ハラヴェン静注 1mg

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 はじめに

エリブリンメシル酸塩（以下，本薬）は，クロイソカイメンから単離された海洋天然物ハリコンドリン B の合成誘導体であり，新規メカニズムに基づく微小管ダイナミクス阻害剤である。

微小管は主にチューブリン分子からなる管状の構造体であり，チューブリンの重合（伸長）と脱重合（短縮）の繰り返し（微小管ダイナミクス）により，細胞内骨格の主要な構成要素として細胞形態の維持や細胞運動に関与し，また有糸分裂時には紡錘体を形成して染色体の分裂移動等に重要な役割を担う。本薬は微小管の伸長端に結合することで，微小管ダイナミクスに対して伸長のみを阻害し短縮を妨げないことにより（Smith JA, et al., 2010），微小管を生理機能のないチューブリン凝集塊に至らしめる。本薬はこの機序により細胞分裂が盛んながん細胞に対しては，紡錘体形成を妨げ細胞周期を G2/M 期で停止させることにより，アポトーシスによる細胞死を誘導する（Towle MJ, et al., 2001; Towle MJ, et al., 2011）。この有糸分裂阻害作用に加え，最近の研究により本薬には腫瘍組織内の微小血管をリモデリングすることで腫瘍内血流を改善し，がん悪性化の要因となる低酸素状態を緩和する作用，また浸潤転移能など悪性度の高いがん細胞がもつ間葉系のフェノタイプを悪性度の低い上皮系の性質に変換する作用があることも報告されている（Funahashi Y, et al., 2014; Yoshida T, et al., 2014）。

本薬は国内で 2011 年 4 月に手術不能又は再発乳癌の効能・効果で承認され，既に世界 50 ヵ国以上（2015 年 10 月時点）において乳癌患者に対する治療薬として承認されている。

本申請は，本薬の医薬品製造販売承認事項に効能・効果として，「悪性軟部腫瘍」を追加するための承認事項一部変更承認申請である。

1.5.2 悪性軟部腫瘍の現状及び薬物治療

1.5.2.1 悪性軟部腫瘍の疫学

悪性軟部腫瘍は，皮下・筋間等の線維性結合組織，腱・靭帯などの線維組織，皮下・筋下等の脂肪組織，横紋筋組織，平滑筋組織，滑膜組織などの様々な軟部組織で発生する腫瘍の総称である。悪性軟部腫瘍は極めて稀な疾患であり，最近の調査結果によると国内における患者数は約 4,000 人（厚生労働省, 2012），年間の死亡数は約 2,000 人と報告されている（厚生労働省, 2014）。

悪性軟部腫瘍は発生部位が極めて多彩であることから，50 種類以上の組織型があることが知られており（Clark MA, et al., 2005），WHO（World Health Organization）あるいは Enzinger & Weiss の分類が広く用いられている（日本整形外科学会診療ガイドライン委員会 軟部腫瘍診断ガイドライン策定委員会, 2012）。悪性軟部腫瘍の代表的なもので，発生頻度の比較的高い組織型として，脂肪肉腫，悪性線維性組織球腫，平滑筋肉腫，滑膜肉腫が知られている。

悪性軟部腫瘍は，組織型ごとに様々な病態像を呈するものの，いずれも 5 cm を超える腫瘍サイズ，腫瘍の発生深度，組織学的悪性度，リンパ節・遠隔転移の有無などの因子が予後を左右する重要な因子とされている。また，組織型別分類に関わらず，周囲組織への浸潤性増殖傾向を示し，血行性の転移を中心とした転移像を示すという特徴がある。このような予後因子や病態の特徴を踏まえていくつかの悪性軟部腫瘍の病期分類が存在するが，代表的なものとして，TNM（Tumor-Nodes-Metastasis）分類定義による AJCC（American Joint Committee on Cancer）病期分類がある。この分類では，遠隔転移がない段階では，組織学的悪性度，腫瘍サイズと深度及びリンパ節転移の有無で病期を I 期から III 期に，遠隔転移がある場合には IV 期に分類する。

病期ごとの 5 年生存率は I 期 80%，II 期 70%，III 期 45%，IV 期 10%と報告されており（国立がん研究センター内科レジデント編, 2013），遠隔転移を有する病期 IV 期の予後は極めて不良であることから，悪性軟部腫瘍に対する新たな治療薬の開発が望まれている。

1.5.2.2 悪性軟部腫瘍の治療の現状

悪性軟部腫瘍に対する治療には，外科療法，化学療法，放射線療法が用いられるが，国内外を問わず治療の主体は原発巣の治癒的切除を目的とした外科療法である。治癒的切除が困難な患者や四肢に発症した患者のうち腫瘍の悪性度が高い患者には，術前・術後に補助的な放射線療法又は化学療法の実施が考慮される（日本整形外科学会診療ガイドライン委員会 軟部腫瘍診断ガイドライン策定委員会, 2012）。治癒的切除が困難となった患者や遠隔転移を有する患者に対しては，化学療法が行われる。日米欧の悪性軟部腫瘍に対する化学療法のガイドラインを表 1.5.2-1 に示す。

悪性軟部腫瘍の化学療法は国内外問わず初回化学療法としてアントラサイクリン系薬剤であるドキソルビシンの単剤療法又はドキソルビシン，イホスファミドを中心とした併用療法が標準的に使用されている（日本整形外科学会診療ガイドライン委員会 軟部腫瘍診断ガイドライン策定委員会, 2012）。これらの治療による客観的奏効率（objective response rate：ORR）は約 5%～25%，無増悪生存期間（progression-free survival：PFS）の中央値は約 2～7 ヵ月，全生存期間（overall survival：OS）の中央値は約 10～14 ヵ月である（Lorigan P, et al., 2007, van Oosterom AT, et al., 2002, Judson I, et al., 2014）。また，初回化学療法後の治療選択肢としてパゾパニブが国内外で承認されている。アントラサイクリン系薬剤治療後の患者に対するパゾパニブの ORR は 6%，PFS の中央値は 4.6 ヵ月，OS の中央値は 12.5 ヵ月である（van der Graaf WT, et al., 2012）。なお，2015 年 9 月にトラベクテジンが，初回化学療法後の治療選択肢として国内で承認された。

外国では初回化学療法が無効若しくは投与継続が困難となった患者に対し，ゲムシタビンとドセタキセルの併用療法，ダカルバジン単剤療法及びダカルバジンとゲムシタビンの併用療法等が治療選択肢として推奨されている。これらの薬剤治療に対する第 2 相試験で報告されている ORR は約 5%～15%，PFS の中央値は約 2～6 ヵ月，OS の中央値は約 8～18 ヵ月である（Maki RG, et al., 2007, García-Del-Muro X, et al., 2011）。国内では上述したダカルバジン等の薬剤は未承認あるいは悪性軟部腫瘍に対する適応症はないため，ドキソルビシン，イホスファミド，パゾパニブ及びトラベクテジン治療に無効若しくは副作用等で治療継続が困難となった患者に対し有効性が期待できる薬剤は存在しない状況である。

以上のように国内における悪性軟部腫瘍の化学療法の治療選択肢は限られている。また，治療を行った場合でも生存期間が 1 年程度であり，化学療法が適応となる悪性軟部腫瘍患者の予後は極めて不良である。さらに，ドキソルビシンでは心毒性，イホスファミドでは腎毒性，パゾパニブ及びトラベクテジンでは肝機能障害の副作用が報告されており，これらの薬剤が不適あるいは副作用により病勢進行前に投与を継続することが困難となる患者も存在する。加えて，外国で使用されているいくつかの薬剤は国内では悪性軟部腫瘍の治療薬としては未承認である。これらのことから，悪性軟部腫瘍に対する化学療法の医療ニーズは満たされておらず，新たな薬剤の開発が求められている。

なお，本薬は米国の悪性軟部腫瘍に対する治療ガイドラインである NCCN（National Comprehensive Cancer Network）ガイドラインに，単剤治療の推奨される薬剤として記載されている。

表 1.5.2-1 日米欧の悪性軟部腫瘍に対する化学療法のガイドライン

国・地域	日本	米国	欧州
ガイドライン	日本整形外科学会診療ガイドライン (日本整形外科学会診療ガイドライン委員会 軟部腫瘍診断ガイドライン策定委員会, 2012)	NCCN ガイドライン [a] (National Comprehensive Cancer Network, 2015a) NCI ガイドライン (National Cancer Institute, 2015)	ESMO（European Society for Medical Oncology）ガイドライン (The ESMO / European Sarcoma Network Working Group, 2014)
推奨されている化学療法	進行症例 [b] ・ドキソルビシン単剤が標準治療として推奨 転移症例 ・ドキソルビシン単剤が標準治療として推奨 ・イホスファミドの単剤，併用療法の有効性も認められている ・有効である可能性が示唆される薬剤 [c] ・ダカルバジン [d] ・ゲムシタビン [d,e] ・ドセタキセル [d,e] ・トラベクテジン [e] ・リポソーマルドキソルビシン [f] ・パクリタキセル [g]	【NCCN ガイドライン】 併用療法として以下のレジメンを推奨 ・ドキソルビシン+ダカルバジン又はイホスファミド ・ドキソルビシン+イホスファミド+ダカルバジン ・イホスファミド+エピルビシン ・ゲムシタビン+ドセタキセル，ビノレルビン又はダカルバジン 単剤治療として下記の薬剤を推奨 ドキソルビシン，イホスファミド，エピルビシン，ゲムシタビン，ダカルバジン，リポソーマルドキソルビシン，テモゾロミド，ビノレルビン，パゾパニブ，エリブリン 【NCI ガイドライン】 第 1 選択治療 ・初回治療としてドキソルビシン又はイホスファミド単剤が標準的に使用される。（ドキソルビシン単剤療法が一般的） ・ドキソルビシンの併用療法も選択肢とされている。 第 2 選択治療 ・標準的治療は確立していないが，イホスファミド，ゲムシタビン等の臨床活性を有する薬剤の中から未使用である薬剤の使用が考慮される。	第 1 選択治療 ・アントラサイクリン系薬剤の単剤療法が標準治療として推奨 ・腫瘍縮小が有用又は PS が良好な患者に対し，アントラサイクリン系薬剤とイホスファミドの併用療法も選択肢の一つとされている。 ・血管肉腫に対し，タキサン系薬剤，ゲムシタビン又はゲムシタビンとドセタキセルの併用療法も選択肢の一つとされている。 ・平滑筋肉腫及び孤在性線維性腫瘍に対し，ドキソルビシンとダカルバジンの併用療法も選択肢の一つとされている。 ・隆起性皮膚線維肉腫に対し，イマチニブが標準治療として推奨 第 2 選択治療 下記の治療が推奨されている。 ・高用量イホスファミド単剤 ・トラベクテジン単剤 ・ゲムシタビンとドセタキセルの併用療法 ・ダカルバジン単剤又はゲムシタビンとの併用療法 ・パゾパニブ単剤

PS = Performance status.
a: 非特異的な組織型の悪性軟部腫瘍に対する化学療法を記載
b: 非円形細胞肉腫に対する化学療法を記載
c: 治療体系が異なる横紋筋肉腫に対する記載を除く
d: 悪性軟部腫瘍に対する適応を有していない
e: ゲムシタビンとドセタキセルの併用やトラベクテジンはそれぞれ平滑筋肉腫や粘液型脂肪肉腫に対する有効性が報告されている
f: エイズ関連カポジ肉腫に対する適応を有し，血管肉腫に対する有効性が報告されている
g: 血管肉腫に対する適応を有する

1.5.3 開発の経緯
1.5.3.1 非臨床試験
1.5.3.1.1 非臨床試験の開発の経緯及び試験の概要

非臨床試験の開発の経緯を以下の図 1.5.3-1 に示す。



図 1.5.3-1　開発の経緯図：非臨床試験

1.5.3.1.2 悪性軟部腫瘍に対する薬理試験

米国 National Cancer Institute が主導した小児非臨床試験プログラム（PPTP）の一環として実施された in vitro 試験において，本薬は横紋筋肉腫 4 種類，横紋筋様肉腫 2 種類，ユーイング肉腫 4 種類の細胞株の増殖を，それぞれ IC_{50} 値の中央値 0.14，0.27，0.14 nmol/L で抑制した。また別途実施した PPTP in vitro 試験において 20 種類のユーイング肉腫細胞株の増殖を IC_{50} 値の中央値 0.38 nmol/L で抑制した。本薬は MES-SA ヒト子宮肉腫細胞株の増殖を IC_{50} 値 1.99 nmol/L で抑制した。

本薬は in vivo のヒト悪性軟部腫瘍細胞（HT-1080，SK-LMS-1，A673）皮下移植マウスモデルにおいて抗腫瘍効果を示した。また PPTP の一環として実施された in vivo 試験において，本薬は，11 種類のヒト軟部腫瘍細胞の皮下移植マウスモデルのうち，8 種類（5 種類のユーイング肉腫モデルのうち 4 種類，4 種類の横紋筋肉腫モデルの全て）に対し完全奏効所見（腫瘍体積が測定限界以下に縮小）を伴う抗腫瘍効果を示した。

1.5.3.2 悪性軟部腫瘍に対する臨床開発の経緯及び試験概要

本承認申請における臨床試験一覧を表 1.5.3-1 に記載した。また，本承認申請における臨床開発の経緯を図 1.5.3-2 に示した。なお，実施された試験の本薬の用法・用量は，既承認の乳癌と同様に 3 週間を 1 サイクル（以下，3 週間サイクル）とし，第 1 及び 8 日目に本薬 1.4 mg/m^2 を静脈内投与する投与スケジュールである。

悪性軟部腫瘍に対する臨床開発は 20[redacted] 年 [redacted] 月より開始し，単剤療法 2 レジメン又は併用療法 1 レジメンまでの前化学療法を受けた患者を対象として第 2 相試験（外国 207 試験）を欧州で実施した。本試験は European Organization for Research and Treatment of Cancer（EORTC）の主導により実施された。本試験において本薬の有効性及び良好な安全性プロファイルが示唆され，平滑筋肉腫及び脂肪肉腫においては事前に設定した有効性の統計基準を満たした。

外国 207 試験の結果を踏まえ，外国では第 3 相試験（外国 309 試験）を 2011 年 3 月より開始した。外国 309 試験では，アントラサイクリン系薬剤を含む少なくとも 2 レジメンの標準化学療法施行後に増悪した平滑筋肉腫及び脂肪肉腫患者を対象として，本薬の有効性及び安全性をダカルバジン単剤と比較することを目的とした。その結果，本薬投与によりダカルバジン単剤と比較して OS の有意な延長が検証され，発現した本薬の副作用は臨床管理可能であった。

国内においては，20[redacted] 年 [redacted] 月に独立行政法人医薬品医療機器総合機構（Pharmaceutical and Medical Devices Agency：PMDA）と医薬品[redacted]相談を実施し，2011 年 11 月より標準化学療法施行後に増悪した患者を対象に第 2 相試験（国内 217 試験）を開始した。[redacted]その結果，国内 217 試験において日本人悪性軟部腫瘍患者に対する本薬の有効性が示された。また，認められた副作用は既承認の乳癌と同様であり，

良好な安全性プロファイルが示された。

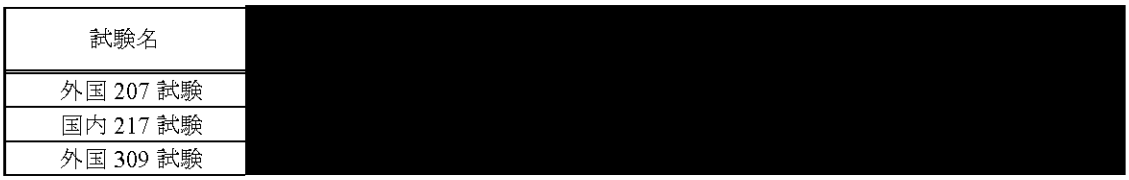
表 1.5.3-1 臨床試験一覧

試験の種類	試験名	対象	試験の主な目的	被験者数	資料区分
第 2 相	外国 207 試験	悪性軟部腫瘍（全ての組織型）[a]	有効性，安全性及び薬物動態の評価	128[b]	評価
第 2 相	国内 217 試験	悪性軟部腫瘍（全ての組織型）[a]	有効性，安全性及び薬物動態の評価	52[b]	評価
第 3 相	外国 309 試験	悪性軟部腫瘍（平滑筋肉腫/脂肪肉腫）	有効性，安全性及び薬物動態の評価	452[c]	評価

a: 以下の組織型を除く。胎児性横紋筋肉腫，軟骨肉腫，骨肉腫，ユーイング肉腫／未熟神経外胚葉性腫瘍（PNET），消化管間質腫瘍，隆起性皮膚線維肉腫，炎症性筋線維芽細胞腫，神経芽細胞腫，悪性中皮腫，子宮の中胚葉性混合腫瘍

b: 登録例数

c: 無作為化例数。本薬群は 228 例



a: 主要評価項目の解析が終了し治験総括報告書を作成したが，投与継続中の被験者が存在する試験

図 1.5.3-2 本承認申請における臨床開発の経緯

1.5.3.2.1 外国臨床試験の概要

1.5.3.2.1.1 外国 207 試験

単剤療法 2 レジメン又は併用療法 1 レジメンまでの前化学療法を受け，投与開始前 6 ヵ月以内に progressive disease（PD）が認められた中～高悪性度の悪性軟部腫瘍患者を対象に，本薬の有効性及び安全性を検討するために，20[redacted] 年 [redacted] 月より第 2 相試験（外国 207 試験）を実施した。本試験では 4 つの組織型（平滑筋肉腫，脂肪肉腫，滑膜肉腫，その他の悪性軟部腫瘍）に被験者を層別し，それぞれの組織型について有効性の検討を行った。本試験における本薬の投与は 3 週間サイクルにて本薬 1.4 mg/m^2 を第 1 及び 8 日目に静脈内投与するスケジュールで行った。

その結果，本薬の有効性が示唆され，発現した副作用は臨床管理可能なものであった。平滑筋肉腫及び脂肪肉腫では，事前に設定した統計基準を満たし良好な結果が得られた。

1.5.3.2.1.2 外国 309 試験

外国 207 試験の結果から平滑筋肉腫及び脂肪肉腫の 2 つの組織型を対象に，第 3 相試験（外国 309 試験）を 2011 年 3 月より実施した。本試験は，アントラサイクリン系抗がん剤を含む少なくとも 2 レジメンの前化学療法を受けた悪性軟部腫瘍患者を対象に本薬（3 週間サイクルにて本薬 1.4 mg/m^2 を第 1 及び 8 日目に静脈内投与）のダカルバジン（3 週間サイクルにてダカルバジンを 850，1000 又は 1200 mg/m^2 のうち治験責任医師が選択した用量を第 1 日目に静脈内投与）に対する有効性及び安全性を比較することを目的とした。

その結果，主要評価項目である OS の解析において，本薬群はダカルバジン群と比較して，統計学的に有意な延長が認められた。また，発現した副作用は臨床管理可能であった。

1.5.3.2.2 国内臨床試験の概要

1.5.3.2.2.1 国内 217 試験

1 レジメン以上の前化学療法を受け，同意取得前 6 ヵ月以内に PD が認められた中～高悪性度の悪性軟部腫瘍患者を対象に，本薬の有効性及び安全性を検討するために，2011 年 11 月より国内 217 試験を実施した。本試験における本薬の投与は 3 週間サイクルにて第 1 及び 8 日目に本薬 1.4 mg/m^2 を静脈内投与するスケジュールで行った。

その結果，日本人の悪性軟部腫瘍患者に対する本薬の有効性が示唆された。また，発現した副作用は臨床管理可能であった。

1.5.3.3 その他の癌腫に対する臨床開発の経緯

乳癌，悪性軟部腫瘍以外のがん腫への適応の可能性に関しても外国で臨床開発が行われている。

1.5.4 対面助言相談

1.5.4.1 医薬品[redacted]相談

外国 207 試験結果及び外国 309 試験の計画を踏まえ，国内 217 試験に関する医薬品[redacted]相談を 20[redacted] 年 [redacted] 月に実施し，以下の点について協議を行った。

(1)[redacted]の妥当性
1)[redacted]するにあたり，[redacted]とすること
2)[redacted]（[redacted]）とすること
3)[redacted]の適切性
・[redacted]は，[redacted]に基づき[redacted]（[redacted]）について[redacted]と設定し，[redacted]とすること
・[redacted]（[redacted]）[redacted]は，[redacted]，[redacted]とすること

(2)「[redacted]」[redacted]の妥当性
1)[redacted]し，[redacted]を用いて，[redacted]「[redacted]」[redacted]すること
2)[redacted]として，[redacted]すること
3)[redacted]において，[redacted]（[redacted]）[redacted]に，[redacted]として，[redacted]する妥当性

上記の点について PMDA と協議の結果，下記の点について[redacted]し，試験を実施した。

(1)[redacted]とすること
(2)[redacted]し，[redacted]（[redacted]）とすること

1.5.5 希少疾病用医薬品の指定

悪性軟部腫瘍は国内における患者数が少なく，進行した場合に予後不良となる重篤な疾患である。また，悪性軟部腫瘍に対し本薬の有効性が期待できたため，希少疾病用医薬品指定申請を行い，以下のとおり指定を受けた。

- 指定日：2014 年 6 月 11 日
- 指定番号：(26 薬) 第 341 号
- 予定される効能又は効果：悪性軟部腫瘍

1.5.6 まとめ

悪性軟部腫瘍に対する本薬の有効性が外国 207 試験，外国 309 試験及び国内 217 試験で認められた。また，本薬投与によって発現した副作用は，本薬の減量，休薬又は延期などの処置により，臨床管理可能であった。

したがって，本薬は悪性軟部腫瘍を適応とする承認申請に必要な試験成績が十分に得られていると判断し，効能・効果を「悪性軟部腫瘍」として，承認事項一部変更承認申請を行うこととした。なお，用法・用量は既に承認されている乳癌と同一である。

1.5.7 参考文献

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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・許可状況

2015 年 10 月現在，エリブリンメシル酸塩は乳癌の治療薬として米国及び欧州等の世界 50 ヵ国以上の国と地域で承認・販売されている。

表 1.6-1 に主要国の承認・許可状況を示した。

2015 年 10 月現在，悪性軟部腫瘍に対する効能・効果で本剤の承認を取得している国はなく，米国及び欧州にて，日本の承認申請と同時期の 2015 年 7 月 29 日に承認申請を行った。また，2015 年 9 月 10 日にスイスにおいて，承認申請を行った。

表 1.6-1　主要国の承認・許可状況（2015 年 10 月現在）

国名	販売名	承認年月日	剤型・含量	承認効能・効果	承認用法・用量
米国	HALAVEN	2010年 11月15日	注射剤 （バイアル） ・1 mg （エリブリン メシル酸塩と して）	HALAVENは，転移性乳癌に対する2レジメン以上の前化学療法歴を有する乳癌患者の治療を適応とする。前治療にはアントラサイクリン系及びタキサン系薬剤を術後化学療法又は転移性乳癌に対する治療法として含むこととする。	エリブリンメシル酸塩 1.4 mg/m^{2}を，21日間サイクルの第1及び8日目に2～5分間かけて静脈内（IV）投与する。
欧州	HALAVEN 注射液 0.44 mg/ml	2011年 3月17日	注射剤 （バイアル） ・0.88 mg 又は 1.32 mg （エリブリン として）	HALAVEN は，局所進行又は転移性乳癌に対する1レジメン以上の前化学療法歴を有する成人の乳癌患者の治療を適応とする。前治療には患者に不適応でない限りアントラサイクリン系及びタキサン系薬剤を術後化学療法又は転移性乳癌に対する治療法として含むこととする。	エリブリンの推奨用量は1.23 mg/m^{2}であり，この用量で21日間サイクルの第1及び8日目に2～5分間かけて静脈内投与する。

1.6.2 外国における添付文書

米国の添付文書及び欧州の製品情報概要（SmPC：Summary of Product Characteristics）の和訳（概要）を表 1.6-2 に記載した。また，米国の添付文書，欧州の製品情報概要（原文）及び Company Core Data Sheet を添付した。

表 1.6-2　米国の添付文書及び欧州の製品情報概要

国名	米国	欧州
承認日	2010 年 11 月 15 日	2011 年 3 月 17 日
引用文書作成年月日	2015 年 10 月 27 日	2015 年 11 月 19 日
販売名	HALAVEN	HALAVEN 注射液 0.44 mg/mL
剤型・含量	バイアル：1 mg /2mL （エリブリンメシル酸塩として）	バイアル：0.88 mg/2 mL 又は 1.32 mg/3 mL （エリブリンとして）
効能・効果	HALAVEN は，転移性乳癌に対する 2 レジメン以上の前化学療法歴を有する乳癌患者の治療を適応とする。前治療にはアントラサイクリン系及びタキサン系薬剤を術後化学療法又は転移性乳癌に対する治療法として含むこととする。	HALAVEN は，局所進行又は転移性乳癌に対する 1 レジメン以上の前化学療法歴を有する成人の乳癌患者の治療を適応とする。前治療には患者に不適応でない限りアントラサイクリン系及びタキサン系薬剤を術後化学療法又は転移性乳癌に対する治療法として含むこととする。
用法・用量	推奨用量 HALAVEN の推奨用量は 1.4 mg/m^2 であり，21 日間サイクルの第 1 及び 8 日目に 2～5 分間かけて静脈内（IV）投与する。 軽度の肝機能障害（Child-Pugh A）を有する患者に対する HALAVEN の推奨用量は 1.1 mg/m^2 であり，21 日間サイクルの第 1 及び 8 日目に 2～5 分間かけて静脈内（IV）投与する。 中等度の肝機能障害（Child-Pugh B）を有する患者に対する HALAVEN の推奨用量は 0.7 mg/m^2 であり，21 日間サイクルの第 1 及び 8 日目に 2～5 分間かけて静脈内（IV）投与する。 中等度の腎機能障害（クレアチニンクリアランス 30-50 mL/min）を有する患者に対する HALAVEN の推奨用量は 1.1 mg/m^2 であり，21 日間サイクルの第 1 及び 8 日目に 2～5 分間かけて静脈内（IV）投与する。 用量調節 投与前に末梢性ニューロパチー及び全血球数を評価する。 推奨される投与の延期 以下に該当する場合，Day 1 又は Day 8 に HALAVEN を投与しないこと。 -好中球絶対数 ＜1,000/mm^3 -血小板数 ＜75,000/mm^3 -Grade 3 又は 4 の非血液毒性	HALAVEN は，資格を有し，細胞障害性抗がん剤の適切な使用に関して経験がある医師の管理下でのみ投薬すべきである。 エリブリンの推奨用量は 1.23 mg/m^2 であり，溶液をそのまま使用可能である。本用量で 21 日間サイクルの第 1 及び 8 日目に 2～5 分間かけて静脈内投与する。 注意： EU における推奨用量は活性体（エリブリン）の量を参照している。患者に投与する用量は，エリブリン 0.44 mg/mL を含む使用可能な溶液を用いて，推奨用量である 1.23 mg/m^2 を計算する。下記に示す推奨減量用量についても本使用可能な溶液量に基づいて記載されている。 ピボタル EMBRACE 試験及びその論文，欧米，スイス等では推奨用量は塩の形態（エリブリンメシル酸塩）に基づいて記載されている。 悪心，嘔吐が発現する場合があるため，ステロイドを含む制吐剤の予防的投与を検討する。 治療中の投与延期 下記に該当する場合 HALAVEN の Day 1 及び Day 8 の投与を延期する。 -好中球絶対数 ＜1 x 10^9/L -血小板数 ＜75 x 10^9/L -Grade 3 又は 4 の非血液毒性

<table>
<tr><th>国名</th><th>米国</th><th>欧州</th></tr>
<tr>
<td></td>
<td>
Day 8 の投与は最大 1 週間延期する。
-もし毒性が Day 15 までに Grade 2 以下に回復又は改善しない場合，投与を休薬する。
-もし毒性が Day15 までに Grade 2 以下に回復又は改善した場合，HALAVEN の用量を減量し，2 週間後以降より次サイクルを開始する。

推奨される用量の減量
-もし毒性によって投与を延期した場合，Grade 2 以下に回復した際には表 1 に示す用量に減量し，HALAVEN の投与を再開する。
-HALAVEN の用量を減量後の再増量は行わない。

表 1 推奨される減量方法
<table>
<tr><th>事象の詳細</th><th>HALAVEN の推奨用量</th></tr>
<tr><td>以下に該当した場合，HALAVEN の用量を 1.4 mg/m^2 より減量する。</td><td></td></tr>
<tr><td>ANC＜500/mm^3 の状態が 7 日間を超えて続く場合
ANC ＜ 1,000/mm^3 であって発熱又は感染が併発した場合
血小板数 ＜25,000/mm^3 未満の場合
血小板数 ＜50,000/mm^3 未満であり，輸血が必要な場合
Grade 3 又は Grade 4 の非血液毒性
毒性により前サイクルの HALAVEN Day 8 の投与を休薬又は延期した場合</td><td>1.1 mg/m^2</td></tr>
<tr><td>1.1 mg/m^2 に減量したにもかかわらず減量を要する毒性が発現した場合</td><td>0.7 mg/m^2</td></tr>
<tr><td>0.7 mg/m^2 に減量したにもかかわらず減量を要する毒性が発現した場合</td><td>HALAVEN 投与中止</td></tr>
</table>
ANC：好中球絶対数
National Cancer Institute（NCI）の Common Terminology Criteria for Adverse Events（CTCAE）に従って Grade を判定
</td>
<td>
治療中の減量
再投与の際の推奨減量用量を下記の表に示す。

推奨される減量方法
<table>
<tr><th>HALAVEN 投与後の有害事象</th><th>エリブリンの推奨用量</th></tr>
<tr><td>血液毒性：</td><td></td></tr>
<tr><td>7 日間を超えて好中球絶対数 ＜0.5 x 10^9/L が継続</td><td></td></tr>
<tr><td>発熱又は感染を伴う好中球絶対数 ＜1 x 10^9/L の好中球減少症</td><td></td></tr>
<tr><td>血小板数 ＜25 x 10^9/L の血小板減少症</td><td>0.97 mg/m^2</td></tr>
<tr><td>出血を伴うか，あるいは輸血又は血小板輸血を必要とする血小板数 ＜50 x 10^9/L の血小板減少症</td><td></td></tr>
<tr><td>非血液毒性：</td><td></td></tr>
<tr><td>前回のサイクルにおける Grade 3 又は 4 の毒性</td><td></td></tr>
<tr><td>上記の血液毒性又は非血液毒性の再発</td><td></td></tr>
<tr><td>0.97 mg/m^2 に減量した場合</td><td>0.62 mg/m^2</td></tr>
<tr><td>0.62 mg/m^2 に減量した場合</td><td>投与中止を考慮</td></tr>
</table>
減量後はエリブリンの用量を増量しないこと。

肝機能障害を有する患者
転移による肝機能障害
軽度の肝機能障害を有する患者（Child-Pugh A）に対するエリブリンの推奨用量は 0.97 mg/m^2 であり，21 日間サイクルの第 1 及び 8 日目に 2～5 分間かけて静脈内投与する。中等度の肝機能障害を有する患者（Child-Pugh B）に対するエリブリンの推奨用量は 0.62 mg/m^2 であり，21 日間サイクルの第 1 及び 8 日目に 2～5 分間かけて静脈内投与する。高度の肝機能障害を有する患者（Child-Pugh C）に対する検討はなされていないが，エリブリンの投与が必要な場合はより顕著な減量が必要
</td>
</tr>
</table>

国名	米国	欧州
		であると考えられる。 肝硬変に伴う肝機能障害 本対象に対する検討はなされてない。軽度又は中等度の障害には上記の用量を推奨するが，再調整を要する場合があるので注意深くモニタリングすること。 腎機能障害を有する患者 高度の腎機能障害を有する患者（クレアチニンクリアランス < 40 ml/min）は減量を要する。本対象に関する至的用量は今後検討されるべきである。注意深く安全性をモニタリングすること。軽度又は中等度の腎機能障害を有する患者に対する減量は推奨されていない。 高齢の患者 患者の年齢に応じた特定の用量調節は推奨されていない。 小児の患者 小児及び青年期の乳癌に対する HALAVEN の使用経験はない。 投与方法 希釈が望ましい場合は，注射用生理食塩液（塩化ナトリウム［NaCl］の 0.9% w/v 水溶液）で 100 mL まで希釈してもよい。5%ブドウ糖液では希釈しないこと。
禁忌	なし。	本剤の成分又は添加剤のいずれかに対する過敏症 授乳婦
警告・使用上の注意	好中球減少症 一週間を超える重度の好中球減少症（ANC < 500/mm^3）が Study 1 において 12%（62/503）の患者に発現し，< 1%の患者が投与中止に至っている。 ALT 又は AST > 3 x ULN（基準値上限）の患者は，これらの値が正常な患者と比較して高頻度に Grade 4 の好中球減少症及び発熱性好中球減少症を発現した。 ビリルビン > 1.5 x ULN の患者も高頻度に Grade 4 の好中球減少症及び発熱性好中球減少症を発現した。 投与前に全血球数の値をモニタリングし，Grade 3 又は 4 の血球減少症を発現した患者においてはモニタリングの頻度を多くすること。	血液毒性 骨髄抑制は用量依存的であり，主として好中球減少症を発現する（「副作用／有害事象」の項を参照）。エリブリンによる治療は，好中球絶対数が 1.5×10^9/L 以上で，血小板数が 100×10^9/L を超える患者に限って開始すべきである。 発熱性好中球減少症はエリブリンを投与した患者の< 5%に認められた。発熱性好中球減少症，高度の好中球減少症又は血小板減少症が発現した患者については，「用法・用量」の項（推奨される用量調節方法）に従って処置すべきである。

国名	米国	欧州
	発熱性好中球減少症又は 7 日間を超えて Grade 4 の好中球減少症を発現した患者では HALAVEN の投与を延期し，次回投与量を減量すること。 HALAVEN の臨床試験ではベースラインの好中球数が 1,500/mm^3 を下回る患者は含まれていない。 末梢性ニューロパチー Grade 3 の末梢性ニューロパチーは Study1 の 8%（40/503）の患者，Grade 4 は 0.4%（2/503）の患者で発現した。末梢性ニューロパチーは HALAVEN の投与中止に至った最も主要な毒性であった（5%の患者；24/503）。1 年を超えて継続するニューロパチーは 5%（26/503）の患者で発現した。22%（109/503）の患者でフォローアップ期間の中央値 269 日（幅 25-662 日）の間に回復しない新規又は悪化したニューロパチーが発現した。患者の末梢機能と感覚性ニューロパチーの兆候を注意深くモニタリングすること。Grade 3 又は 4 の末梢性ニューロパチーを発現した患者は Grade 2 以下に回復するまで HALAVEN の投与を休薬すること。 胚胎児毒性 妊娠中の女性に対する十分な HALAVEN の臨床試験は実施されていない。HALAVEN は微小管阻害剤であることから妊娠中の女性に対して胎児へ障害を与える可能性がある。体表面積あたりでヒトの推奨用量の約半量のエリブリンメシル酸塩を投与したラットにおいて胚胎児毒性及び催奇形性が認められている。もし妊娠中又は妊娠予定の患者に本薬を使用する場合は，患者に胎児への潜在的な危険性について通告すること。 QT 間隔延長 26 例の患者を対象とした心電図のオープン試験において Day 1 に QT 間隔の延長が認められなかった患者に，エリブリン濃度に依らず Day 8 に QT 間隔の延長が認められた。うっ血性心不全，徐脈性不整脈を有する患者，クラス Ia 及び III の抗不整脈薬等，QT 間隔を延長する薬剤を使用している患者，電解質異常を有する患者には心電図のモニタリングが推奨される。HALAVEN 投与前には低カリウム血症，低マグネウム血症に対する治療を実施し，定期的にこれらの電解質をモニタリングすること。先天的な QT 延長症候群を有する患者には HALAVEN を	高度の好中球減少症は G-CSF 又はそれに準ずる薬剤により，ガイドラインを参照して医師の指示により適切に管理すること。 末梢性ニューロパチー 末梢性ニューロパチーの徴候を示した患者を注意深くモニタリングすること。高度の末梢性神経毒性を発現した患者は投与を休薬又は延期すること。 臨床試験では，Grade 2 を超えるニューロパチーの合併症を有する患者は除外された。Grade 1 又は 2 のニューロパチーの合併症を有する患者は合併症がない状態で試験に登録した患者の場合と比較して，新たな症状の発現頻度又は症状の悪化の程度に差はみられなかった。 QT 間隔延長 26 例の患者を対象とした心電図のオープン試験において Day 1 に QT 間隔の延長が認められなかった患者に，エリブリン濃度に依らず Day 8 に QT 間隔の延長が認められた。うっ血性心不全，徐脈性不整脈を有する患者，クラス Ia 及び III の抗不整脈薬等，QT 間隔を延長する薬剤を使用している患者，電解質異常を有する患者には心電図のモニタリングが推奨される。HALAVEN 投与前には低カリウム血症，低マグネウム血症に対する治療を実施し，定期的にこれらの電解質をモニタリングすること。先天的な QT 延長症候群を有する患者には HALAVEN を投与しないこと。 抗 HER2 療法との併用 エリブリンと抗 HER2 療法を併用した臨床試験は実施されていない。 添加物 本薬には少量のエタノール（アルコール）が投与量あたり 100 mg 以下の用量で含まれている。

国名	米国	欧州
	投与しないこと。	
相互作用	HALAVEN に対する他の薬物の影響 CYP3A4 阻害剤，誘導剤又は P 糖タンパク質阻害剤との薬物間相互作用はないと考えられる。強力な CYP3A4 阻害及び P 糖タンパク質阻害剤であるケトコナゾール及び CYP3A4 誘導剤であるリファンピシンとの併用投与でも，エリブリンメシル酸塩単独投与時に比較して，エリブリンの暴露量（AUC）の臨床的に意義のある差は認められなかった。 他の薬物に対する HALAVEN の影響 エリブリンは，臨床的に適切な濃度において CYP1A2，CYP2C9，CYP2C19，CYP2D6，CYP2E1 又は CYP3A4 酵素を阻害せず，CYP1A2，CYP2C9，CYP2C19 又は CYP3A4 酵素を誘導せず，これらの酵素の基質となる他の薬物の血漿中濃度も変化させないと考えられる。	カルバマゼピン，フェニトイン，セイヨウオトギリソウといった誘導物質との併用によりエリブリンの血漿中濃度が上昇する可能性は否定できず，これらの誘導物質と併用する際は有効性が減弱する潜在的危険性に注意すべきである。CYP3A4 の誘導剤であるリファンピシンとの併用においてエリブリンの暴露量（AUC 及び C_{max}）に特筆すべき影響はなかった。しかしながらリファンピシンはそのトランスポーター阻害能から，エリブリンの排出を潜在的に誘導する可能性がある。 CYP3A4 阻害剤との薬物相互作用はないと考えられる。CYP3A4 及び P 糖タンパク質阻害物質であるケトコナゾールとの併用投与では，エリブリンの暴露量（AUC 及び C_{max}）に影響はなかった。 他の薬物の薬物動態に対するエリブリンの影響 エリブリンは重要な薬物代謝酵素である CYP3A4 を阻害する可能性がある。これは in vitro のデータより示唆されたが，in vivo のデータはない。 CYP3A4 により代謝される薬物と併用する際は，当該薬物の血漿中濃度が上昇する可能性があるため，有害事象の発現を注意深くモニタリングすること。薬剤の治療域が狭い場合は併用投与を避けること。 エリブリンは，臨床的に適切な濃度において CYP1A2，2B6，2C8，2C9，2C19，2D6 又は 2E1 酵素を阻害しない。
副作用 /有害事象	次の副作用については，他の項において詳細に考察した。 ・好中球減少症（「警告・使用上の注意」の項を参照） ・末梢性ニューロパチー（「警告・使用上の注意」の項を参照） ・QT 間隔延長（「警告・使用上の注意」の項を参照） HALAVEN を投与した患者で最も多く報告された有害事象（25%以上）は，好中球減少症，貧血，無力症／疲労，脱毛症，末梢性ニューロパチー，悪心及び便秘であった。最も多く報告された重篤な有害事象は発熱性好中球減少症（4%）及び好中球減少症（2%）であった。	下表に，5 つの第 II 相試験及び 2 つの第 III 相試験において，推奨用量を使用した 1503 例の乳癌患者に関してみられた有害事象の発現率を示した。発現頻度は，次のように定義した： 「極めて多い」（≥1/10），「多い」（≥1/100，<1/10），「多くない」（≥1/1,000，<1/100），「稀」（≥1/10,000，<1/1,000），「極めて稀」（<1/10,000）。各頻度グループにおいて，副作用を発現頻度の高い順に記載した。Grade 3／4 の副作用が発現した場合は，全ての Grade 及び Grade 3/4 の，実際の発現頻度を示した。

国名：米国

HALAVEN の投与中止に至った副作用で最も多かったのは，末梢性ニューロパチー（5%）であった。

臨床試験では，複数のがん腫を含む 1222 例の患者に HALAVEN が投与され，そのうち 240 例に 6 ヵ月間以上の長期にわたって投与された。患者の年齢は 26 歳から 91 歳の範囲（中央値：58 歳）であり，82%が女性で，白人が 83%，黒人が 5%，アジア人が 2%，並びにその他の人種が 5%であった。

表 2 に，Study 1 において 750 例の患者で認められた有害事象をまとめた。Study 1 では患者は HALAVEN（21 日間を 1 サイクルとして 1.4 mg/m2 を Day 1 及び 8 に投与）及び主治医によって選択された単剤治療（対照群）に 2:1 に割付けられた。計 503 例が HALAVEN を投与され，対照群の 247 例が主治医選択治療［化学療法 97%（アントラサイクリン系薬剤 10%，カペシタビン 18%，ゲムシタビン 19%，タキサン系薬剤 15%，ビノレルビン 25%，その他の化学療法剤 11%）及びホルモン療法 3%］を投与された。投与期間の中央値は，HALAVEN 投与群が 118 日間，主治医選択治療群が 63 日間であった。表 2 に最も多く認められた（いずれかの群で 10%以上）有害事象をまとめた。

表 2 Study 1 において
10%以上で発現した有害事象

MedDRA ver 10.0	HALAVEN n＝503		主治医選択治療 n＝247	
	All grades	≥Grade 3	All grades	≥Grade 3
血液及びリンパ系障害 [a]				
好中球減少症	82%	57%	53%	23%
貧血	58%	2%	55%	4%
神経系障害				
末梢性ニューロパチー[b]	35%	8%	16%	2%
頭痛	19%	<1%	12%	<1%

欧州

器官別大分類	副作用 －全 Grade			
	極めて多い（頻度%）	多い（頻度%）	多くない（頻度%）	稀
感染症及び寄生虫症		尿路感染（8.0%）（G3/4: 0.5%） 肺炎(1.2%) (G3/4: 0.8%) 口腔カンジダ症 口腔ヘルペス 上気道感染 鼻咽頭炎 鼻炎	敗血症 (0.5%) (G3/4: 0.2%)[a] 好中球減少性敗血症 (0.1%) (G3/4: 0.1%) 帯状疱疹	
血液及びリンパ系障害	好中球減少症 (57.0%) (G3/4: 49.7%) 白血球減少症 (29.3%) (G3/4: 17.3%) 貧血(20.6%) (G3/4: 2.0%)	リンパ球減少症(4.9%) (G3/4: 1.4%) 発熱性好中球減少症(4.7%) (G3/4: 4.5%) [a] 血小板減少症 (4.3%) (G3/4: 0.7%)		播種性血管内凝固症候群 [b]
代謝及び栄養障害	食欲減退 (21.9%) (G3/4: 0.7%)	低カリウム血症(6.1%) (G3/4: 1.7%) 低マグネシウム血症(2.9%) (G3/4: 0.2%) 脱水(2.8 %) (G3/4: 0.5%) 高血糖 低リン酸血症		
精神障害		不眠症 うつ病		

国名：米国

全身障害及び投与局所様態				
無力症／疲労	54%	10%	40%	11%
粘膜の炎症	9%	1%	10%	2%
発熱	21%	<1%	13%	<1%
胃腸障害				
便秘	25%	1%	21%	1%
下痢	18%	0	18%	0
悪心	35%	1%	28%	3%
嘔吐	18%	1%	18%	1%
臨床検査				
体重減少	21%	1%	14%	<1%
代謝及び栄養障害				
食欲不振	20%	1%	13%	1%
呼吸器，胸郭及び縦隔障害				
咳嗽	14%	0	9%	0
呼吸困難	16%	4%	13%	4%
皮膚及び皮下組織障害				
脱毛症	45%	NA[C]	10%	NA[C]
感染症及び寄生虫症				
尿路感染	10%	1%	5%	0

a：臨床検査値に基づく
b：末梢性ニューロパチー，ニューロパチー，末梢性運動ニューロパチー，多発ニューロパチー，末梢性感覚ニューロパチー及び錯感覚が含まれる。
c：該当せず；脱毛症には Grade 2 を超える定義がない

血球減少症：Study 1 で HALAVEN を投与した患者の 28%（143/503）が Grade 3，29%（144/503）が Grade 4 の好中球減少症を発現した。発熱性好中球減少症は 5%（23/503）の患者で発現し，2 例（0.4%）の患者が発熱性好中球減少症の合併により死亡した。好中球減少症に伴い

欧州

神経系障害	末梢性ニューロパチー[c](35.6%) (G3/4: 7.6%) 頭痛(17.2%) (G3/4: 0.8%)	味覚異常 浮動性めまい (7.9%) (G3/4: 0.5%) 感覚鈍麻 嗜眠 神経毒性		
眼障害		流涙増加 (6.0%) (G3/4: 0.1%) 結膜炎		
耳及び迷路障害		回転性めまい	耳鳴	
心臓障害		頻脈		
血管障害		ほてり	深部静脈血栓症 肺塞栓症	
呼吸器，胸郭及び縦隔障害	呼吸困難 (13.9%)[a] (G3/4: 3.1%) 咳嗽 (13.6%) (G3/4: 0.6%)	口腔咽頭痛 鼻出血 鼻漏		間質性肺炎
胃腸障害	悪心(33.8%) (G3/4: 1.1%) 便秘(19.6%) (G3/4: 0.6%) 下痢(17.9%) (G3/4: 0.8%) 嘔吐(17.6%) (G3/4: 0.9%)	腹痛 口内炎(9.3%) (G3/4: 0.8%) 口内乾燥 消化不良(5.9%) (G3/4: 0.2%) 胃食道逆流性疾患 口腔内潰瘍形成 腹部膨満		膵炎[b]

<table>
<tr><td>国名</td><td>米国</td><td colspan="5">欧州</td></tr>
<tr><td></td><td>12%（62/503）の患者が減量を要し，<1%の患者が投与を中止した。サイクル内における最低値は約 13 日目（平均値）にあらわれ，高度の好中球減少症（< 500/mm^3）からの回復に約 8 日間（平均値）を要した。Grade 3 以上の血小板減少症が 1%（7/503）の患者に認められた。G-CSF（顆粒球コロニー刺激因子）又は GM-CSF（顆粒球マクロファージコロニー刺激因子）は HALAVEN を投与した患者の 19%使用された。

末梢性ニューロパチー：Study 1 に登録された患者のうち，17%が Grade 1，3%が Grade 2 の末梢性ニューロパチーをベースライン時に合併していた。HALAVEN を投与した患者の 3%（14/503）の患者が末梢性ニューロパチーにより減量を要した。4%（20/503）の患者が末梢性運動ニューロパチーを発現し，2%（8/503）が Grade 3 であった。

肝機能検査値障害：ベースライン時に ALT の値が Grade 0 又は Grade 1 であった患者のうち，HALAVEN を投与した 18%の患者が Grade 3 以上の ALT 上昇を発現した。HALAVEN を投与した肝転移がなく，Grade 2 の ALT 及びビリルビン上昇を合併していた 1 例の患者ではこれらの異常は回復し，HALAVEN の再投与により再発しなかった。

その他の副作用：以下に示すその他の副作用が HALAVEN 投与群の 5%以上 10%未満の患者で報告された。

眼障害：流涙増加
胃腸障害：消化不良，上腹部痛，腹痛，口内乾燥
全身障害及び投与局所様態：末梢性浮腫
感染症及び寄生虫症：上気道感染
代謝及び栄養障害：低カリウム血症
筋骨格系及び結合組織障害：筋痙縮，筋力低下
神経系障害：味覚異常，浮動性めまい
精神障害：不眠症，不安
皮膚及び皮下組織障害：発疹</td><td>肝胆道系障害</td><td></td><td>アラニン・アミノトランスフェラーゼ増加
(7.6%)
(G3/4: 2.1%)[d]
アスパラギン酸アミノトランスフェラーゼ増加
(7.4%)
(G3/4: 1.5%)
γ-グルタミルトランスフェラーゼ増加
(1.8%)
(G3/4: 0.9%)
高ビリルビン血症
(1.5%)
(G3/4: 0.3%)</td><td>肝臓毒性
(1.0%)
(G3/4: 0.6%)</td><td></td></tr>
<tr><td>皮膚及び皮下組織障害</td><td>脱毛症</td><td>発疹
そう痒症
(3.9%)
(G3/4: 0.1%)
爪の障害
寝汗
皮膚乾燥
紅斑
多汗症</td><td>手掌・足底発赤知覚不全</td><td>血管性浮腫</td></tr>
<tr><td>筋骨格系及び結合組織障害</td><td>関節痛及び筋痛
(19.4%)
(G3/4: 1.1%)
背部痛
(13.0%)
(G3/4:1.5%)
四肢痛
(10.0%)
(G3/4: 0.7%)</td><td>骨痛
(9.6%)
(G3/4: 1.7%)
筋痙縮
(5.1%)
(G3/4: 0.1%)
筋骨格痛及び筋骨格系胸痛
筋力低下</td><td></td><td></td></tr>
</table>

国名	米国	欧州

腎及び尿路障害		排尿困難	血尿 蛋白尿 腎不全	
全身障害及び投与局所様態	疲労／無力症 (47.9%) (G3/4 : 7.8%) 発熱 (20.4%) (G3/4: 0.6%)	粘膜の炎症 (8.3%) (G3/4: 1.1%)[d] 末梢性浮腫 疼痛 悪寒 胸痛 インフルエンザ様疾患		
臨床検査	体重減少 (11.3%) (G3/4: 0.3%)			

a：1 又は 2 例の Grade 5 のを含む
b：自発報告
c：基本語として，末梢性ニューロパチー，末梢性運動ニューロパチー，多発ニューロパチー，錯感覚，末梢性感覚ニューロパチー，末梢性感覚運動ニューロパチー及び脱髄性多発ニューロパチーを含む。
d：Grade 4 なし

代表的な副作用

好中球減少症：認められた好中球減少症は可逆的であり，蓄積性はなかった。最低値までの時間の平均値は 13 日間であり，高度の好中球減少症（0.5×10^9/L 未満）から回復するまでの時間の平均値は 8 日間であった。
好中球数 0.5×10^9/L 未満の 7 日間以上の継続は，EMBRACE 試験における乳癌患者の 13%に認められた。
高度の好中球減少症を発現した場合は G-CSF 又はそれに準ずる薬剤を，ガイドラインを参照の上，医師の指示の元使用すること。臨床第 3 相試験ではエリブリンを投与した乳癌患者のうち 18%に G-CSF を投与した。
投与中止に至った好中球減少症の発現は，エリブリン投与例の 1%未満であった。

国名	米国	欧州
		播種性血管内凝固症候群：好中球減少症及び/又は敗血症と関連した播種性血管内凝固症候群が報告されている。 **末梢性ニューロパチー**：1503 例の乳癌患者において，エリブリンの投与中止に至った副作用で最も多かったのは，末梢性ニューロパチー（3.3%）であった。Grade 2 の末梢性ニューロパチーを発現するまでの期間の中央値は 85.5 日（4 サイクル以降）であった。 Grade 3 又は 4 の末梢性ニューロパチーはエリブリンを投与した乳癌患者の 7.7%で発現した。臨床試験では，ニューロパチーの合併を有する患者は，登録時に合併のなかった患者に比較して，新たな症状又は症状の悪化を発現しやすいということはなかった。 Grade 1 又は 2 の末梢性ニューロパチーを合併していた患者において治療を要する Grade 3 の末梢性ニューロパチーの発現は 14%であった。 肝毒性：エリブリンの治療前に肝酵素が正常/異常であった何例かの症例でエリブリン治療後の肝酵素の増加が認められた。多くの症例において，このような上昇はエリブリン治療後 1-2 サイクルの早期に認められ，エリブリン投与による肝臓の適応のためであり，多数の症例において重要な肝毒性の兆候ではないと考えられたが，肝毒性の報告もあった。 <u>特別な集団</u> <u>高齢集団</u> エリブリンの推奨用量にて 1503 例の患者に投与された試験合計では，209 例（13.9%）が 65 歳超から 75 歳であり，24 例（1.6%）が 75 歳超であった。高齢患者（65 歳超）におけるエリブリンの安全性プロファイルは，65 歳以下の患者の場合と類似していたが，無力症/疲労において年齢によって増加する傾向が認められた。患者の年齢に基づく用量の調節は推奨しない。 <u>肝障害を有する患者</u> ALT 又は AST が施設基準値上限の 3 倍を超える患者では，Grade 4 の好中球減少症及び発熱性好中球減少症がより高い頻度で発現した。データは限られているが，ビリルビンが施設基準値上限の 1.5 倍を超える患者でも Grade 4 の好中球減少症及び発熱性好中球減少症がより高い頻度

国名	米国	欧州
		で発現した。「警告・使用上の注意」の項を参照のこと。
高齢者への投与	Study 1 では 65 歳以上がより若い被験者と比較して異なる反応を示すか否かを検出する十分な被験者数は含まれていなかった。HALAVEN の推奨を投与した 827 例中，121 例（15%）が 65 歳以上，17 例（2%）が 75 歳以上であった。これらの被験者と若い被験者の間に安全性上の違いは認められなかった。	患者の年齢に基づいた用量調節に関し，特別な推奨事項はない。「副作用／有害事象」の項を参照のこと。
妊婦への投与	妊娠カテゴリーD（「警告・使用上の注意」の項を参照）	妊婦におけるエリブリンの使用に関する情報はない。エリブリンは，ラットにおいて胚毒性，胎児毒性，及び催奇形性を示し，ラット及びイヌにおいて精巣毒性を示すことが明らかとなっている。HALAVEN の必要性が明らかであり，母親に対する必要性と胎児に対するリスクを十分に考慮した場合でない限り，本剤を妊娠中に投与するべきではない。 妊娠の可能性があるものは HALAVEN を投与する場合は，治療から 3 カ月間適切に避妊すべきである。
授乳婦への投与	HALAVEN がヒト乳汁中に移行するかどうかは不明である。ヒト又は動物において乳汁中に HALAVEN が移行するか検討した試験は実施されていない。多くの薬物がヒト乳汁中に排泄されるので，また，HALAVEN によって哺育中の乳児に重大な副作用が発現する可能性があるので，母親に対する HALAVEN の重要性を考慮しながら，授乳を中止するかあるいは HALAVEN の投与を中止するかを決定しなければならない。	エリブリン又はその代謝物がヒト又は動物の乳汁中に排泄されるかどうかに関する情報は不十分である。新生児又は幼児に対する危険性は除外できず，したがって，HALAVEN は授乳中に使用すべきでない（「禁忌」の項を参照）。
小児への投与	小児患者（18 歳以下）における HALAVEN の安全性及び有効性は確立されていない。	小児及び青年期の乳癌に対する HALAVEN の使用経験はない。
過量投与	HALAVEN の過量投与例は，推奨用量の 4 倍の投与が報告されており，7 日間続く Grade 3 の好中球減少症及び 1 日続く Grade 3 の過敏症を発現した。 HALAVEN の過量投与に対する解毒薬は知られていない。	エリブリンの過量投与例は，1 例が報告されており，エリブリン 7.6 mg（計画した用量の約 4 倍）が投与され，第 3 日目に過敏症反応（Grade 3），第 7 日目に好中球減少症（Grade 3）が発現した。ともに支持療法で解消した。 HALAVEN の過量投与に対する解毒薬は知られていない。過量投与が起こった場合は，当該患者を綿密に観察すべきである。過量投与の管理には，その時点でみられる臨床症状に対処する支持療法が行われるべきである。

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

HALAVEN® (eribulin mesylate) Injection
For intravenous administration
Initial US Approval: 2010

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

Dosage and Administration, Recommended Dose (2.1)	12/2014
Dosage and Administration, Dose Modification (2 2)	12/2014

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

HALAVEN is a microtubule inhibitor indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. P rior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting (1)

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

- Administer 1.4 mg/m^2 intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle (2.1)
- Reduce dose in patients with hepatic impairment or with moderate or severe renal impairment (2.1)
- Do not mix with other drugs or administer with dextrose-containing solutions (2.3)

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

Intravenous administration (3)
Eribulin mesylate injection, 1 mg per 2 mL (0.5 mg per mL) (3)

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

None.

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

- **Neutropenia**: Monitor peripheral blood cell counts and adjust dose as appropriate (2.2, 5.1, 6)
- **Peripheral Neuropathy**: Monitor for signs of neuropathy. Manage with dose delay and adjustment (2 2, 5.2, 6)
- **Embryo-Fetal Toxicity**: Fetal harm can occur when administered to a pregnant woman (5 3) (8.1)
- **QT Prolongation**: Monitor for prolonged QT intervals in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid in patients with congenital long QT syndrome (5.4)

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

The most common adverse reactions (incidence ≥25%) were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at (1-877-873-4724) or contact FDA at 1-800-FDA-1088 or www.fda gov/medwatch

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

- Nursing Mothers: Discontinue drug or nursing, taking into consideration the importance of the drug to the mother (8 3)
- Hepatic Impairment: A lower starting dose is recommended for patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. Patients with severe hepatic impairment (Child-Pugh C) were not studied (8.6)
- Renal Impairment: A lower starting dose is recommended for patients with moderate (CrCl 30-49 mL/min) or severe (CrCl 15-29 mL/min) renal impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: October 2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HALAVEN is indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of HALAVEN is 1.4 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

The recommended dose of HALAVEN in patients with mild hepatic impairment (Child-Pugh A) is 1.1 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle [*see Use in Specific Populations (8.6)*].

The recommended dose of HALAVEN in patients with moderate hepatic impairment (Child-Pugh B) is 0.7 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle [*see Use in Specific Populations (8.6)*].

The recommended dose of HALAVEN in patients with moderate or severe renal impairment (creatinine clearance (CrCl) 15-49 mL/min) is 1.1 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle [*see Use in Specific Populations (8.7)*].

2.2 Dose Modification

Assess for peripheral neuropathy and obtain complete blood cell counts prior to each dose.

Recommended dose delays

- Do not administer HALAVEN on Day 1 or Day 8 for any of the following:
  - ANC < 1,000/mm^3
  - Platelets < 75,000/mm^3
  - Grade 3 or 4 non-hematological toxicities.

- The Day 8 dose may be delayed for a maximum of 1 week.
  - If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
  - If toxicities resolve or improve to ≤ Grade 2 severity by Day 15, administer HALAVEN at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions

- If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume HALAVEN at a reduced dose as set out in Table 1.

- Do not re-escalate HALAVEN dose after it has been reduced.

Table 1 Recommended Dose Reductions

Event Description	Recommended HALAVEN Dose
Permanently reduce the 1.4 mg/m^2 HALAVEN dose for any of the following: ANC <500/mm^3 for >7 days ANC <1,000 /mm^3 with fever or infection Platelets <25,000/mm^3 Platelets <50,000/mm^3 requiring transfusion Non-hematologic Grade 3 or 4 toxicities Omission or delay of Day 8 HALAVEN dose in previous cycle for toxicity	1.1 mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m^2	0.7 mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue HALAVEN

ANC = absolute neutrophil count.
Toxicities graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

2.3 Instructions for Preparation and Administration

Aseptically withdraw the required amount of HALAVEN from the single-use vial and administer undiluted or diluted in 100 mL of 0.9% Sodium Chloride Injection, USP.

Do not dilute in or administer through an intravenous line containing solutions with dextrose. Do not administer in the same intravenous line concurrent with the other medicinal products.

Store undiluted HALAVEN in the syringe for up to 4 hours at room temperature or for up to 24 hours under refrigeration (40°F or/ 4°C). Store diluted solutions of HALAVEN for up to 4 hours at room temperature or up to 24 hours under refrigeration.

Discard unused portions of the vial.

3 DOSAGE FORMS AND STRENGTHS

HALAVEN (eribulin mesylate) Injection, 1 mg/2 mL (0.5 mg/mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

Severe neutropenia (ANC < 500/mm^3) lasting more than one week occurred in 12% (62/503) of patients in Study 1, leading to discontinuation in <1% of patients [*see Adverse Reactions (6)*]. Patients with alanine aminotransferase or aspartate aminotransferase > 3 × ULN (upper limit of normal) experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal aminotransferase levels. Patients with bilirubin > 1.5 × ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia.

Monitor complete blood counts prior to each dose; increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration of HALAVEN and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days [*see Dosage and Administration (2.2)*]. Clinical studies of HALAVEN did not include patients with baseline neutrophil counts below 1,500/mm^3.

5.2 Peripheral Neuropathy

Grade 3 peripheral neuropathy occurred in 8% (40/503) of patients, and Grade 4 in 0.4% (2/503) of patients in Study 1. Peripheral neuropathy was the most common toxicity leading to discontinuation of HALAVEN (5% of patients; 24/503). Neuropathy lasting more than one year occurred in 5% (26/503) of patients. Twenty-two percent (109/503) of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days). Monitor patients closely for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less [*see Dosage and Administration (2.2)*].

5.3 Embryo-Fetal Toxicity

There are no adequate and well-controlled studies of HALAVEN in pregnant women. HALAVEN is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats that received eribulin mesylate at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

5.4 QT Prolongation

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and monitor these electrolytes periodically during therapy. Avoid HALAVEN in patients with congenital long QT syndrome.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

- Neutropenia [*see Warnings and Precautions (5.1)*].
- Peripheral neuropathy [*see Warnings and Precautions (5.2)*].
- QT interval prolongation [*see Warnings and Precautions (5.4)*].

The most common adverse reactions (≥25%) reported in patients receiving HALAVEN were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving HALAVEN were febrile neutropenia (4%) and neutropenia (2%). The most common adverse reaction resulting in discontinuation of HALAVEN was peripheral neuropathy (5%).

In clinical trials, HALAVEN has been administered to 1,222 patients with multiple tumor types, including 240 patients exposed to HALAVEN for 6 months or longer. The majority of the 1,222 patients were women (82%) with a median age of 58 years (range: 26 to 91 years). The racial and ethnic distribution was Caucasian (83%), Black (5%), Asian (2%), and other (5%).

The adverse reactions described in Table 2 were identified in 750 patients treated in Study 1 [*see Clinical Studies (14)*]. In Study 1, patients were randomized (2:1) to receive either HALAVEN (1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle) or single agent treatment chosen by their physician (control group). A total of 503 patients received HALAVEN, and 247 patients in the control group received therapy consisting of chemotherapy [total 97% (anthracyclines 10%, capecitabine 18%, gemcitabine 19%, taxanes 15%, vinorelbine 25%, other chemotherapies 10%)] or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving HALAVEN and 63 days for patients receiving control therapy. Table 2 reports the most common adverse reactions occurring in at least 10% of patients in either group.

Table 2 Adverse Reactions with a Per-Patient Incidence of at Least 10% in Study 1

MedDRA ver 10.0	HALAVEN n=503		Control Group n=247	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Blood and Lymphatic System Disorders [a]				
Neutropenia	82%	57%	53%	23%
Anemia	58%	2%	55%	4%
Nervous system disorders				
Peripheral neuropathy[b]	35%	8%	16%	2%
Headache	19%	<1%	12%	<1%
General disorders and administrative site conditions				
Asthenia/Fatigue	54%	10%	40%	11%
Mucosal inflammation	9%	1%	10%	2%
Pyrexia	21%	<1%	13%	<1%
Gastrointestinal disorders				
Constipation	25%	1%	21%	1%
Diarrhea	18%	0	18%	0
Nausea	35%	1%	28%	3%
Vomiting	18%	1%	18%	1%
Musculoskeletal and connective tissue disorders				
Arthralgia/Myalgia	22%	<1%	12%	1%
Back pain	16%	1%	7%	2%
Bone pain	12%	2%	9%	2%
Pain in extremity	11%	1%	10%	1%
Investigations				
Weight decreased	21%	1%	14%	<1%
Metabolism and nutrition disorders				
Anorexia	20%	1%	13%	1%
Respiratory, thoracic, and mediastinal disorders				
Cough	14%	0	9%	0
Dyspnea	16%	4%	13%	4%
Skin and subcutaneous tissue disorders				
Alopecia	45%	NA[c]	10%	NA[c]
Infections and Infestations				
Urinary Tract Infection	10%	1%	5%	0

[a] based upon laboratory data.
[b] includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.
[c] not applicable; (grading system does not specify > Grade 2 for alopecia).

Cytopenias: Grade 3 neutropenia occurred in 28% (143/503) of patients who received HALAVEN in Study 1, and 29% (144/503) of patients experienced Grade 4 neutropenia. Febrile neutropenia occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia. Dose reduction due to neutropenia was required in 12% (62/503) of patients and discontinuation was required in <1% of patients. The mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (<500/mm^3) was 8 days. Grade 3 or greater thrombocytopenia occurred in 1% (7/503) of patients. G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte–macrophage colony-stimulating factor) was used in 19% of patients who received HALAVEN.

Peripheral Neuropathy: In Study 1, 17 % of enrolled patients had Grade 1 peripheral neuropathy and 3% of patients had Grade 2 peripheral neuropathy at baseline. Dose reduction due to peripheral neuropathy was required by 3% (14/503) of patients who received HALAVEN. Four percent (20/503) of patients experienced peripheral motor neuropathy of any grade and 2% (8/503) of patients developed Grade 3 peripheral motor neuropathy.

Liver Function Test Abnormalities: Among patients with Grade 0 or 1 ALT levels at baseline, 18% of HALAVEN-treated patients experienced Grade 2 or greater ALT elevation. One HALAVEN-treated patient without documented liver metastases had concomitant Grade 2 elevations in bilirubin and ALT; these abnormalities resolved and did not recur with re-exposure to HALAVEN.

Less Common Adverse Reactions: The following additional adverse reactions were reported in ≥5% to <10% of the HALAVEN-treated group:

- **Eye Disorders:** increased lacrimation
- **Gastrointestinal Disorders:** dyspepsia, abdominal pain, stomatitis, dry mouth
- **General Disorders and Administration Site Conditions:** peripheral edema
- **Infections and Infestations:** upper respiratory tract infection
- **Metabolism and Nutrition Disorders:** hypokalemia
- **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, muscular weakness
- **Nervous System Disorders:** dysgeusia, dizziness
- **Psychiatric Disorders:** insomnia, depression
- **Skin and Subcutaneous Tissue Disorders:** rash

6.2 Postmarketing Experience

The following adverse drug reactions have been identified during post-approval of HALAVEN. 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.

- **Blood and Lymphatic System Disorders:** lymphopenia
- **Gastrointestinal Disorders:** pancreatitis
- **Hepatobiliary Disorders:** hepatotoxicity
- **Immune System Disorders:** drug hypersensitivity
- **Infections and Infestations:** pneumonia, sepsis/neutropenic sepsis
- **Metabolism and Nutrition Disorders:** hypomagnesemia, dehydration
- **Respiratory, thoracic and mediastinal disorders:** interstitial lung disease
- **Skin and Subcutaneous Tissue Disorders:** pruritus

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on HALAVEN

No drug-drug interactions are expected with CYP3A4 inhibitors, CYP3A4 inducers or P-glycoprotein (P-gp) inhibitors. Clinically meaningful differences in exposure (AUC) were not observed in patients with advanced solid tumors when HALAVEN was administered with or without ketoconazole (a strong inhibitor of CYP3A4 and a P-gp inhibitor) and when HALAVEN was administered with or without rifampin (a CYP3A4 inducer) *[see Clinical Pharmacology (12.3)]*.

7.2 Effect of HALAVEN on Other Drugs

Eribulin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 enzymes or induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 enzymes at relevant clinical concentrations. Eribulin is not expected to alter the plasma concentrations of drugs that are substrates of these enzymes *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category D [*see Warnings and Precautions (5.3)]*

There are no adequate and well-controlled studies with HALAVEN in pregnant women. HALAVEN is a microtubule inhibitor, therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats that received eribulin mesylate at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

In a developmental toxicity study, pregnant rats received intravenous infusion of eribulin mesylate during organogenesis (Gestation Days 8, 10, and 12) at doses approximately 0.04, 0.13, 0.43 and 0.64 times the recommended human dose, based on body surface area (mg/m^2). Increased abortion and severe external or soft tissue malformations were observed in offspring at doses 0.64 times the recommended human dose based on body surface area (mg/m^2), including the absence of a lower jaw, tongue, stomach and spleen. Increased embryo-fetal death/resorption, reduced fetal weights, and minor skeletal anomalies consistent with developmental delay were also reported at or above doses of 0.43 times the recommended human dose.

Maternal toxicity of eribulin mesylate was reported in rats at or above doses of 0.43 times the recommended human dose (mg/m^2), and included enlarged spleen, reduced maternal weight gain and decreased food consumption.

8.3 Nursing Mothers

It is not known whether HALAVEN is excreted into human milk. No studies in humans or animals were conducted to determine if HALAVEN is excreted into milk. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in human milk fed infants from HALAVEN, a decision should be made whether to discontinue nursing or to discontinue HALAVEN taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of HALAVEN in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

Study 1 did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Of the 827 subjects who received the recommended dose and schedule of HALAVEN in clinical studies, 15% (121/827) were 65 and older, and 2% (17/827) patients were 75 and older. No overall differences in safety were observed between these subjects and younger subjects.

8.6 Hepatic Impairment

Administration of HALAVEN at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function. Therefore, a lower starting dose of 1.1 mg/m^2 is recommended for patients with mild hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh B). HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

For patients with moderate or severe renal impairment (CrCl 15-49 mL/min), reduce the starting dose to 1.1 mg/m^2 *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

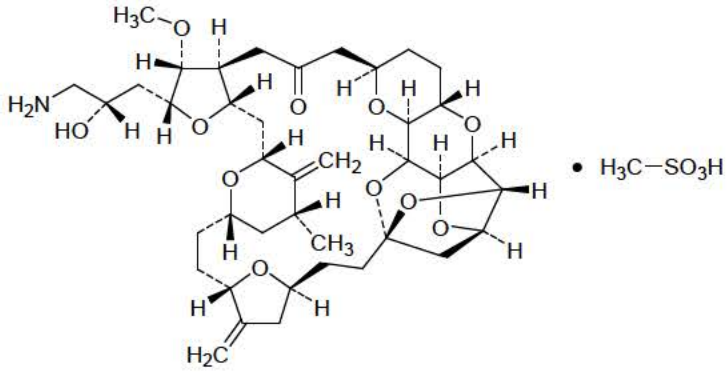
Overdosage of HALAVEN has been reported at approximately 4 times the recommended dose, which resulted in Grade 3 neutropenia lasting seven days and a Grade 3 hypersensitivity reaction lasting one day.

There is no known antidote for HALAVEN overdose.

11 DESCRIPTION

HALAVEN Injection contains eribulin mesylate, a microtubule dynamics inhibitor. Eribulin mesylate is a synthetic analogue of halichondrin B, a product isolated from the marine sponge *Halichondria okadai*. The chemical name for eribulin mesylate is 11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one,2-[(2*S*)-3-amino-2-

hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-, methanesulfonate (salt). It has a molecular weight of 826.0 (729.9 for free base). The empirical formula is $C_{40}H_{59}NO_{11}•CH_4O_3S$. Eribulin mesylate has the following structural formula:



HALAVEN is a clear, colorless, sterile solution for intravenous administration. Each vial contains 1 mg of eribulin mesylate as a 0.5 mg/mL solution in ethanol: water (5:95).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G_2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

In addition, eribulin treatment of human breast cancer cells caused changes in morphology and gene expression as well as decreased migration and invasiveness in vitro. In mouse xenograft models of human breast cancer, eribulin treatment was associated with increased vascular perfusion and permeability in the tumor cores, resulting in reduced tumor hypoxia, and changes in the expression of genes in tumor specimens associated with a change in phenotype.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of eribulin is linear with a mean elimination half-life of approximately 40 hours, a mean volume of distribution of 43 L/m^2 to 114 L/m^2 and mean clearance of 1.16 L/hr/m^2 to 2.42 L/hr/m^2 over the dose range of 0.25 mg/m^2 to 4.0 mg/m^2. The human plasma protein binding of eribulin at concentrations of 100 ng/mL to 1,000 ng/mL ranges from 49% to 65% Eribulin exposure after multiple dosing is comparable to that following a single dose. No accumulation of eribulin is observed with weekly administration.

Metabolism

Unchanged eribulin was the major circulating species in plasma following administration of ^{14}C-eribulin to patients. Metabolite concentrations represented <0.6% of parent compound, confirming that there are no major human metabolites of eribulin. Cytochrome P450 3A4 (CYP3A4) negligibly metabolizes eribulin *in vitro*.

Elimination

Eribulin is eliminated primarily in feces unchanged. After administration of ^{14}C-eribulin to patients, approximately 82% of the dose was eliminated in feces and 9% in urine. Unchanged eribulin accounted for approximately 88% and 91% of the dose in feces and urine, respectively.

Effects of Age, Gender, and Race

Based on a population pharmacokinetic analysis with data collected from 340 patients, gender, race, and age do not have a clinically meaningful effect on the PK of eribulin.

Drug Interactions

Effect of Other Drugs on HALAVEN

The effect of a strong CYP3A4 inhibitor and a P-gp inhibitor, ketoconazole, on the PK of eribulin was studied in a crossover trial of 12 patients with advanced solid tumors. No clinically relevant PK interaction was observed when HALAVEN was administered with or without ketoconazole (the geometric mean ratio of the AUC: 0.97; 90%CI: 0.83, 1.12).

The effect of a CYP3A4 inducer, rifampin, on the PK of eribulin was studied in a crossover trial of 14 patients with advanced solid tumors. No clinically relevant PK interaction was observed when HALAVEN was administered with or without rifampin (the geometric mean ratio of the AUC: 1.10; 90CI%: 0.91, 1.34).

Effect of HALAVEN on Other Drugs

Eribulin shows no induction potential for CYP1A, CYP2C9, CYP2C19, and CYP3A in primary human hepatocytes. Eribulin inhibits CYP3A4 activity in human liver microsomes, but it is unlikely that eribulin will substantially increase the plasma levels of CYP3A4 substrates. No significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 was detected with eribulin concentrations up to 5 μM in pooled human liver microsomes. *In vitro* drug interaction studies indicate that eribulin does not inhibit drugs that are substrates of these enzymes and it is unlikely that eribulin will affect plasma levels of drugs that are substrates of CYP enzymes. Eribulin is a substrate and a weak inhibitor of the drug efflux transporter P-gp *in vitro*.

Specific Populations

Hepatic Impairment

A study evaluated the PK of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=5) hepatic impairment. Compared to patients with normal hepatic function (n=6), eribulin exposures increased 1.8-fold and 2.5-fold in patients with mild and moderate hepatic impairment, respectively. Administration of HALAVEN at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function *[see Dosage and Administration (2.1), Use in Specific Populations (8.6)]*.

Renal Impairment

A study evaluated the PK of eribulin in patients with moderate (CrCl: 30-49 mL/min; n=7) and severe (CrCl: 15-29 mL/min; n=6) renal impairment. Compared to patients with normal renal function (CrCl ≥ 80 mL/min; n=6), patients with moderate and severe renal impairment have 1.5-fold higher eribulin dose-normalized exposures. However for patients with mild renal impairment the data indicate no dose adjustment is necessary *[see Dosage and Administration (2.1), Use in Specific Populations (8.7)]*.

12.6 Cardiac Electrophysiology

The effect of HALAVEN on the QTc interval was assessed in an open-label, uncontrolled, multicenter, single-arm dedicated QT trial. A total of 26 patients with solid tumors received 1.4 mg/m^2 of HALAVEN on Days 1 and 8 of a 21-day cycle. A delayed QTc prolongation was observed on Day 8, with no prolongation observed on Day 1. The maximum mean QTcF change from baseline (95% upper confidence interval) was 11.4 (19.5) ms.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with eribulin mesylate.

Eribulin mesylate was not mutagenic in *in vitro* bacterial reverse mutation assays (Ames test). Eribulin mesylate was positive in mouse lymphoma mutagenesis assays, and was clastogenic in an *in vivo* rat bone marrow micronucleus assay.

The effects of HALAVEN on human fertility are unknown. Fertility studies have not been conducted with eribulin mesylate in humans or animals. However, nonclinical findings in repeated-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rats exhibited testicular toxicity (hypocellularity of seminiferous epithelium with hypospermia/aspermia) following dosing with eribulin mesylate at or above 0.43 times the recommended human dose (mg/m^2) given once weekly for 3 weeks, or at or above 0.21 times the recommended human dose (mg/m^2) given once weekly for 3 out of 5 weeks, repeated for 6 cycles. Testicular toxicity was also observed in dogs given 0.64 times the recommended human dose (mg/m^2) weekly for 3 out of 5 weeks, repeated for 6 cycles.

14 CLINICAL STUDIES

Study 1 was an open-label, randomized, multicenter trial of 762 patients with metastatic breast cancer who received at least two chemotherapeutic regimens for the treatment of metastatic disease and experienced disease progression within 6 months of their last chemotherapeutic regimen. Patients were required to receive prior anthracycline- and taxane- based chemotherapy for adjuvant or metastatic disease. Patients were randomized (2:1) to receive HALAVEN (n=508) or a single agent therapy selected prior to randomization (control arm, n=254). Randomization was stratified by geographic region, HER2/*neu* status, and prior capecitabine exposure. HALAVEN was administered at a dose of 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle. HALAVEN-treated patients received a median of 5 cycles (range: 1 to 23 cycles) of therapy. Control arm therapy consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy), and 3% hormonal therapy. The main efficacy outcome was overall survival.

Patient demographic and baseline characteristics were comparable between the treatment arms. The median age was 55 (range: 27 to 85 years) and 92% were White. Sixty-four percent of patients were enrolled in North America/Western Europe/Australia, 25% in Eastern Europe/Russia, and 11% in Latin America/South Africa. Ninety-one percent of patients had a baseline ECOG performance status of 0 or 1. Tumor prognostic characteristics, including estrogen receptor status (positive: 67%, negative: 28%), progesterone receptor status (positive: 49%, negative: 39%), HER2/*neu* receptor status (positive: 16%, negative: 74%), triple negative status (ER^-, PR^-, HER2/*neu*$^-$: 19%), presence of visceral disease (82%, including 60% liver and 38% lung) and bone disease (61%), and number of sites of metastases (greater than two: 50%), were also similar in the HALAVEN and control arms. Patients received a median of four prior chemotherapy regimens in both arms.

In Study 1, a statistically significant improvement in overall survival was observed in patients randomized to the HALAVEN arm compared to the control arm (see Table 3). An updated, unplanned survival analysis, conducted when 77% of events had been observed (see Figure 1), was consistent with the primary analysis. In patients randomized to HALAVEN, the objective response rate by the RECIST criteria was 11% (95% CI: 8.6%, 14.3%) and the median response duration was 4.2 months (95% CI: 3.8, 5.0 months).

Table 3 Comparison of Overall Survival in HALAVEN and Control Arm - Study 1

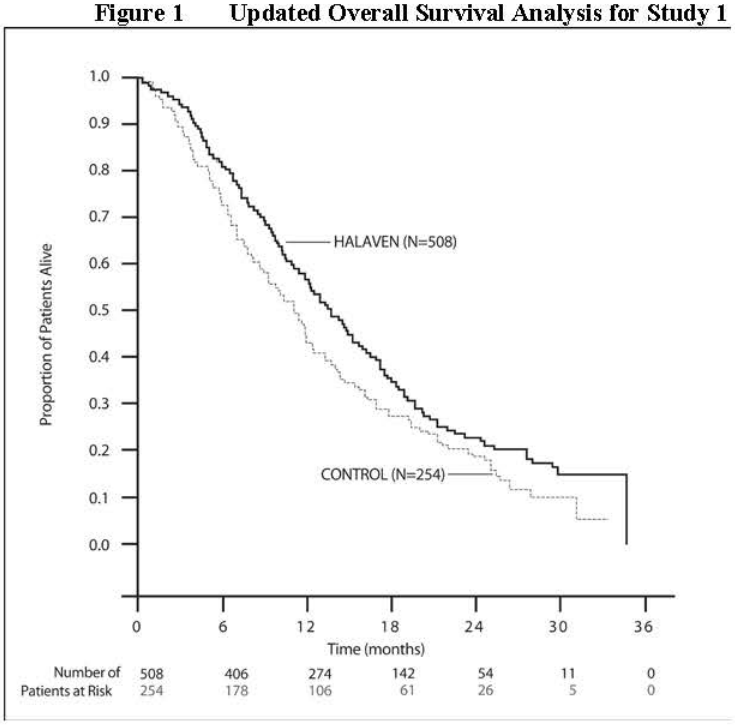
Overall Survival	HALAVEN (n=508)	Control Arm (n=254)
Primary survival analysis		
Number of deaths	274	148
Median, months (95% CI)	13.1 (11.8, 14.3)	10.6 (9.3, 12.5)
Hazard Ratio (95% CI)[a]	0.81 (0.66, 0.99)	
P value[b]	0.041	
Updated survival analysis		
Number of deaths	386	203
Median, months (95% CI)	13.2 (12.1, 14.4)	10.6 (9.2, 12.0)

CI = confidence interval

[a] Based on Cox proportional hazards model stratified by geographic region, HER2 status, and prior capecitabine therapy.

[b] Based on a log-rank test stratified by geographic region, HER2 status, and prior capecitabine therapy.

Figure 1 Updated Overall Survival Analysis for Study 1



16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 62856-389-01

Eribulin mesylate injection, 1 mg/2 mL, in a single-use vial. One vial per carton.

Store at 25°C (77°F); excursions permitted to 15° – 30° C (59° -86° F). Do not freeze. Store the vials in their original cartons.

17 PATIENT COUNSELING INFORMATION

- Advise patients to contact their health care provider for a fever of 100.5°F or greater or other signs or symptoms of infection such as chills, cough, or burning or pain on urination [*see Warnings and Precautions (5.1)*].

- Advise women of childbearing potential to avoid pregnancy and to use effective contraception during treatment with HALAVEN [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)*].

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Eisai Inc.
Woodcliff Lake, NJ 07677

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PATIENT INFORMATION

HALAVEN® (HAL-ih-ven)

(eribulin mesylate) Injection

Read this leaflet before you start receiving HALAVEN and before each injection. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

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

Your healthcare provider should do blood tests regularly to check your blood cell counts before you receive each dose of HALAVEN.

- HALAVEN can cause a decrease in white blood cell count (neutropenia). This can make you more likely to get serious infections that could lead to death. You may need treatment in the hospital with antibiotic medicines.
- Call your healthcare provider right away if you develop any of these symptoms of infection while you are receiving HALAVEN:
    - fever (temperature above 100.5°F)
    - chills
    - cough
    - burning or pain when you urinate.
- HALAVEN can cause numbness, tingling, or burning in your hands and feet (neuropathy). Tell your healthcare provider if you have any of these symptoms.

See "**What are possible side effects of HALAVEN?**" for more information about side effects.

What is HALAVEN?

HALAVEN is a prescription medicine used to treat people with breast cancer:

- that has spread to other parts of their body, and
- who have already received certain types of anticancer medicines after their breast cancer has spread.

What should I tell my healthcare provider before receiving HALAVEN?

Before you receive HALAVEN, tell your healthcare provider if you:

- have liver or kidney problems.

- have heart problems, including a problem called "congenital long QT syndrome."
- are pregnant or plan to become pregnant. **HALAVEN may harm your unborn baby.** Talk with your healthcare provider about birth control methods to prevent pregnancy while you receive HALAVEN. Tell your healthcare provider right away if you become pregnant or think you are pregnant while you are receiving HALAVEN
- are breastfeeding or planning to breastfeed. It is not known if HALAVEN passes into your breast milk. You and your healthcare provider should decide if you will take HALAVEN or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

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

How will I receive HALAVEN?

- HALAVEN is injected directly into your vein.
- HALAVEN is given in "cycles" of treatment, with each cycle lasting 21 days.
- You will receive an injection 1 time each week for two weeks in a row (day 1 and day 8 of a treatment cycle).
- Your healthcare provider may need to decrease your dose of HALAVEN or change how often you receive it, depending on your blood test results.

What are the possible side effects of HALAVEN?

HALAVEN may cause serious side effects, including:

- See "**What is the most important information I should know about HALAVEN?**"
- **HALAVEN can cause changes in your heartbeat (called QTc prolongation).** This can cause irregular heartbeats that may lead to death. Your healthcare provider will decide if you need heart monitoring (electrocardiogram or ECG), or blood tests during your treatment with HALAVEN to watch for this problem.

The most common side effects of HALAVEN include:

- weakness or tiredness
- hair loss
- nausea
- constipation

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of HALAVEN. For more information, ask your healthcare provider or pharmacist.

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

General information about HALAVEN

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. This leaflet summarizes the most important information about HALAVEN. If you would like more information, **talk with your healthcare provider.** You can ask your pharmacist or healthcare provider for information about HALAVEN that is written for health professionals.

For more information, go to www.HALAVEN.com or call Eisai Inc. at 1-877-873-4724.

What are the ingredients in HALAVEN?

Active Ingredients: eribulin mesylate

Inactive Ingredients: ethanol, water

HALAVEN® is a registered trademark used by Eisai Inc. under license from Eisai R&D Management Co., Ltd.

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Eisai Inc.
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If you would like a leaflet with larger printing, please contact Eisai Inc. at 1-877-873-4724.
Revised: October 2015

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

HALAVEN 0.44 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains eribulin mesilate equivalent to 0.44 mg eribulin.
Each 2 ml vial contains eribulin mesilate equivalent to 0.88 mg eribulin.
Each 3 ml vial contains eribulin mesilate equivalent to 1.32 mg eribulin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HALAVEN is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (see section 5.1). Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.

4.2 Posology and method of administration

HALAVEN should be administered in units specialised in the administration of cytotoxic chemotherapy and only under the supervision of a qualified physician experienced in the appropriate use of cytotoxic medicinal products.

Posology

The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.

Please note:
In the EU the recommended dose refers to the base of the active substance (eribulin). Calculation of the individual dose to be administered to a patient must be based on the strength of the ready to use solution that contains 0.44 mg/ml eribulin and the dose recommendation of 1.23 mg/m^2. The dose reduction recommendations shown below are also shown as the dose of eribulin to be administered based on the strength of the ready to use solution.

In the pivotal EMBRACE trial, the corresponding publication and in some other regions e.g. the United States and Switzerland, the recommended dose is based on the salt form (eribulin mesilate).

Patients may experience nausea or vomiting. Antiemetic prophylaxis including corticosteroids should be considered.

Dose delays during therapy

The administration of HALAVEN should be delayed on Day 1 or Day 8 for any of the following:
- Absolute neutrophil count (ANC) < 1 x 10^9/l
- Platelets < 75 x 10^9/l
- Grade 3 or 4 non-hematological toxicities.

Dose reduction during therapy

Dose reduction recommendations for retreatment are shown in the following table.

Dose reduction recommendations

Adverse reaction after previous HALAVEN administration	**Recommended dose of eribulin**
Haematological:	
ANC < 0.5 x 10^9/l lasting more than 7 days	0.97 mg/m^2
ANC < 1 x 10^9/l neutropenia complicated by fever or infection	
Platelets < 25 x 10^9/l thrombocytopenia	
Platelets < 50 x 10^9/l thrombocytopenia complicated by haemorrhage or requiring blood or platelet transfusion	
Non-haematological:	
Any Grade 3 or 4 in the previous cycle	
Reoccurrence of any haematological or non-haematological adverse reactions as specified above	
Despite reduction to 0.97 mg/m^2	0.62 mg/m^2
Despite reduction to 0.62 mg/m^2	Consider discontinuation

The dose of eribulin should not be re-escalated after it has been reduced.

Patients with hepatic impairment

Impaired liver function due to metastases
The recommended dose of eribulin in patients with mild hepatic impairment (Child-Pugh A) is 0.97 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. The recommended dose of eribulin in patients with moderate hepatic impairment (Child-Pugh B) is 0.62 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. Severe hepatic impairment (Child-Pugh C) has not been studied but it is expected that a more marked dose reduction is needed if eribulin is used in these patients.

Impaired liver function due to cirrhosis
This patient group has not been studied. The doses above may be used in mild and moderate impairment but close monitoring is advised as the doses may need readjustment.

Patients with renal impairment

Some patients with moderately or severely impaired renal function (creatinine clearance <50 ml/min) may have increased eribulin exposure and may need a reduction of the dose. For all patients with renal impairment, caution and close safety monitoring is advised. (See section 5.2)

Elderly patients

No specific dose adjustments are recommended based on the age of the patient (see section 4.8).

Paediatric population

There is no relevant use of HALAVEN in children and adolescents for the indication of breast cancer.

Method of administration

HALAVEN is for intravenous use. The dose may be diluted in up to 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. It should not be diluted in glucose 5% infusion solution. For instructions on the dilution of the medicinal product before administration, see section 6.6. Good peripheral venous access, or a patent central line, should be ensured prior to administration. There is no evidence that eribulin mesilate is a vesicant or an irritant. In the event of extravasation, treatment should be symptomatic. For information relevant to the handling of cytotoxic medicinal products see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Breast-feeding

4.4 Special warnings and precautions for use

Haematology

Myelosuppression is dose dependent and primarily manifested as neutropenia (section 4.8). Monitoring of complete blood counts should be performed on all patients prior to each dose of eribulin. Treatment with eribulin should only be initiated in patients with ANC values $\geq 1.5 \times 10^9$/l and platelets $> 100 \times 10^9$/l.

Febrile neutropenia occurred in < 5% of breast cancer patients treated with eribulin. Patients experiencing febrile neutropenia, severe neutropenia or thrombocytopenia, should be treated according to the recommendations in section 4.2.

Patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit of normal (ULN) experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin >1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia.

Severe neutropenia may be managed by the use of granulocyte colony-stimulating factor (G-CSF) or equivalent at the physician's discretion in accordance with relevant guidelines (see section 5.1).

Peripheral neuropathy

Patients should be closely monitored for signs of peripheral motor and sensory neuropathy. The development of severe peripheral neurotoxicity requires a delay or reduction of dose (see section 4.2)

In clinical trials, patients with pre-existing neuropathy greater than Grade 2 were excluded. However, patients with pre-existing neuropathy Grade 1 or 2 were no more likely to develop new or worsening symptoms than those who entered the study without the condition.

QT prolongation

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias or concomittant treatment with medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Hypokalemia or hypomagnesemia should be

corrected prior to initiating HALAVEN and these electrolytes should be monitored periodically during therapy. Eribulin should be avoided in patients with congenital long QT syndrome.

Use in combination with anti-HER2 therapy

The efficacy and safety of using eribulin in combination with anti-HER2 therapy have not been established.

Excipients

This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose.

4.5 Interaction with other medicinal products and other forms of interaction

Eribulin is mainly (up to 70%) eliminated through biliary excretion. The transport protein involved in this process is unknown. Complete inhibition of the transport could in theory give rise to a more than 3-fold increase in plasma concentrations. It is not recommended to use substances which are inhibitors of hepatic transport proteins such as organic anion-transporting proteins (OATPs) and multidrug resistant proteins (MRPs) etc concomitantly with eribulin. Inhibitors of such transporters include but are not limited to: cyclosporine, ritonavir, saquinavir, lopinavir and certain other protease inhibitors, efavirenz, emtricitabine, quinine, quinidine, disopyramide etc.

It cannot be excluded that concomitant treatment with inducing substances, such as carbamazepine, phenytoin, St John´s wort (Hypericum perforatum), could give rise to reduced plasma concentrations of eribulin, and co-administration with inducers should be carried out with caution considering a potential risk for reduced drug efficacy. No marked effects on eribulin exposure (AUC and C_{max}) were observed during treatment with the CYP3A4 inducer rifampicin. However, rifampicin may due to its transporter inhibitory property counteract its possible inducing effect on eribulin elimination. Therefore, the effect of rifampicin may not presently be extrapolated to other inducers.

No drug-drug interactions are expected with CYP3A4 inhibitors. Eribulin exposure (AUC and C_{max}) was unaffected by ketoconazole, a CYP3A4 and P glycoprotein (Pgp) inhibitor.

Effects of eribulin on the pharmacokinetics of other drugs

In vitro data indicate that eribulin is a mild inhibitor of the important drug metabolising enzyme CYP3A4. No *in vivo* data are available. Caution and monitoring for adverse events is recommended with concomitant use of substances that have a narrow therapeutic window and that are eliminated mainly via CYP3A4-mediated metabolism (eg alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).

Eribulin does not inhibit the CYP enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 at relevant clinical concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of eribulin in pregnant women. Eribulin is embryotoxic, foetotoxic, and teratogenic in rats. HALAVEN should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.

Women of childbearing potential must be advised to avoid becoming pregnant whilst they or their male partner are receiving HALAVEN and have to use effective contraception during and up to 3 months after treatment.

Breast-feeding

It is unknown whether eribulin/metabolites are excreted in human or animal breast milk. A risk to newborns/infants cannot be excluded and therefore HALAVEN must not be used during breast-feeding (see section 4.3).

Fertility

Testicular toxicity has been observed in rats and dogs (see section 5.3). Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with HALAVEN.

4.7 Effects on ability to drive and use machines

HALAVEN may cause adverse reactions such as tiredness and dizziness which may lead to minor or moderate influence on the ability to drive or use machines. Patients should be advised not to drive or use machines if they feel tired or dizzy.

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions related to HALAVEN, are bone marrow suppression manifested as neutropenia, leucopenia, anaemia, thrombocytopenia with associated infections. New onset or worsening of pre-existing peripheral neuropathy has also been reported. Gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, and stomatitis are among reported undesirable effects. Other undesirable effects include fatigue, alopecia, increased liver enzymes, sepsis and musculoskeletal pain syndrome.

Tabulated list of adverse reactions

Unless otherwise noted, the table shows the incidence rates of adverse reactions observed in 1503 breast cancer patients who received the recommended dose in five Phase 2 and two Phase 3 studies.

Frequency categories are defined as: 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) and very rare (< 1/10,000).
Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Where Grade 3 or 4 reactions occurred, the actual total frequency and the frequency of Grade 3 or 4 reactions are given.

System Organ Class	**Adverse Reactions – all Grades**			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Infections and infestations		Urinary tract infection (8.0%) (G3/4: 0.5%) Pneumonia (1.2%) (G3/4: 0.8%) Oral candidiasis Oral herpes Upper respiratory tract infection Nasopharyngitis Rhinitis	Sepsis (0.5%) (G3/4: 0.2%)[a] Neutropenic sepsis (0.1%) (G3/4: 0.1%) Herpes zoster	

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Blood and lymphatic system disorders	Neutropenia (57.0%) (G3/4: 49.7%) Leukopenia (29.3%) (G3/4: 17.3%) Anaemia (20.6%) (G3/4: 2.0%)	Lymphopenia (4.9%) (G3/4: 1.4%) Febrile neutropenia (4.7%) (G3/4: 4.5%)[a] Thrombocytopenia (4.3%) (G3/4: 0.7%)		Disseminated intravascular coagulation[b]
Metabolism and nutrition disorders	Decreased appetite (21.9%) (G3/4: 0.7%)	Hypokalaemia (6.1%) (G3/4: 1.7%) Hypomagnesaemia (2.9%) (G3/4: 0.2%) Dehydration (2.8 %) (G3/4: 0.5%) Hyperglycaemia Hypophosphataemia		
Psychiatric disorders		Insomnia Depression		
Nervous system disorders	Peripheral neuropathy[c] (35.6%) (G3/4: 7.6%) Headache (17.2%) (G3/4: 0.8%)	Dysgeusia Dizziness (7.9%) (G3/4: 0.5%) Hypoaesthesia Lethargy Neurotoxicity		
Eye disorders		Lacrimation increased (6.0%) (G3/4: 0.1%) Conjunctivitis		
Ear and labyrinth disorders		Vertigo	Tinnitus	
Cardiac disorders		Tachycardia		
Vascular disorders		Hot flush	Deep vein thrombosis Pulmonary embolism	
Respiratory, thoracic and mediastinal disorders	Dyspnoea (13.9%)[a] (G3/4: 3.1%) Cough (13.6%) (G3/4: 0.6%)	Oropharyngeal pain Epistaxis Rhinorrhoea		Interstitial lung disease
Gastrointestinal disorders	Nausea (33.8%) (G3/4: 1.1%) Constipation (19.6%) (G3/4: 0.6%) Diarrhoea (17.9%) (G3/4: 0.8%) Vomiting (17.6%) (G3/4: 0.9%)	Abdominal pain Stomatitis (9.3%) (G3/4: 0.8%) Dry mouth Dyspepsia (5.9%) (G3/4: 0.2%) Gastrooesophageal reflux disease Mouth ulceration Abdominal distension		Pancreatitis[b]

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Hepatobiliary disorders		Alanine aminotransferase increased (7.6%) (G3/4: 2.1%)[d] Aspartate aminotransferase increased (7.4%) (G3/4: 1.5%) Gamma glutamyl transferase increased (1.8%) (G3/4: 0.9%) Hyperbilirubinaemia (1.5%) (G3/4: 0.3%)	Hepatotoxicity (1.0%) (G3/4: 0.6%)	
Skin and subcutaneous tissue disorders	Alopecia	Rash Pruritus (3.9%) (G3/4: 0.1%) Nail disorder Night sweats Dry skin Erythema Hyperhidrosis	Palmar plantar erythrodysaesthesia	Angioedema
Musculoskeletal and connective tissue disorders	Arthralgia and myalgia (19.4%) (G3/4: 1.1%) Back pain (13.0%) (G3/4:1.5%) Pain in extremity (10.0%) (G3/4: 0.7%)	Bone pain (9.6%) (G3/4: 1.7%) Muscle spasms (5.1%) (G3/4: 0.1%) Musculoskeletal pain and musculoskeletal chest pain Muscular weakness		
Renal and urinary disorders		Dysuria	Haematuria Proteinuria Renal failure	
General disorders and administration site conditions	Fatigue/Asthenia (47.9%) (G3/4 : 7.8%) Pyrexia (20.4%) (G3/4: 0.6%)	Mucosal Inflammation (8.3%) (G3/4: 1.1%)[d] Peripheral oedema Pain Chills Chest pain Influenza like illness		
Investigations	Weight decreased (11.3%) (G3/4: 0.3%)			

[a] Includes 1 or 2 Grade 5
[b] From spontaneous reporting
[c] Includes preferred terms of peripheral neuropathy, peripheral motor neuropathy, polyneuropathy, paraesthesia, peripheral sensory neuropathy, peripheral sensorimotor neuropathy and demyelinating polyneuropathy
[d] No Grade 4

Description of selected adverse reactions

Neutropenia
The neutropenia observed was reversible and not cumulative; the mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (< 0.5 x 10^9/l) was 8 days.

Neutrophil counts of < 0.5 x 10^9/l that lasted for more than 7 days occurred in 13% of breast cancer patients treated with eribulin in the EMBRACE study.
Severe neutropenia may be managed by the use of G-CSF or equivalent at the physician's discretion in accordance with relevant guidelines. 18% of breast cancer patients treated in a phase 3 study with eribulin received G-CSF.
Neutropenia resulted in discontinuation in < 1% of patients receiving eribulin.

Disseminated intravascular coagulation
Cases of disseminated intravascular coagulation have been reported, typically in association with neutropenia and/or sepsis.

Peripheral neuropathy
In the 1503 breast cancer patients the most common adverse reaction resulting in discontinuation of treatment with eribulin was peripheral neuropathy (3.3%). The median time to Grade 2 peripheral neuropathy was 85.5 days (post 4 cycles).
Development of Grade 3 or 4 peripheral neuropathy occurred in 7.7% of eribulin treated breast cancer patients. In clinical trials, patients with pre-existing neuropathy were as likely to develop new or worsening symptoms as those who entered the study without the condition.
In patients with pre-existing Grade 1 or 2 peripheral neuropathy the frequency of treatment-emergent Grade 3 peripheral neuropathy was 14%.

Hepatotoxicity
In some patients with normal/abnormal liver enzymes prior treatment with eribulin, increased levels of liver enzymes have been reported with initiation of eribulin treatment. Such elevations appeared to have occurred early with eribulin treatment in cycle 1 – 2 for the majority of these patients and whilst thought likely to be a phenomenon of adaptation to eribulin treatment by the liver and not a sign of significant liver toxicity in most patients, hepatotoxicity has also been reported.

Special populations

Elderly population
Of the 1503 breast cancer patients treated with the recommended dose of eribulin, 209 patients (13.9%) were > 65 - 75 years of age and 24 patients (1.6%) were > 75 years of age. The safety profile of eribulin in elderly patients (> 65 years of age) was similar to that of patients ≤ 65 years of age except for asthenia/fatigue which showed an increasing trend with age. No dose adjustments are recommended for the elderly population.

Patients with hepatic impairment
Patients with ALT or AST > 3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin > 1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia (see also sections 4.2 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In one case of overdose the patient inadvertently received 7.6 mg of eribulin (approximately 4 times the planned dose) and subsequently developed a hypersensitivity reaction (Grade 3) on Day 3 and neutropenia (Grade 3) on Day 7. Both adverse reactions resolved with supportive care.

There is no known antidote for eribulin overdose. In the event of an overdose, the patient should be closely monitored. Management of overdose should include supportive medical interventions to treat the presenting clinical manifestations.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX41

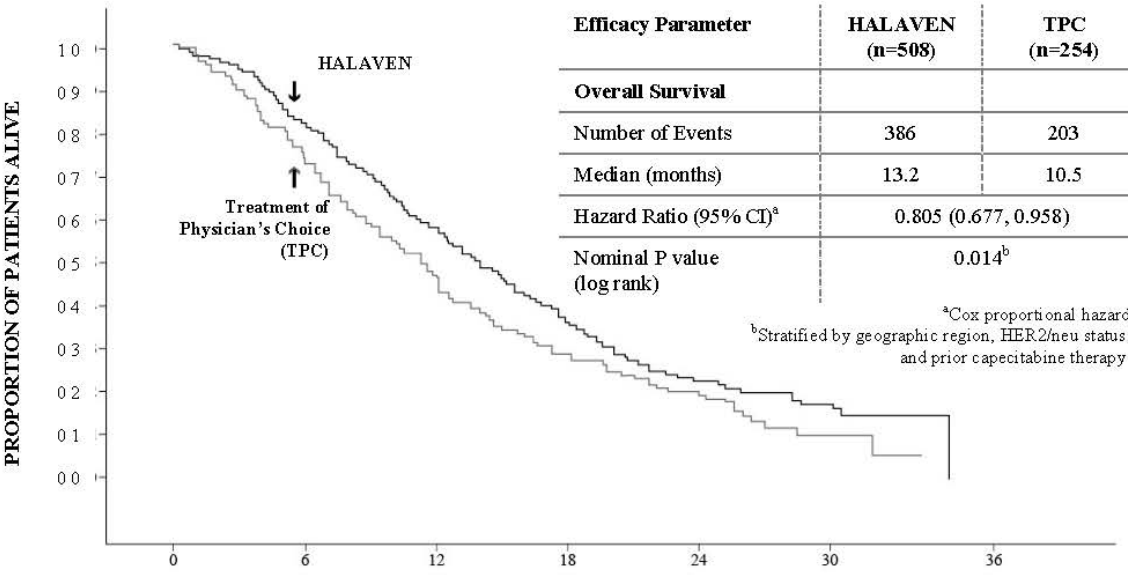
Eribulin mesilate is a non-taxane, microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. It is a structurally simplified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai.*

Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G_2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

Clinical efficacy

The efficacy of HALAVEN in breast cancer is primarily supported by two randomized Phase 3 comparative studies.
The 762 patients in the pivotal Phase 3 EMBRACE study (Study 305) had locally recurrent or metastatic breast cancer, and had previously received at least two and a maximum of five chemotherapy regimens, including an anthracycline and a taxane (unless contraindicated). Patients must have progressed within 6 months of their last chemotherapeutic regimen. The HER2 status of the patients was: 16.1% positive, 74.2% negative and 9.7% unknown, whilst 18.9% of patients were triple negative. They were randomized 2:1 to receive either HALAVEN, or treatment of physician's choice (TPC), which consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy), or 3% hormonal therapy.
The study met its primary endpoint with an overall survival (OS) result that was statistically significantly better in the eribulin group compared to TPC at 55% of events.
This result was confirmed with an updated overall survival analysis carried out at 77% of events.

Study 305 - Updated Overall Survival (ITT Population)



Efficacy Parameter	HALAVEN (n=508)	TPC (n=254)
Overall Survival		
Number of Events	386	203
Median (months)	13.2	10.5
Hazard Ratio (95% CI)[a]	0.805 (0.677, 0.958)	
Nominal P value (log rank)	0.014[b]	

[a]Cox proportional hazard
[b]Stratified by geographic region, HER2/neu status, and prior capecitabine therapy

NUMBER OF PATIENTS AT RISK

HALAVEN	508	406	274	142	54	11	0
TPC	254	178	106	61	26	5	0

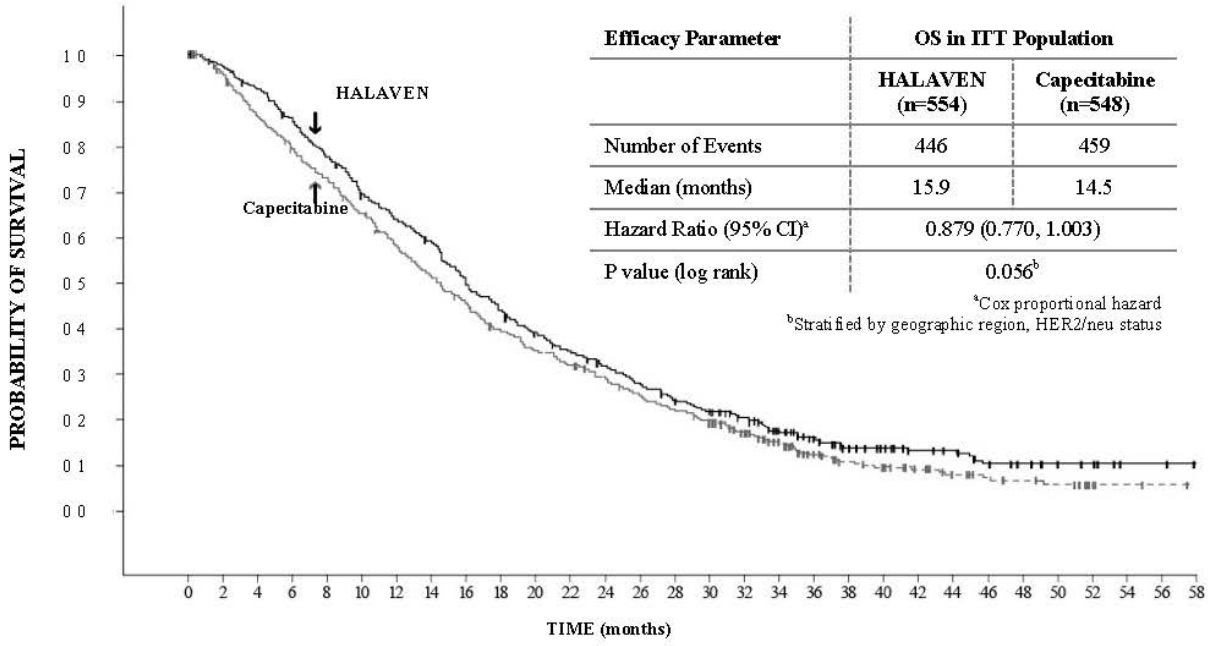
By independent review, the median progression free survival (PFS) was 3.7 months for eribulin compared to 2.2 months for the TPC arm (HR 0.865, 95% CI: 0.714, 1.048, p=0.137). In response evaluable patients, the objective response rate by the RECIST criteria was 12.2% (95% CI: 9.4%, 15.5%) by independent review for the eribulin arm compared to 4.7% (95% CI: 2.3%, 8.4%) for the TPC arm.

The positive effect on OS was seen in both taxane-refractory and non-refractory groups of patients . In the OS update, the HR for eribulin versus TPC was 0.90 (95% CI: 0.71, 1.14) in favour of eribulin for taxane-refractory patients and 0.73 (95% CI: 0.56, 0.96) for patients not taxane-refractory.

The positive effect on OS was seen both in capecitabine-naïve and in capecitabine pre-treated patient groups. The updated OS analysis showed a survival benefit for the eribulin group compared to TPC both in capecitabine pre-treated patients with a HR of 0.787 (95% CI: 0.645, 0.961), and for the capecitabine-naïve patients with a corresponding HR of 0.865 (95% CI: 0.606, 1.233).

The second Phase 3 study in earlier line metastatic breast cancer, Study 301, was an open-label, randomized, study in patients (n=1102) with locally advanced or metastatic breast cancer to investigate the efficacy of HALAVEN monotherapy compared to capecitabine monotherapy in terms of OS and PFS as co-primary endpoint. Patients had previously received up to three prior chemotherapy regimens, including both an anthracycline and a taxane and a maximum of two for advanced disease, with the percentage who had received 0, 1 or 2 prior chemotherapy treatments for metastatic breast cancer being 20.0%, 52.0% or 27.2% respectively. The HER2 status of the patients was: 15.3% positive, 68.5% negative and 16.2% unknown, whilst 25.8% of patients were triple negative.

Study 301 - Overall Survival (ITT Population)



Efficacy Parameter	OS in ITT Population	
	HALAVEN (n=554)	Capecitabine (n=548)
Number of Events	446	459
Median (months)	15.9	14.5
Hazard Ratio (95% CI)[a]	0.879 (0.770, 1.003)	
P value (log rank)	0.056[b]	

[a]Cox proportional hazard
[b]Stratified by geographic region, HER2/neu status

NUMBER OF PATIENTS AT RISK

HALAVEN	554	530	505	464	423	378	349	320	268	243	214	193	173	151	133	119	99	77	52	38	32	26	22	15	13	9	7	2	2	0
Capecitabine	548	513	466	426	391	352	308	277	242	214	191	175	155	135	122	108	81	62	42	33	27	23	17	13	12	10	2	2	1	0

Progression free survival assessed by independent review was similar between eribulin and capecitabine with medians of 4.1 months vs 4.2 months (HR 1.08; [95% CI: 0.932, 1.250]) respectively. Objective response rate as assessed by independent review was also similar between eribulin and capecitabine; 11.0% (95% CI: 8.5, 13.9) in the eribulin group and 11.5% (95% CI: 8.9, 14.5) in the capecitabine group.

The overall survival in patients in HER2 negative and HER2 positive patients in the eribulin and control groups in Study 305 and Study 301 is shown below:

Efficacy Parameter	Study 305 Updated Overall Survival ITT Population			
	HER2 Negative		HER2 Positive	
	HALAVEN (n = 373)	TPC (n = 192)	HALAVEN (n = 83)	TPC (n = 40)
Number of Events	285	151	66	37
Median months	13.4	10.5	11.8	8.9
Hazard Ratio (95% CI)	0.849 (0.695, 1.036)		0.594 (0.389, 0.907)	
p-value (log rank)	0.106		0.015	

Efficacy Parameter	Study 301 Overall Survival ITT Population			
	HER2 Negative		HER2 Positive	
	HALAVEN (n = 375)	Capecitabine (n = 380)	HALAVEN (n = 86)	Capecitabine (n = 83)
Number of Events	296	316	73	73
Median months	15.9	13.5	14.3	17.1
Hazard Ratio (95% CI)	0.838 (0.715, 0.983)		0.965 (0.688, 1.355)	
p-value (log rank)	0.030		0.837	

Note: Concomitant anti-HER2 therapy was not included in Study 305 and Study 301.

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

5.2 Pharmacokinetic properties

Distribution

The pharmacokinetics of eribulin are characterized by a rapid distribution phase followed by a prolonged elimination phase, with a mean terminal half-life of approximately 40 h. It has a large volume of distribution (range of means 43 to 114 l/m^2).

Eribulin is weakly bound to plasma proteins. The plasma protein binding of eribulin (100-1000 ng/ml) ranged from 49% to 65% in human plasma.

Biotransformation

Unchanged eribulin was the major circulating species in plasma following administration of ^{14}C-eribulin to patients. Metabolite concentrations represented <0.6% of parent compound, confirming that there are no major human metabolites of eribulin.

Elimination

Eribulin has a low clearance (range of means 1.16 to 2.42 l/h/m^2). No significant accumulation of eribulin is observed on weekly administration. The pharmacokinetic properties are not dose or time dependent in the range of eribulin doses of 0.22 to 3.53 mg/m^2.

Eribulin is eliminated primarily by biliary excretion. The transport protein involved in the excretion is presently unknown. Preclinical in vitro studies indicate that eribulin is transported by Pgp. However it has been shown that at clinically relevant concentrations eribulin is not a Pgp inhibitor in vitro. Additionally, in vivo, concomitant administration of ketoconazole, a Pgp inhibitor, has no effect on eribulin exposure (AUC and C_{max}). In vitro studies have also indicated that eribulin is not a substrate for OCT1.

After administration of ^{14}C-eribulin to patients, approximately 82% of the dose was eliminated in faeces and 9% in urine indicating that renal clearance is not a significant route of eribulin elimination.

Unchanged eribulin represented most of the total radioactivity in faeces and urine.

Hepatic impairment

A study evaluated the pharmacokinetics of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=4) hepatic impairment due to liver metastases. Compared to patients with normal hepatic function (n=6), eribulin exposure increased 1.8-fold and 3-fold in patients with mild and moderate hepatic impairment, respectively. Administration of HALAVEN at a dose of 0.97 mg/m^2 to patients with mild hepatic impairment and 0.62 mg/m^2 to patients with moderate hepatic impairment resulted in a somewhat higher exposure than after a dose of 1.23 mg/m^2 to patients with normal hepatic function. HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C). There is no study in patients with hepatic impairment due to cirrhosis. See section 4.2 for dosage recommendation.

Renal impairment

Increased eribulin exposure was seen in some patients with moderately or severely impaired renal function, with high between-subject variability. The pharmacokinetics of eribulin were evaluated in a Phase 1 study in patients with normal renal function (Creatinine clearance: ≥ 80 ml/min; n=7),

moderate (30-50 ml/min; n=6) or severe (15-<30 ml/min; n=6) renal impairment. Creatinine clearance was estimated with the Cockcroft-Gault formula. A 1.5-fold (90% CI: 0.9-2.5) higher dose-normalised $AUC_{(0\text{-}inf)}$ was observed in patients with moderate and severe renal impairment. See section 4.2 for treatment recommendations.

5.3 Preclinical safety data

Eribulin was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test). Eribulin was positive in the mouse lymphoma mutagenesis assay and was clastogenic in the *in vivo* rat micronucleus assay.

No carcinogenicity studies have been conducted with eribulin.

A fertility study was not conducted with eribulin, but based on non-clinical findings in repeated-dose studies where testicular toxicity was observed in both rats (hypocellularity of seminiferous epithelium with hypospermia/aspermia) and dogs, male fertility may be compromised by treatment with eribulin. An embryofoetal development study in rat confirmed the developmental toxicity and teratogenic potential of eribulin. Pregnant rats were treated with eribulin mesilate equivalent to 0.009, 0.027, 0.088 and 0.133 mg/kg eribulin at gestation days 8, 10 and 12. Dose related increased number of resorptions and decreased foetal weight were observed at doses ≥ 0.088 mg/kg and increased incidence of malformations (absence of lower jaw, tongue, stomach and spleen) was recorded at 0.133 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol anhydrous
Water for injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

4 years.

In-use shelf life

From a microbiological point of view unless the method of opening precludes the risk of microbial contamination the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

If not used immediately HALAVEN as the undiluted solution in a syringe should not normally be stored longer than 4 hours at 25°C and ambient lighting, or 24 hours at 2°C - 8°C.

Diluted solutions of HALAVEN (0.018 mg/ml to 0.18 mg/ml eribulin in sodium chloride 9 mg/ml (0.9%)) solution for injection should not be stored longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml type I glass vial, with teflon-coated, butyl rubber stopper and flip-off aluminium over seal, containing 2 ml of solution.
5 ml type I glass vial, with teflon-coated, butyl rubber stopper and flip-off aluminium over seal, containing 3 ml of solution.

The pack sizes are cartons of 1 or 6 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

HALAVEN is a cytotoxic anticancer medicinal product and, as with other toxic compounds, caution should be exercised in its handling. The use of gloves, goggles, and protective clothing is recommended. If the skin comes into contact with the solution it should be washed immediately and thoroughly with soap and water. If it contacts mucous membranes, the membranes should be flushed thoroughly with water. HALAVEN should only be prepared and administered by personnel appropriately trained in handling of cytotoxic agents. Pregnant staff should not handle HALAVEN.

Using aseptic technique HALAVEN can be diluted up to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose. It must not be mixed with other medicinal products and should not be diluted in glucose 5% infusion solution.

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

7. MARKETING AUTHORISATION HOLDER

Eisai Europe Ltd
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/678/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 March 2011
Date of latest renewal:

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 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 RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Eisai Manufacturing Ltd.
European Knowledge Centre
Mosquito Way
Hatfield, Herts AL10 9SN
United Kingdom

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton 2ml vial

1. NAME OF THE MEDICINAL PRODUCT

HALAVEN 0.44 mg/ml solution for injection
Eribulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 2 ml vial contains eribulin mesilate equivalent to 0.88 mg eribulin

3. LIST OF EXCIPIENTS

Ethanol anhydrous,Water for injections,Hydrochloric acid,Sodium hydroxide
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial of 2 ml
6 vials of 2 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use

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

CYTOTOXIC

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Ltd
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/678/001 1 vial
EU/1/11/678/002 6 vials

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial 2 ml vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

HALAVEN 0.44 mg/ml injection
Eribulin
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contains 0.88 mg eribulin in 2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton 3 ml vial

1. NAME OF THE MEDICINAL PRODUCT

HALAVEN 0.44 mg/ml solution for injection
Eribulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 3 ml vial contains eribulin mesilate equivalent to 1.32 mg eribulin

3. LIST OF EXCIPIENTS

Ethanol anhydrous,Water for injections, Hydrochloric acid, Sodium hydroxide
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial of 3 ml
6 vials of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use

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

CYTOTOXIC

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Ltd
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/678/003 1 vial
EU/1/11/678/004 6 vials

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial 3 ml vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

HALAVEN 0.44 mg/ml injection
Eribulin
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contains 1.32 mg eribulin in 3 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

HALAVEN 0.44 mg/ml solution for injection
eribulin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What HALAVEN is and what it is used for
2. What you need to know before you use HALAVEN
3. How to use HALAVEN
4. Possible side effects
5. How to store HALAVEN
6. Contents of the pack and other information

1. What HALAVEN is and what it is used for

HALAVEN contains the active substance eribulin and is an anti-cancer medicine which works by stopping the growth and spread of cancer cells.

It is used for locally advanced or metastatic breast cancer (breast cancer that has spread beyond the original tumour) when at least one other therapy has been tried but has lost its effect.

2. What you need to know before you use HALAVEN

Do not use HALAVEN:
- if you are allergic to eribulin mesilate or any of the other ingredients of this medicine (listed in section 6)
- if you are breast-feeding

Warnings and precautions
Talk to your doctor or nurse before using HALAVEN:
- if you have liver problems
- if you have a fever or an infection
- if you experience numbness, tingling, prickling sensations, sensitivity to touch or muscle weakness
- if you have heart problems

If any of these affects you, tell your doctor who may wish to stop treatment or reduce the dose.

Other medicines and HALAVEN
Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy, breast-feeding and fertility
HALAVEN may cause serious birth defects and should not be used if you are pregnant unless it is thought clearly necessary after carefully considering all the risk to you and the baby. It may also cause future permanent fertility problems in men if they take it and they should discuss this with their doctor before starting treatment. Women of childbearing age should use effective contraception during and up to 3 months after treatment with HALAVEN.

HALAVEN must not be used during breast-feeding because of the possibility of risk to the child.

Driving and using machines
HALAVEN may cause side effects such as tiredness (very common) and dizziness (common). Do not drive or use machines if you feel tired or dizzy.

HALAVEN contains ethanol (alcohol)
This medicine contains small amounts of ethanol (alcohol), less than 100 mg in a vial.

3. How to use HALAVEN

HALAVEN will be given to you by a doctor or nurse as an injection into a vein, over a period of 2 to 5 minutes. The dose you will receive is based on your body surface area (expressed in squared metres, or m^2) which is calculated from your weight and height. The usual dose of HALAVEN is 1.23 mg/m^2, but this may be adjusted by your doctor based on your blood test results or other factors. To ensure that the whole dose of HALAVEN is given it is recommended that a saline solution is flushed into the vein after HALAVEN is given.

How often will you be given HALAVEN?
HALAVEN is usually given on Days 1 and 8 of every 21-day cycle. Your doctor will determine how many cycles of treatment you should receive. Depending on the results of your blood tests, the doctor may need to delay administration of the medicine until the blood tests return to normal. The doctor may also then decide to reduce the dose you are given.

If you have any further questions about the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any of the following rare but serious symptoms, stop taking HALAVEN and seek medical attention straightaway:

- Any difficulty breathing, or swelling of your face, mouth, tongue or throat. These could be signs of an allergic reaction.

Other side effects:

Very common side effects (may affect more than 1 in 10 people) are:

- Decrease in the number of white blood cells or red blood cells
- Tiredness or weakness
- Nausea, vomiting, constipation, diarrhoea
- Numbness, tingling or prickling sensations
- Fever
- Loss of appetite, weight loss

- Difficulty breathing, cough
- Pain in the joints, muscles and back
- Headache
- Hair loss

Common side effects (may affect up to 1 in 10 people) are:
- Decrease in the number of platelets (which may result in bruising or taking longer to stop bleeding)
- Infection with fever, pneumonia, chills
- Fast heart rate, flushing
- Vertigo, dizziness
- Increased production of tears, conjunctivitis (redness and soreness of the surface of the eye), nosebleed
- Dehydration, dry mouth, mouth ulcers, cold sores, oral thrush, indigestion, heartburn, abdominal pain or swelling
- Swelling of soft tissues, pains (in particular chest, back and bone pain), muscle spasm or weakness
- Mouth, respiratory and urinary tract infections, painful urination
- Sore throat, sore or runny nose, flu-like symptoms, throat pain
- Liver function test abnormalities, altered level of sugar, bilirubin, phosphates, potassium or magnesium in the blood
- Inability to sleep, depression, changed sense of taste
- Rash, itching, nail problems, dry or red skin
- Excessive sweating (including night sweats)

Uncommon side effects (may affect up to 1 in 100 people) are:
- Severe infections with blood poisoning (sepsis), shingles
- Ringing in the ears
- Blood clots
- Abnormal liver function tests (hepatoxicity)
- Swelling of the skin and numbness of the hands and feet
- Kidney failure, blood or protein in the urine

Rare side effects (may affect up to 1 in 1000 people) are:
- Inflammation of the pancreas
- Widespread inflammation of the lungs which may lead to scarring
- Widespread development of blood clots in the very tiny blood vessels with associated inability for the blood to clot in the bigger blood vessels leading to internal bleeding throughout the body

Reporting of side effects
If you get any side effects, talk to your doctor 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 HALAVEN

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What HALAVEN contains

- The active substance is eribulin. Each 2 ml vial contains eribulin mesilate equivalent to 0.88 mg eribulin. Each 3 ml vial contains eribulin mesilate equivalent to 1.32 mg eribulin.
- The other ingredients are ethanol and water for injections, with hydrochloric acid and sodium hydroxide possibly present in very small amounts.

What HALAVEN looks like and contents of the pack

HALAVEN is a clear, colourless aqueous solution for injection provided in glass vials containing 2 ml or 3ml of solution. Each carton contains either 1 or 6 vials.

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Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

Eribulin:
Company Core Data Sheet

