で混合し、0.1μg/mL のトラスツズマブを添加し、4 時間培養した（37℃、5%CO_2）。chrome release assay により ADCC 活性を測定した。

ヒト乳腺上皮細胞 184A1 株（HER2 発現レベル[注)]＝0.3）
ヒト乳癌細胞 MCF7 株（HER2 発現レベル＝1.2）
ヒト胃癌細胞 MKN7 株（HER2 発現レベル＝16.7）
ヒト乳癌細胞 SK-BR-3 株（HER2 発現レベル＝33.0）
注）ヒト乳腺上皮細胞 184 株の HER2 発現レベルを 1.0 としたときの相対値

その結果、いずれの作用細胞：標的細胞比率においても、細胞傷害活性と HER2 発現レベルの間には高い相関が認められ（作用細胞：標的細胞＝25：1、12.5：1、6.25：1、3.13：1 の時、それぞれ R^2＝0.93、0.92、0.87、0.66）、トラスツズマブは HER2 高発現細胞に、より強い細胞傷害活性を発揮することが示された [27)]。ただし、HER2 低発現の腫瘍株（MCF7）では、in vitro の試験において、トラスツズマブ惹起の ADCC 活性は極めて微弱であり、また、直接的な細胞増殖抑制作用（トラスツズマブのマウス親抗体である 4D5 を用いて行われた）は認められなかった [27)]。

18.4 HER2 分子数の抑制作用

ヒト乳癌細胞 SK-BR-3（HER2 高レベル発現株（細胞当たりの HER2 レセプター数＝9.0×10^5））及び MCF7（HER2 低レベル発現株（細胞当たりの HER2 レセプター数＝2.2×10^4））を本薬 150μg/mL の存在、非存在下で 1 日あるいは 5 日間培養した後、細胞の HER2 数を求めたところ、いずれの細胞でも HER2 のレベルが低下した [29)]。

19. 有効成分に関する理化学的知見

一般的名称

トラスツズマブ（遺伝子組換え）（Trastuzumab（Genetical Recombination））（JAN）

分子式

軽鎖（$C_{1032}H_{1603}N_{277}O_{335}S_6$）
重鎖（$C_{2192}H_{3387}N_{583}O_{671}S_{16}$）

分子量

148,000

構造式

アミノ酸 214 個の軽鎖 2 分子とアミノ酸 449 個の重鎖 2 分子からなる糖たん白質

22. 包装

〈ハーセプチン注射用 60〉

1 バイアル（日局注射用水 3.0mL×1 アンプル 添付）

〈ハーセプチン注射用 150〉

1 バイアル（日局注射用水 7.2mL×1 アンプル 添付）

23. 主要文献

1) 医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書：トラスツズマブ（遺伝子組換え）HER2 過剰発現が確認された乳癌における術前補助化学療法

2) 医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書：トラスツズマブ（遺伝子組換え）HER2 過剰発現が確認された乳癌に対する術後補助化学療法としての A 法（1 週間間隔投与）の用法・用量の追加

3) 医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書：トラスツズマブ（遺伝子組換え）HER2 過剰発現が確認された転移性乳癌について、3 週間 1 回投与の用法・用量の追加

4) 動物実験 胎児移行性（2001 年 4 月 4 日承認、申請資料概要へ.2-2-3）

5) 動物実験 乳汁中移行（2001 年 4 月 4 日承認、申請資料概要へ.2-4-2）

6) 国内第I相試験－初回投与時の血中濃度（2001 年 4 月 4 日承認、申請資料概要ヘ.3-1-1-2）
7) 国内第I相試験－反復投与時の血中濃度（2001 年 4 月 4 日承認、申請資料概要ヘ.3-1-2-4）
8) 社内資料：薬物動態〈HERA 試験における PK サブスタディー中間解析結果〉
9) 海外第III相試験－反復投与（2001 年 4 月 4 日承認、申請資料概要ヘ.3-1-2-3）
10) Bruno R, et al. Cancer Chemother Pharmacol. 2005;56:361-9.
11) 動物実験　臓器・組織中濃度（2001 年 4 月 4 日承認、申請資料概要ヘ.2-2-1）
12) 動物実験　代謝物（2001 年 4 月 4 日承認、申請資料概要ヘ.2-3-1）
13) 国内第I相試験－排泄（2001 年 4 月 4 日承認、申請資料概要ヘ.3-2-1）
14) 動物実験　尿糞中排泄（2001 年 4 月 4 日承認、申請資料概要ヘ.2-4-1）
15) 国内第I相臨床試験（MKC-454-02 試験）（2001 年 4 月 4 日承認、申請資料概要ト.1-1-1-1）
16) 海外第II相臨床試験（H0551g 試験）（2001 年 4 月 4 日承認、申請資料概要ト.2-3-1）
17) 海外第II相臨床試験（H0552g 試験）（2001 年 4 月 4 日承認、申請資料概要ト.2-3-2）
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20) 海外臨床試験（H0650g 試験）（2001 年 4 月 4 日承認、申請資料概要ト.2-5-1）
21) 海外臨床試験（H0659g 試験）（2001 年 4 月 4 日承認、申請資料概要ト.2-5-2）
22) 海外臨床試験（H0693g 試験）（2001 年 4 月 4 日承認、申請資料概要ト.2-5-3）
23) 社内資料：臨床成績〈HERA 試験－中間解析結果〉
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26) 社内資料：国内第Ⅱ相試験〈HUON-003-01 試験〉
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28) 作用機作〈抗体依存性細胞障害作用（ADCC）〉（2001 年 4 月 4 日承認、申請資料概要ホ.1-1-1）
29) 作用機作〈HER2 受容体数抑制作用〉（2001 年 4 月 4 日承認、申請資料概要ホ.1-1-5）
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32) Fujimoto-Ouchi K, et al. Cancer Chemother Pharmacol. 2007;59:795-805.
33) 社内資料：抗腫瘍効果〈ヒト胃癌 xenograft モデルにおける抗腫瘍効果の検討〉

24. 文献請求先及び問い合わせ先

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Ⓡ 登録商標

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1.10 毒薬・劇薬等の指定審査資料のまとめ 2

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	ヒト IgG1に由来するフレーム構造領域及びマウスモノクローナル抗 HER2抗体の相補的抗原認識領域を含むヒト化モノクローナル抗体組換えDNAの発現により，チャイニーズハムスター卵巣細胞で産生される214個のアミノ酸残基（$C_{1032}H_{1603}N_{277}O_{335}S_6$：分子量：23,443.1）の軽鎖2分子と449個のアミノ酸残基（$C_{2192}H_{3387}N_{583}O_{671}S_{16}$：分子量：49,156.5）の重鎖2分子からなる糖たん白質（分子量：約148,000，四本鎖型95%以上）（別名トラスツズマブ（遺伝子組換え））及びその製剤
構造式	アミノ酸配列は別紙のとおり
効能・効果	○ HER2過剰発現が確認された乳癌 ○ HER2過剰発現が確認された治癒切除不能な進行・再発の胃癌
用法・用量	HER2過剰発現が確認された乳癌にはA法又はB法を使用する。 HER2過剰発現が確認された治癒切除不能な進行・再発の胃癌には他の抗悪性腫瘍剤との併用でB法を使用する。 A 法：通常，成人に対して1日1回，トラスツズマブ（遺伝子組換え）として初回投与時には4mg/kg（体重）を，2回目以降は2mg/kg を90分以上かけて1週間間隔で点滴静注する。 B 法：通常，成人に対して1日1回，トラスツズマブ（遺伝子組換え）として初回投与時には8mg/kg（体重）を，2回目以降は6mg/kg を90分以上かけて3週間間隔で点滴静注する。 なお，初回投与の忍容性が良好であれば，2回目以降の投与時間は30分間まで短縮できる。
劇薬等の指定	生物由来製品，処方せん医薬品
市販名及び有効成分・分量	原体：トラスツズマブ（遺伝子組換え） 製剤：ハーセプチン注射用60（1バイアル中 トラスツズマブ（遺伝子組換え）60 mg 含有），ハーセプチン注射用150（1バイアル中 トラスツズマブ（遺伝子組換え）150 mg 含有）
毒性	単回　動物種　投与経路　致死量（mg/kg） マウス　静脈内　♂♀ ＞200 mg/kg サル　静脈内　♂♀ ＞200 mg/kg 反復　動物種　投与期間　投与経路　投与量（mg/kg/日）　無毒性量　主な所見 亜急性　マウス　4週間（7回/週）　静脈内　5.9，17.7，59　17.7 mg/kg/日　17.7 mg/kg/日以上群の雌で極軽度の無機リンの上昇，59 mg/kg/日群で肝臓 Kupffer 細胞過形成及び類洞内白血球の増加（雌雄） サル　4週間（7回/週）　静脈内　3.54，10.62，35.4　10.62 mg/kg/日　10.62 mg/kg/日群の雌で4週目にγ-グロブリンの上昇，35.4 mg/kg/日群の雌雄で2及び4週に単球の軽度増加，γ-グロブリンの上昇及び A/G 比の減少，雌で肝臓 Kupffer 細胞過形成及び類洞内白血球の増加

毒性

	サル	4週間（2回/週）	静脈内	2.35，11.75，23.5	23.5 mg/kg/回	23.5 mg/kg/回群の雄で投与部位硬結例の極軽度増加
	サル	3カ月間（2回/週）	静脈内	1，5，25	25 mg/kg/回	特になし
慢性	マウス	6カ月間（2回/週）	静脈内	6，20，59	59 mg/kg/回	59 mg/kg/回群の雄で胸腺の絶対及び相体重量の軽度減少
	サル	6カ月間（1回/週）	静脈内	1，5，25	25 mg/kg/回	1 mg/kg/回群雌1例で5～26週目に中和抗体の産生

副作用

＜HER2過剰発現が確認された転移性乳癌＞

1. 国内

総症例18例中14例（77.8%）に副作用または臨床検査値異常が認められた。

1) 国内の副作用

副作用発現率　14/18 = 77.8%

副作用の種類	件数
発熱	8
嘔吐	3
悪寒	3
等	

2) 国内の臨床検査値異常

臨床検査値異常発現率　7/18 = 38.9%

臨床検査値異常の種類	件数
GOT 上昇	4
GPT 上昇	2
AL-p 上昇	2
γ-GTP 上昇	1
プロトロンビン時間延長	1
活性化トロンボプラスチン時間延長	1
等	

2. 海外

1) 海外の副作用

副作用発現率　959/1298 = 73.9%

副作用の種類（感染症を含む）	件数
発熱	359
さむけ	355
無力症	257
嘔気	252
疼痛	165
等	

＜HER2過剰発現が確認された乳癌における術後補助化学療法＞

国内外で実施した国際共同第Ⅲ相臨床試験（HERA 試験）のうち本剤が投与された症例1,678例において，副作用が600例（35.8%）に認められた。このうち，国内登録症例41例において，副作用が23例（56.1%）に認められた。なお，臨床検査値に関しては，薬剤との関連性はデータとして取得していないことから，本剤投与前後で NCI-CTC（version 2.0）のグレードが3又は4グレード悪化した臨床検査値を集計した。

(1)試験全体（本剤1年投与群）

1) 副作用発現率　600/1678 = 35.8%

副作用の種類	例数
悪寒	75
頭痛	61
発熱	58
悪心	52
疲労	51
駆出率低下	51

等

2) 臨床検査値異常発現率

集計していない

3又は4グレード悪化した臨床検査値の種類

臨床検査値の種類	例数
カリウム増加	12
カリウム減少	5
ナトリウム減少	5
ASAT（SGOT）増加	5
ナトリウム増加	4
好中球数減少	3

等

(2) 国内登録症例（本剤1年投与群）

1) 副作用発現率　23/41 = 56.1%

副作用の種類	例数
悪寒	6
頭痛	5
発熱	5
疲労	5
爪の障害	5

等

2) 臨床検査値異常発現率

集計していない

本剤投与群において臨床検査値が3又は4グレード悪化した被験者はいなかった。

＜HER2過剰発現が確認された治癒切除不能な進行・再発の胃癌＞

国内外で実施した国際共同第Ⅲ相臨床試験（ToGA 試験）のうち本剤が投与された症例294例において，副作用が283例（96.3%）に認められた。このうち，国内登録症例51例において，副作用が50例（98.0%）に認められた。なお，臨床検査値に関しては，薬剤との関連性はデータとして取得していないことから，本剤投与前後で NCI-CTC（version 3.0）のグレードが3又は4グレード悪化した臨床検査値を集計した。

(1)試験全体

1) 副作用発現率　283/294 = 96.3%

副作用の種類	例数
悪心	186
好中球減少症	154
嘔吐	129
食欲不振	121
疲労	87
下痢	85

等

(2) 国内登録症例

1) 副作用発現率　50/51 = 98.0%

副作用の種類	例数
食欲不振	43
悪心	41
腎機能障害	31
好中球減少症	30
嘔吐	29
疲労	29

等

	2) 臨床検査値異常発現率 集計していない 3又は4グレード悪化した 臨床検査値の種類　例数 好中球減少　100 ナトリウム減少　31 白血球減少　30 カリウム減少　25 ヘモグロビン減少　18 等	2) 臨床検査値異常発現率 集計していない 3又は4グレード悪化した 臨床検査値の種類　例数 好中球減少　24 ナトリウム減少　9 ヘモグロビン減少　8 白血球減少　6 カリウム減少　4 等
会社	中外製薬株式会社　　原体：輸入，製剤：輸入	

（変更）

下線：追加及び変更箇所

化学名 ・別名	
構造式	
効能・効果	○HER2 過剰発現が確認された乳癌 ○HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌 ○HER2 陽性の根治切除不能な進行・再発の唾液腺癌
用法・用量	HER2 過剰発現が確認された乳癌には A 法又は B 法を使用する。 HER2 過剰発現が確認された治癒切除不能な進行・再発の胃癌には他の抗悪性腫瘍剤との併用で B 法を使用する。 HER2 陽性の根治切除不能な進行・再発の唾液腺癌にはドセタキセル製剤との併用で B 法を使用する。 A 法：通常、成人に対して 1 日 1 回、トラスツズマブ（遺伝子組換え）として初回投与時には 4mg/kg(体重)を、2 回目以降は 2mg/kg を 90 分以上かけて 1 週間間隔で点滴静注する。 B 法：通常、成人に対して 1 日 1 回、トラスツズマブ（遺伝子組換え）として初回投与時には 8mg/kg(体重)を、2 回目以降は 6mg/kg を 90 分以上かけて 3 週間間隔で点滴静注する。なお、初回投与の忍容性が良好であれば、2 回目以降の投与時間は 30 分間まで短縮できる。
劇薬等の指定	
市販名及び有効成分・分量	
毒性	
副作用	**＜HER2過剰発現が確認された転移性乳癌＞** 1. 国内 総症例18例中14例（77.8%）に副作用または臨床検査値異常が認められた。 1) 国内の副作用　副作用発現率　14/18＝77.8% 副作用の種類　件数 発熱　8 嘔吐　3 悪寒　3 等 2) 国内の臨床検査値異常　臨床検査値異常発現率　7/18＝38.9% 臨床検査値異常の種類　件数 GOT 上昇　4 GPT 上昇　2 AL-p 上昇　2 γ-GTP 上昇　1 プロトロンビン時間延長　1 活性化トロンボプラスチン時間延長　1 等

2. 海外

1) 海外の副作用

副作用発現率　959/1298 = 73.9%

副作用の種類

（感染症を含む）	件数
発熱	359
さむけ	355
無力症	257
嘔気	252
疼痛	165

等

＜HER2過剰発現が確認された乳癌における術後補助化学療法＞

国内外で実施した国際共同第Ⅲ相臨床試験（HERA 試験）のうち本剤が投与された症例1,678例において，副作用が600例（35.8%）に認められた。このうち，国内登録症例41例において，副作用が23例（56.1%）に認められた。なお，臨床検査値に関しては，薬剤との関連性はデータとして取得していないことから，本剤投与前後で NCI-CTC（version 2.0）のグレードが3又は4グレード悪化した臨床検査値を集計した。

(1)試験全体（本剤1年投与群）

1) 副作用発現率　600/1678 = 35.8%

副作用の種類	例数
悪寒	75
頭痛	61
発熱	58
悪心	52
疲労	51
駆出率低下	51

等

2) 臨床検査値異常発現率

集計していない

3又は4グレード悪化した

臨床検査値の種類	例数
カリウム増加	12
カリウム減少	5
ナトリウム減少	5
ASAT（SGOT）増加	5
ナトリウム増加	4
好中球数減少	3

等

(2) 国内登録症例（本剤1年投与群）

1) 副作用発現率　23/41 = 56.1%

副作用の種類	例数
悪寒	6
頭痛	5
発熱	5
疲労	5
爪の障害	5

等

2) 臨床検査値異常発現率

集計していない

本剤投与群において臨床検査値が3又は4グレード悪化した被験者はいなかった。

＜HER2過剰発現が確認された治癒切除不能な進行・再発の胃癌＞

国内外で実施した国際共同第Ⅲ相臨床試験（ToGA 試験）のうち本剤が投与された症例294例において，副作用が283例（96.3%）に認められた。このうち，国内登録症例51例において，副作用が50例（98.0%）に認められた。なお，臨床検査値に関しては，薬剤との関連性はデータとして取得していないことから，本剤投与前後で NCI-CTC（version 3.0）のグレードが3又は4グレード悪化した臨床検査値を集計した。

(1)試験全体

1) 副作用発現率　283/294 = 96.3%

副作用の種類	例数
悪心	186
好中球減少症	154
嘔吐	129
食欲不振	121
疲労	87
下痢	85
等	

2) 臨床検査値異常発現率

集計していない

3又は4グレード悪化した

臨床検査値の種類	例数
好中球減少	100
ナトリウム減少	31
白血球減少	30
カリウム減少	25
ヘモグロビン減少	18
等	

(2) 国内登録症例

1) 副作用発現率　50/51 = 98.0%

副作用の種類	例数
食欲不振	43
悪心	41
腎機能障害	31
好中球減少症	30
嘔吐	29
疲労	29
等	

2) 臨床検査値異常発現率

集計していない

3又は4グレード悪化した

臨床検査値の種類	例数
好中球減少	24
ナトリウム減少	9
ヘモグロビン減少	8
白血球減少	6
カリウム減少	4
等	

＜HER2陽性の根治切除不能な進行・再発の唾液腺癌＞

国内で実施した HER2陽性の根治切除不能な進行・再発の唾液腺癌を対象とした HUON003-01試験において，副作用が12例（75.0%）に認められた。また，臨床検査値異常は10例（62.5%）に認められた。主な副作用とグレード3又は4に悪化した臨床検査値異常の内訳を以下に示す。

全体

副作用の種類	例数	(%)
副作用発現率	12	(75.0)
貧血	9	(56.3)
倦怠感	6	(37.5)
末梢性浮腫	6	(37.5)
低アルブミン血症	5	(31.3)
注入に伴う反応	4	(25.0)
胸水	4	(25.0)

臨床検査値異常

副作用の種類	例数	(%)
臨床検査値異常発現率	10	(62.5)
グレード3又は4に悪化した臨床検査値異常	10	(62.5)
好中球数減少	10	(62.5)
白血球数減少	9	(56.3)
リンパ球数減少	2	(12.5)

会社

別紙

1 Asp-Ile-Gln-Met-Thr-Gln-Ser-Pro-Ser-Ser-Leu-Ser-Ala-Ser-Val-Gly-Asp-Arg-Val-Thr-Ile-Thr-Cys-Arg-Ala-
26 Ser-Gln-Asp-Val-Asn-Thr-Ala-Val-Ala-Typ-Tyr-Gln-Gln-Lys-Pro-Gly-Lys-Ala-Pro-Lys-Leu-Leu-Ile-Tyr-Ser-
51 Ala-Ser-Phe-Leu-Tyr-Ser-Gly-Val-Pro-Ser-Arg-Phe-Ser-Gly-Ser-Arg-Ser-Gly-Thr-Asp-Phe-Thr-Leu-Thr-Ile-
76 Ser-Ser-Leu-Gln-Pro-Glu-Asp-Phe-Ala-Thr-Tyr-Tyr-Cys-Gln-Gln-His-Tyr-Thr-Thr-Pro-Pro-Thr-Phe-Gly-Gln-
101 Gly-Thr-Lys-Val-Glu-Ile-Lys-Arg-Thr-Val-Ala-Ala-Pro-Ser-Val-Phe-Ile-Phe-Pro-Pro-Ser-Asp-Glu-Gln-Leu-
126 Lys-Ser-Gly-Thr-Ala-Ser-Val-Val-Cys-Leu-Leu-Asn-Asn-Phe-Tyr-Pro-Arg-Glu-Ala-Lys-Val-Gln-Trp-Lys-Val-
151 Asp-Asn-Ala-Leu-Gln-Ser-Gly-Asn-Ser-Gln-Glu-Ser-Val-Thr-Glu-Gln-Asp-Ser-Lys-Asp-Ser-Thr-Tyr-Ser-Leu-
176 Ser-Ser-Thr-Leu-Thr-Leu-Ser-Lys-Ala-Asp-Tyr-Glu-Lys-His-Lys-Val-Tyr-Ala-Cys-Glu-Val-Thr-His-Gln-Gly-
201 Leu-Ser-Ser-Pro-Val-Thr-Lys-Ser-Phe-Asn-Arg-Gly-Glu-Cys

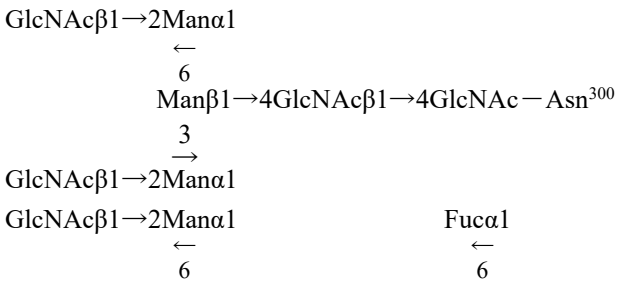
軽　鎖

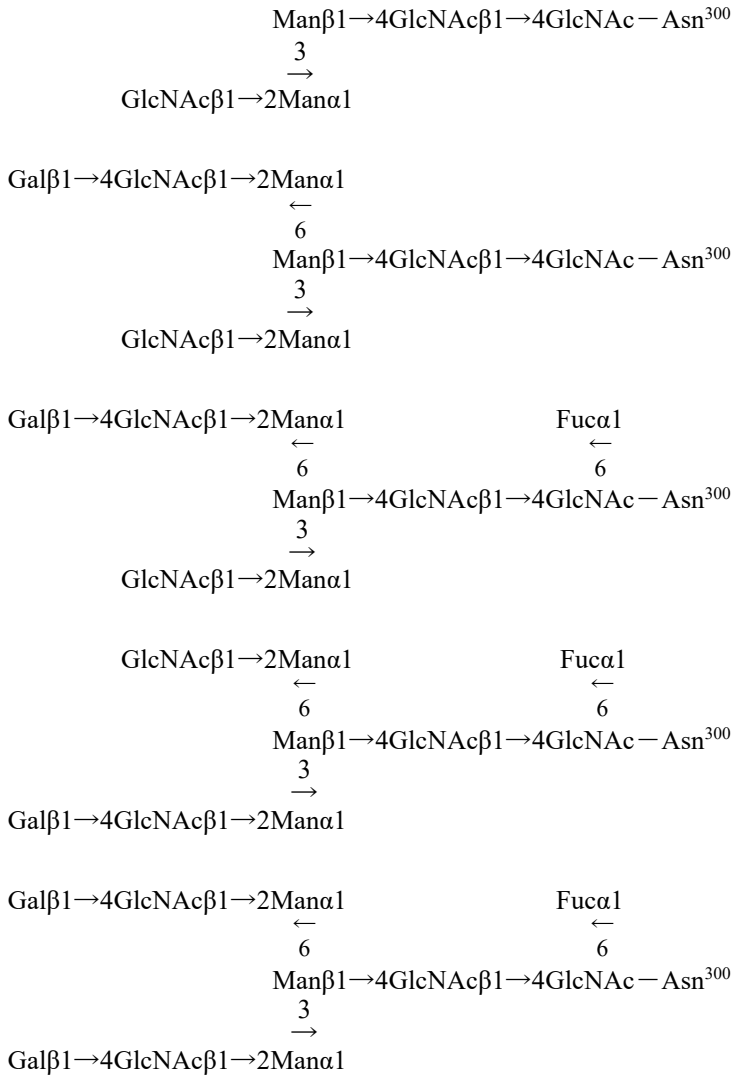
1 Glu-Val-Gln-Leu-Val-Glu-Ser-Gly-Gly-Gly-Leu-Val-Gln-Pro-Gly-Gly-Ser-Leu-Arg-Leu-Ser-Cys-Ala-Ala-Ser-
26 Gly-Phe-Asn-Ile-Lys-Asp-Thr-Tyr-Ile-His-Trp-Val-Arg-Gln-Ala-Pro-Gly-Lys-Gly-Leu-Glu-Trp-Val-Ala-Arg-
51 Ile-Tyr-Pro-Thr-Asn-Gly-Tyr-Thr-Arg-Tyr-Ala-Asp-Ser-Val-Lys-Gly-Arg-Phe-Thr-Ile-Ser-Ala-Asp-Thr-Ser-
76 Lys-Asn-Thr-Ala-Tyr-Leu-Gln-Met-Asn-Ser-Leu-Arg-Ala-Glu-Asp-Thr-Ala-Val-Tyr-Tyr-Cys-Ser-Arg-Trp-Gly-
101 Gly-Asp-Gly-Phe-Tyr-Ala-Met-Asp-Tyr-Trp-Gly-Gln-Gly-Thr-Leu-Val-Thr-Val-Ser-Ser-Ala-Ser-Thr-Lys-Gly-
126 Pro-Ser-Val-Phe-Pro-Leu-Ala-Pro-Ser-Ser-Lys-Ser-Thr-Ser-Gly-Gly-Thr-Ala-Ala-Leu-Gly-Cys-Leu-Val-Lys-
151 Asp-Tyr-Phe-Pro-Glu-Pro-Val-Thr-Val-Ser-Trp-Asn-Ser-Gly-Ala-Leu-Thr-Ser-Gly-Val-His-Thr-Phe-Pro-Ala-
176 Val-Lue-Gln-Ser-Ser-Gly-Leu-Tyr-Ser-Leu-Ser-Ser-Val-Val-Thr-Val-Pro-Ser-Ser-Ser-Leu-Gly-Thr-Gln-Thr-
201 Tyr-Ile-Cys-Asn-Val-Asn-His-Lys-Pro-Ser-Asn-Thr-Lys-Val-Asp-Lys-Lys-Val-Glu-Pro-Lys-Ser-Cys-Asp-Lys-
226 Thr-His-Thr-Cys*-Pro-Pro-Cys**-Pro-Ala-Pro-Glu-Leu-Leu-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-Lys-Pro-
251 Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-Val-Val-Asp-Val-Ser-His-Glu-Asp-Pro-Glu-
276 Val-Lys-Phe-Asn-Trp-Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Aal-Lys-Thr-Lys-Pro-Arg-Glu-Glu-Gln-Tyr-Asn-
301 Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-Cys-Lys-
326 Val-Ser-Asn-Lys-Ala-Leu-Pro-Ala-Pro-Ile-Glu-Lys-Thr-Ile-Ser-Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-
351 Val-Tyr-Thr-Leu-Pro-Pro-Ser-Arg-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-Leu-Val-Lys-Gly-Phe-
376 Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro-Val-
401 Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Lys-Leu-Thr-Val-Asp-Lys-Ser-Arg-Typ-Gln-Gln-Gly-Asn-Val-
426 Phe-Ser-Cys-Ser-Val-Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-Leu-Ser-Pro-Gly

重　鎖

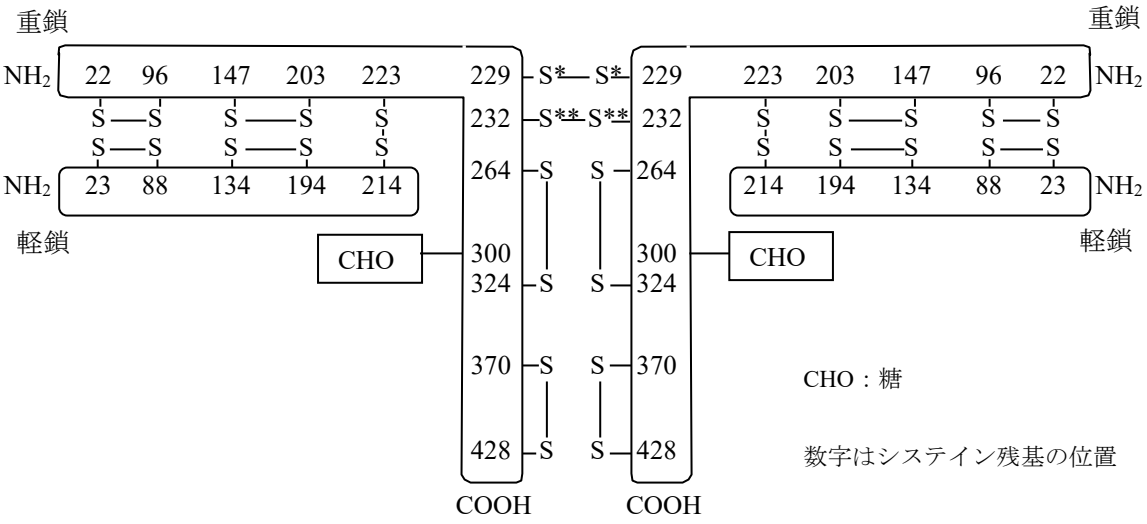
Asn：糖鎖結合部位

重鎖 Asn300部位糖鎖構造





Fuc：L-フコース
GlcNAc：N-アセチルグルコサミン
Man：D-マンノース
Gal：D-ガラクトース



4本鎖構造模式図

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該当資料なし

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該当資料なし

第 4 部　参考文献

該当資料なし

第 5 部　臨床試験報告書

資料番号	表題	国内/海外	社内資料/公表文献	評価資料/参考資料	申請電子データの有無
5.2	臨床試験一覧表	国内	社内資料	評価資料	有

資料番号	試験番号	表題	国内/海外	社内資料/公表文献	評価資料/参考資料	申請電子データの有無
5.3.1　生物薬剤学試験報告書						
5.3.1.1　バイオアベイラビリティ（BA）試験報告書：該当資料なし						
5.3.1.2　比較 BA 試験及び生物学的同等性（BE）試験報告書：該当資料なし						
5.3.1.3　*In Vitro-In Vivo* の関連を検討した試験報告書：該当資料なし						
5.3.1.4　生物学的及び理化学的分析法検討報告書：該当資料なし						
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						
5.3.2.1　血漿蛋白結合試験報告書：該当資料なし						
5.3.2.2　肝代謝及び薬物相互作用試験報告書：該当資料なし						
5.3.2.3　他のヒト生体試料を用いた試験報告書：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：該当資料なし						
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						
5.3.4.1　健康被験者における PD 試験及び PK/PD 試験報告書：該当資料なし						
5.3.4.2　患者における PD 試験及び PK/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						

資料番号	試験番号	表題	国内/海外	社内資料/公表文献	評価資料/参考資料	申請電子データの有無
5.3.5.2　非対照試験報告書						
5.3.5.2-1	HUON-003-01	HER2 陽性再発転移の唾液腺癌に対するトラスツズマブ及びドセタキセルの併用薬物療法第Ⅱ相試験	国内	社内資料	評価資料	有
5.3.5.3　複数の試験成績を併せて解析した報告書：該当資料なし						
5.3.5.4　その他の試験報告書：該当資料なし						
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/ Periodic Safety Update Report 1103351	海外	社内資料	参考資料	無
5.3.7　患者データ一覧及び症例記録						
5.3.7-1	HUON-003-01	被験者の内訳	国内	社内資料	評価資料	無
5.3.7-2	HUON-003-01	有害事象一覧	国内	社内資料	評価資料	有
5.3.7-3	HUON-003-01	重篤な有害事象一覧	国内	社内資料	評価資料	有
5.3.7-4	HUON-003-01	個々の臨床検査異常値の一覧	国内	社内資料	評価資料	有
5.3.7-5	HUON-003-01	臨床検査値の個別推移	国内	社内資料	評価資料	無

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資料番号	表題 / 著者 / 掲載誌	報告書の種類 (国内/海外)
5.4.1	Airoldi M, et al., Paclitaxel and carboplatin for recurrent salivary gland malignancies. Anticancer Res. 2000; 20(5C): 3781-3783.	海外
5.4.2	Cancer Registry Committee 2020, Report of Head and Neck Cancer Registry of Japan, Japan Society for Head and Neck Cancer.	海外
5.4.3	Firwana B, et al, Trastuzumab for Her2/neu-positive metastatic salivary gland carcinoma, Case report and review of the literature. Avicenna J Med. 2012;2(3):71-73.	海外
5.4.4	Gilbert J, et al., Phase II trial of taxol in salivary gland malignancies (E1394): a trial of the Eastern Cooperative Oncology Group. Head Neck, 2006; 28(3):197-204.	海外
5.4.5	Kaidar-Person O,et al. Targeted therapy with trastuzumab for advanced salivary ductal carcinoma: case report and literature review. Med Oncol. 2012;29(2):704-706.	海外
5.4.6	Krishnamurthy J, et al. Salivary duct carcinoma responding to trastuzumab-based therapy: Case report and review of the literature. Head Neck 2013;35(12): E372-375.	海外
5.4.7	Kurzrock R, et al. Targeted therapy for advanced salivary gland carcinoma based on molecular profiling: results from MyPathway, a phase IIa multiple basket study. Ann Oncol. 2020 Mar;31(3): 412-421.	海外
5.4.8	Lagha A, et al. Systemic therapy in the management of metastatic or advanced salivary gland cancers. Head & Neck Oncol. 2012;4:19.	海外
5.4.9	Limaye SA, et al. Trastuzumab for the treatment of salivary duct carcinoma. Oncologist 2013;18(3):294-300.	海外
5.4.10	Nabili V, et al. Salivary duct carcinoma: a clinical and histologic review with implications for trastuzumab therapy. Head & Neck. 2007;29(10):907-912.	海外
5.4.11	Nakano K, et al. Combination chemotherapy of carboplatin and paclitaxel for advanced/ metastatic salivary gland carcinoma patients: differences in responses by different pathological diagnoses. Acta Oto-Laryngologica. 2016;136 (9): 948-951.	海外
5.4.12	Nashed M, et al.. Biological therapy of salivary duct carcinoma, J Laryngol Otol. 2009;123(2): 250-252.	海外
5.4.13	Prat A, et al. Successful treatment of pulmonary metastatic salivary ductal carcinoma with trastuzumab-based therapy. Head Neck, 2008;30(5):680-683.	海外
5.4.14	Raguse J, et al. Docetaxel(Taxotere) in recurrent high grade mucoepidermoid carcinoma. Oral Onc Extra. 2004 Jan;40(1):5.	海外
5.4.15	Scholl S, et al. Targeting HER2 in other tumor types, Ann Oncol. 2001;12(suppl 1): S81-S87.	海外
5.4.16	Takahashi H, et al. Phase II Trial of Trastuzumab and Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2-Positive Salivary Duct Carcinoma, J Clin Oncol. 2019,37(2):125-134.	海外
5.4.17	Takase.S, et.al. Biomarker immunoprofile in salivary duct carcinomas:clinicopathological and prognostic implications with evaluation of the revised classification. Oncotarget, 2017; (35):59023-59035.	海外
5.4.18	Uijen M, et al. Systemic therapy in the management of recurrent or metastatic salivary ductcarcinoma: A systematic review. Cancer Treatment Reviews 2020;89:102069.	海外

資料番号	表題 / 著者 / 掲載誌	報告書の種類 (国内/海外)
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5.4.24	医薬品申請前相談（P[redacted]）対面助言記録 令和[redacted] 年[redacted] 月[redacted] 日	国内
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