リサイオ点滴静注液100mg
に関する資料

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大日本住友製薬株式会社

チオテパ

製造販売承認申請

CTD 第 1 部

1.5　起原又は発見の経緯及び開発の経緯

大日本住友製薬株式会社

1. 起原又は発見の経緯

1.1 チオテパについて

チオテパは、American Cyanamid 社が開発した[文献 1)]エチレンイミン系に属する抗腫瘍性アルキル化剤であり、DNA 合成阻害作用を有する。国内ではテスパミン錠、テスパミン注射液（注射用蒸留水付）、テスパミン®注射液として、住友化学工業株式会社が 1957 年[redacted]月[redacted]日付で医薬品製造許可申請を行い、1958 年[redacted]月[redacted]日付で許可された。その後、更に臨床成績が集積され、効能を追加する許可事項変更許可申請を 1959 年[redacted]月[redacted]日付で行い、テスパミン錠およびテスパミン®注射液は同年 9 月[redacted]日付で、テスパミン注射液（注射用蒸留水付）は 9 月[redacted]日付で承認を取得した。[redacted]年[redacted]月[redacted]日に再評価申請を行い、1982 年 8 月 10 日に再評価結果が通知されたことに伴い、[redacted]で再評価結果に適合させるための医薬品製造承認事項一部変更承認申請を行い、同年[redacted]月[redacted]付で承認を取得した。その後、1984 年 10 月[redacted]日に住友製薬株式会社に承継し、テスパミン®注射液は[redacted]年[redacted]月[redacted]日に承認整理届出が行われ、テスパミン錠は[redacted]年[redacted]月[redacted]日に承認整理届出が行われた。テスパミン注射液（注射用蒸留水付）は、2005 年 10 月[redacted]日に大日本製薬株式会社に承継し、同日付で大日本住友製薬株式会社に社名変更された。しかし、チオテパ原薬の製造会社から、設備老朽化を理由に工場を閉鎖しチオテパの製造を中止する旨の連絡を受け、2010 年 9 月[redacted]日付で承認整理届出を行ったため現在国内では製造販売されていない。テスパミン注射液（注射用蒸留水付）の当時の効能・効果及び用法・用量は次のとおりである。

【1959 年 9 月[redacted]日許可取得時の効能・効果】

白血病（慢性骨髄性・亜急性骨髄性・慢性リンパ性）・赤血球過多症・ホジキン氏病・リンパ肉腫・細網肉腫・乳癌・肺癌

卵巣癌・子宮癌・胃癌・膵臓癌・膀胱腫瘍・悪性絨毛上皮腫・及びこれらの転移病巣並びに癌性腹膜炎の自覚的並びに他覚的症状の緩解。

【1959 年 9 月[redacted]日許可取得時の用法・用量】

1. 単独で使用する場合

チオテパとして、通常成人 1 日 1 回 3～15 mg を、静脈内、筋肉内又は動脈内に注射する。また、必要に応じて胸・腹腔内、膀胱内又は腫瘍内に注入する。なお、年齢、症状により適宜減量する。

2. 他の抗腫瘍剤と併用する場合

単独で使用する場合に準じ、適宜減量する。

【再評価から承認整理までの効能・効果】

下記疾患の自覚的並びに他覚的症状の緩解

慢性リンパ性白血病、慢性骨髄性白血病、乳癌、卵巣癌、膀胱腫瘍

ただし、下記の疾患については、他の抗腫瘍剤と併用することが必要である。

悪性リンパ腫（ホジキン病、リンパ肉腫、細網肉腫）、胃癌、肺癌、子宮頸癌、子宮体癌

【再評価から承認整理までの用法・用量】

1. 単独で使用する場合

チオテパとして、通常成人 1 日 1 回 3～15 mg を、静脈内、筋肉内又は動脈内に注射する。また、必要に応じて胸・腹腔内、膀胱内又は腫瘍内に注入する。

なお、年齢、症状により適宜増減する。

2. 他の抗腫瘍剤と併用する場合

単独で使用する場合に準じ、適宜減量する。

海外でチオテパの臨床開発は 1950 年代中盤に開始され、さまざまな腫瘍性疾患（慢性白血病、非ホジキンリンパ腫、ホジキンリンパ腫、乳腺癌、卵巣腺癌、黒色腫、小児腫瘍及び胚腫瘍など）の治療に用いられてきた。欧州では 2010 年までチオテパの適応に、HSCT の前治療は含まれていなかった。チオテパには、血液毒性が認められるが非血液毒性は軽度であるか認められないことが明らかになり、1980 年代の終わりには HSCT の前治療として高用量で使用可能な薬剤の一つとみなされていた。高用量のチオテパは、欧州の医療機関で 10 年以上もの間、体系的に使用されてきた。そのため欧州ではチオテパ製剤の Tepadina®について 2008 年 7 月 4 日に ADIENNE 社が欧州医薬品庁（EMA）に対して「成人および小児における造血幹細胞移植の前治療」の効能・効果で中央審査方式の承認申請を行い、2010 年 3 月 15 日に“well-established medicinal use”に相当する医薬品との位置づけで、非臨床試験及び臨床試験を新たに実施することなく、公知情報（文献）に基づいて以下の効能・効果で承認取得した。米国でもチオテパ製剤は 1959 年に承認されたが、2017 年 2 月 3 日に Tepadina® が承認されるまで、チオテパの適応に HSCT の前治療は含まれておらず、現在も「小児固形腫瘍における自家 HSCT の前治療」の効能・効果は有していない。

【欧州で承認された Tepadina®の効能・効果】

in combination with other chemotherapy medicinal products:

1) with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients;

2) when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.

国内では、テスパミン注射液（注射用蒸留水付）が供給されなくなるまでの間、HSCT の前治療の適応を有していないにもかかわらず、チオテパは血液疾患及び固形腫瘍に対して HSCT の前治療として他の化学療法薬と併用して臨床使用されてきた。チオテパの販売が中止され供給されなくなったこと、及び Tepadina®が欧州で承認されていたことを踏まえ、国内の学会から Tepadina®の効能・効果、用法・用量に基づき未承認薬・適応外薬の要望書（要望番号 II-125 及び II-126）が提出された。チオテパは HSCT の前治療薬として医療上の必要

性が高い薬剤であると判断された。その後、要望内容を既に国内外の有効性及び安全性に関するエビデンスが蓄積している範囲に限定するため、悪性リンパ腫及び小児固形癌の HSCT における前治療薬と変更され、第 34 回医療上の必要性の高い未承認薬・適応外薬検討会議で報告された。

2. 開発の経緯

上記を受け、厚生労働省から開発企業の募集が行われ、当社は 2013 年 9 月に厚生労働省に開発の意思の申し出を提出し、凍結乾燥注射剤の Tepadina®とは異なる、チオテパを含有する溶液製剤であるリサイオ点滴静注液 100mg の開発に着手した。

チオテパは HSCT の前治療としての臨床成績が国内外で豊富に報告されていることから、公表論文等によりチオテパの有用性が医学薬学上公知であることが説明できれば、新たな臨床試験を実施することなく公表文献等で申請できると考えられた。チオテパの有効性及び安全性は、以下の資料から説明することとした。

- 国内のチオテパの HSCT の前治療としての使用実績（学会データベース）
- チオテパの HSCT の前治療としての有効性及び安全性に関する国内外の使用実績（公表文献等）
- テスパミン®注射液投与時の安全性情報

しかしながら、日本人にチオテパを投与した際の薬物動態が評価できる公表文献が存在しなかったため、薬物動態試験として国内第 1 相試験（DA901012）を実施することとした。当初、学会からの要望ではチオテパの効能・効果及び用法・用量は Tepadina®の欧州での承認範囲と同様であったが、当社は、適正使用の観点から、本臨床試験の対象患者は「現在、医療上チオテパの有用性が高く、ニーズのある患者」に絞るべきと考えた。そこで、国内でのチオテパに対するニーズの高い効能・効果及び用法・用量について、チオテパの開発を要望した医師及び学会にヒアリングした。その結果、チオテパは悪性リンパ腫、及び小児固形腫瘍へのニーズが高かったことから、効能・効果を悪性リンパ腫及び小児固形腫瘍に絞って国内第 1 相試験を実施した。また、特に小児固形腫瘍に関する医療ニーズが高いことを踏まえ、今回まずは以下の効能・効果、用法・用量に絞って承認申請することとした。

【効能・効果】

小児固形腫瘍における自家 HSCT の前治療

【用法・用量】

通常、メルファランとの併用において、チオテパとして 200 mg/m^2 を 1 日 1 回 2 日間投与し、5 日休薬した後、さらに 2 日間投与する。なお、年齢、患者の状態により適宜減量する。

国内第 1 相試験における併用薬に関しては、試験結果に対する併用薬の影響を最小限にするため、悪性リンパ腫に対してはブスルファン、小児脳腫瘍・小児固形腫瘍に対してはメルファランと規定した。国内第 1 相試験では、対象患者を小児固形腫瘍・小児脳腫瘍と記載したが、申請時には小児脳腫瘍は小児固形腫瘍と区別せず「小児固形腫瘍」とすることとし

た。

2.1 品質に関する試験

(1) 原薬

リサイオ点滴静注液 100mg に用いる原薬であるチオテパは[redacted]の[redacted]で製造されており、原薬等登録原簿に登録されている（登録番号[redacted]、登録年月日[redacted]）。また、チオテパは米国薬局方に収載されている。規格及び試験方法は米国薬局方を参考にし、「新医薬品の規格及び試験方法の設定について」（平成 13 年 5 月 1 日付医薬審発第 568 号）及び原薬等登録原簿の規格及び試験方法に基づき設定した（2.3.S.4 項参照）。「安定性試験ガイドラインの改定について」（平成 15 年 6 月 3 日付医薬審発第 0603001 号）及び「新原薬及び新製剤の光安定性試験ガイドラインについて」（平成 9 年 5 月 28 日付薬審第 422 号）に準拠し、長期保存試験、加速試験及び苛酷試験（温度及び光）を実施した（2.3.S.7 項参照）。

(2) 製剤

チオテパは水に対して不安定であることから、リサイオ点滴静注液 100mg は非水系溶剤を用いた溶液製剤とした。静脈内投与における使用前例、物性及びチオテパの溶解性などから候補となる溶剤を選定した結果、チオテパとの適合性に問題がないこと、添加剤としての安全性に懸念が少ないことなどから、マクロゴール 400 を選択した。想定される用法用量を満たすため、1 容器当たりのチオテパ含有量は 100 mg とし、薬液抜取り時の損失を考慮して 0.5 mL の過量充塡（実充塡量 3.0 mL）を行う（2.3.P.2 項参照）。

規格及び試験方法は、原薬の物理的化学的性質、実測値の結果及び安定性試験の成績、並びに「新医薬品の規格及び試験方法の設定について」（平成 13 年 5 月 1 日付医薬審発第 568 号）に基づいて設定した（2.3.P.5 項参照）。「安定性試験ガイドラインの改定について」（平成 15 年 6 月 3 日付医薬審発第 0603001 号）及び「新原薬及び新製剤の光安定性試験ガイドラインについて」（平成 9 年 5 月 28 日付薬審第 422 号）に準拠し、長期保存試験、加速試験及び苛酷試験（光）を実施した（2.3.P.8 項参照）。

(3) 添加剤

マクロゴール 400 は日本薬局方に収載されているが、配合量が使用前例を上回ることから新規添加剤に該当する。リサイオ点滴静注液 100mg の製造には、日本薬局方「マクロゴール 400」を使用する（2.3.P.4 項参照）。

2.2 非臨床試験

(1) 薬理試験

チオテパは、化学療法薬並びに造血幹細胞移植の前治療として多くの非臨床データが報

告されているため、新たな非臨床試験は実施せず、テスパミン®注射液の国内申請に利用された申請資料及び文献を基に評価した。特に、非臨床薬効薬理では今回申請する効能・効果（案）に鑑み、脳腫瘍を含む抗がん作用及び造血幹細胞移植の前治療への効果を示唆する情報を中心に考察した。

チオテパは、in vitro 試験において、ヒト髄芽腫由来 TE-671、D283MED 及び Daoy 細胞、ヒトラブドイド腫瘍由来 BT16 細胞、ヒト乳癌由来 MCF-7 細胞又はマウス白血球由来 P388 細胞に対してそれぞれコロニー形成阻害作用、増殖阻害作用、殺細胞作用又は増殖阻害作用を示し、チオテパの主代謝物である TEPA もチオテパと同様にヒト乳癌由来 MCF-7 細胞又はマウス白血病由来 P388 細胞に対して、殺細胞作用又は細胞増殖阻害作用を示した。また、in vivo 試験でもチオテパはヒト髄芽腫由来 Daoy 細胞脳内移植モデルマウスや皮下移植モデルマウスを含め、複数のマウス癌細胞移植モデルマウスで有意な生存期間の延長、細胞増殖阻害作用、殺細胞作用を示した。また、ヒト髄芽腫由来 Daoy 細胞脳内移植モデルでは、チオテパはメルファラン、シクロホスファミド、イホスファミド、又はフェニルケトシクロホスファミドよりも生存期間を延長した。

チオテパは、B 細胞白血病マウス由来の脾細胞自家移植モデルでブスルファンよりも優れた白血病発症抑制効果を示した。また、チオテパは、B 細胞白血病マウス由来の脾細胞自家移植モデルにおいて、メルファラン投与による白血病発症抑制効果やシクロホスファミド、メルファラン、シトシンアラビノシド、カルムスチン及びエトポシドの 5 剤併用による白血病発症抑制効果と拮抗しないことが示された。

以上、チオテパはそのアルキル化作用に基づき、複数の固形がんに対する抗がん作用を示し、また脳内に形成されたがんにも効果を発揮することから、造血幹細胞移植の前治療として有効性を発揮することが期待される。

チオテパは、既に臨床で使用されていることから、安全性薬理試験は実施せず、テスパミン®注射液の国内申請に利用された申請資料及び公知の文献を基に評価した。テスパミン®注射液の一般薬理試験及び文献報告では、チオテパは生命維持に重要な器官系（中枢神経系、心血管系及び呼吸系）に関連する影響として幼若ラットでの神経毒性やウサギ摘出心房での収縮力抑制が認められた。しかしながら、神経毒性はラットで致死的な高用量で認められた変化であったこと、収縮力抑制については、国内のテスパミン®注射液の安全性情報ではチオテパとの関連性が疑われる副作用として心臓障害に関する副作用が数例報告されているのみであることから、いずれもヒトへの外挿性は低いと推察された。既に臨床では動物実験の LD_{10} 値等を上回る用量が投与されており、今回評価した安全性薬理試験項目に係る各器官系に及ぼす影響は十分な曝露での評価とはいえないため、チオテパは臨床での使用実績を基に適切な投与量を患者に投与する必要がある。

(2) 薬物動態試験

テスパミン®注射液の国内申請に利用された申請資料及び文献を基に評価した。

チオテパの体内動態は各動物種で類似しており、静脈内投与したチオテパは速やかに血中から消失した。イヌ及びサルでは代謝物 TEPA の血漿中濃度は投与後 1～2 時間で最大値

に達した後に緩やかに減少し、その曝露量はチオテパと同等以上であった。マウス及びラットに放射性標識したチオテパを静脈内投与したとき、放射能は脳を含む全身組織に広範に分布した。イヌでも ^{32}P-チオテパ由来の放射能が脳及び CSF に分布した。アカゲザルではチオテパ及び TEPA は CSF に移行し、それらの血漿中濃度と CSF 中濃度はほぼ同等であった。以上の結果から、チオテパ及び TEPA は血液脳関門を通過し、中枢へ移行すると考えられた。ヒトでの主代謝経路は、酸化的脱硫反応による TEPA の生成とそれに続くモノクロロ TEPA の生成、およびグルタチオン抱合を経由したメルカプツール酸抱合体の生成と推察された。チオテパから TEPA への代謝には CYP3A4 及び CYP2B6 が関与すると考えられた。チオテパは CYP2B6 による薬物代謝を阻害し、ヒト肝ミクロソームでの Ki 値は 4.8 μmol/L であった。チオテパは臨床において CYP2B6 基質との併用により薬物間相互作用を示す可能性が考えられた。各動物種における投与放射能の尿中への回収率は 69～90%と高く、チオテパの主な消失経路は尿中排泄であると推察された。一方で、イヌでの尿中未変化体排泄率は投与量の 1%未満であった。胆汁排泄の検討は実施していないが、チオテパは肝臓で代謝を受けた後に、その代謝物の大部分が尿中へ排泄されると推察された。

(3) 毒性試験

チオテパの毒性はテスパミン®注射液の国内申請に利用された申請資料及び文献を基に評価した。チオテパ製剤の添加物であるマクロゴール 400 は使用前例を上回るため、その毒性について文献を基に評価した。チオテパ製剤は長期保存時に類縁物質B群が増加し、「新有効成分含有医薬品のうち製剤の不純物に関するガイドラインの改定について」（平成 15 年 6 月 24 日付 医薬審発第 0624001 号）に記載されている「安全性の確認が必要とされる閾値」を上回ることが予想されたため、分取した類縁物質B群のラット 7 日間反復静脈内投与毒性試験（予備試験及び本試験）を実施した。

チオテパの単回投与では、マウス、ラット及びウサギの静脈内投与による LD_{50} 値はそれぞれ 14.5 mg/kg、10.5 mg/kg 及び 5 mg/kg 超であり、投与経路の違いはあるものの、主として本剤の薬理作用である細胞毒性に起因した骨髄機能抑制、並びに肝臓、脾臓、腎臓及び消化管への影響が認められた。また、死戦期の急性症状として下痢、衰弱、食欲不振、鼻部出血及び体重減少がみられ、死因は呼吸麻痺と推察された。反復投与では、マウス及びラットの 5 日間静脈内投与による LD_{10} 値はそれぞれ 4.5 又は 5.1 mg/kg/日及び 2.2 又は 3.4 mg/kg/日であり、主として本剤の薬理作用である細胞毒性に起因した骨髄機能抑制、並びに肝臓、脾臓及び消化管への影響が認められた。なお、既に臨床では動物実験の LD_{10} 値等を含む毒性用量を上回る用量が投与されているため、臨床での使用実績を基に適切な用量を患者に投与する必要がある。

遺伝毒性は、遺伝子突然変異試験、染色体異常試験及び小核試験を含め、実施された試験はいずれも陽性であった。がん原性試験では、マウスで肺腫瘍、造血器系腫瘍及び扁平上皮癌が、ラットで造血器系腫瘍、扁平上皮癌及び腺癌を含めた多臓器でのがんの発生率の上昇が認められた。したがって、チオテパは遺伝毒性発がん物質であり、患者に投与する際には、

治療上のリスク及びベネフィットを十分に考慮する必要がある。

生殖発生毒性として、マウス及びラットで精子形成障害に伴う授胎能の低下が、マウス、ラット及びウサギで催奇形性又は胚・胎児致死作用が、マウスで出生児の発育及び生存性への影響が認められた。また、チオテパを含むアルキル化剤では、ヒトの生殖細胞に影響を及ぼすこと、妊娠第1三半期での投与で胎児の異常、流産及び子宮内膜胎児死亡のリスクが増加することが知られている。したがって、男性、女性ともにチオテパ投与により一時的又は永久的な不妊症に陥る危険性があること、また、小児でも性腺の発達に影響を及ぼす可能性があることから、患者に投与する際には、治療上のリスクとベネフィットを十分に考慮する必要がある。更に妊婦又は妊娠している可能性のある女性には投与を避けるべきであり、また、授乳中の女性への投与を避け、やむを得ず投与する場合は授乳を中止させるべきである。

マクロゴール400では、マウス、ラット及びウサギの単回静脈内投与によるLD_{50}値はそれぞれ8.6 g/kg、4.7 g/kg及び10 g/kg超であった。イヌの30日間反復静脈内投与では4.23 g/kg/日（HED：2350 mg/kg/日）で血清電解質（Na及びCl）の上昇、6.34 g/kg/日（HED：3522 mg/kg/日）以上で口渇及び鼻粘膜の乾燥、8.45 g/kg/日（HED：4694 mg/kg/日）で腎細胞の混濁腫脹及び糸球体容積増加の病理組織学的変化が認められた。また、ヒヒの29日間反復静脈内投与では1000 mg/kg/日（HED：556 mg/kg/日）の雌で体重減少が、ラットの4週間反復静脈内投与では2500 mg/kg/日（HED：403 mg/kg/日）の雌で呼吸数及び網赤血球数の増加が、ウサギの5週間及び30日間反復静脈内投与では350mg/kg/日（HED：113 mg/kg/日）以上で肝臓及び腎臓に軽微な毒性所見が認められた。遺伝毒性はみられず、静脈内投与によるがん原性及び胎児毒性は認められなかった。

チオテパ製剤の類縁物質B群につき、ラット7日間反復静脈内投与毒性試験を実施した結果、高用量である0.9 mg/kg/日群の雄で白血球系パラメータの低値がみられたのみで、全身毒性はチオテパと同様に薬理作用に基づく骨髄機能抑制であり、更にその強さはチオテパと比較して極めて弱かった（4.2.3.7.6.2）。

以上、チオテパ投与により動物実験で致死作用、骨髄機能抑制等の一般毒性、遺伝毒性、発がん性及び生殖発生毒性（精子形成障害、催奇形性、胚・胎児致死作用など）が認められた。チオテパ製剤の添加物であるマクロゴール400は高用量で軽微な毒性変化がみられたものの、遺伝毒性はなく、静脈内投与によるがん原性及び胎児毒性は認められなかった。チオテパ製剤の保存中に増加する類縁物質B群でも骨髄機能抑制が認められたが、その強さはチオテパと比較して極めて弱かった。

2.3 臨床試験の経緯

2016年11月より薬物動態試験（DA901012）を開始し、これを評価資料とした。

自家造血幹細胞移植を施行する予定の小児固形腫瘍・小児脳腫瘍患者及び悪性リンパ腫患者を対象に、自家造血幹細胞移植の前治療としてDSP-1958を静脈内投与したときの薬物動態を検討することを目的とする非盲検、無対照、多施設共同試験を実施した（2016年11月～2017年5月、転帰調査は2017年8月まで）。小児固形腫瘍・小児脳腫瘍患者ではDSP-

1958 とメルファランの併用、悪性リンパ腫患者では DSP-1958 とブスルファンの併用をプロトコール治療とした。DSP-1958 の 1 回あたりの用法・用量は小児固形腫瘍・小児脳腫瘍患者では体表面積あたり 200 mg/m^2 を 24 時間かけて、悪性リンパ腫患者では体表面積あたり 200 mg/m^2 を 2 時間かけて投与とした。

当該治験の臨床試験成績は本資料第 2 部 2.5 項、2.7 項に詳細を記載した。

開発の経緯図

<table>
<tr><td colspan="2"></td><td colspan="3">[redacted]</td></tr>
<tr><td colspan="2">品質に関する試験</td><td colspan="3"></td></tr>
<tr><td rowspan="2">非臨床試験
毒性試験</td><td>DSP-1958 注類縁物質群のラットにおける 7 日間反復静脈内投与毒性試験
([redacted]-352)</td><td colspan="3" rowspan="2">[redacted]</td></tr>
<tr><td>DSP-1958 注類縁物質群のラットにおける 7 日間反復静脈内投与毒性試験（本試験）
([redacted]-360)</td></tr>
<tr><td rowspan="2">臨床試験</td><td>DSP-1958 の薬物動態試験（DA901012）</td><td></td><td>11
▲</td><td>9
■
▲</td></tr>
<tr><td>拡大治験
(DA901014)</td><td></td><td></td><td>9
▲
(2018.12)</td></tr>
</table>

▲：開始月、■：終了月、（ ）：終了予定月

参考文献

1) Sykes MP, Karnofsky DA, Philips FS, Burchenal JH. Clinical studies on triethylenephosphoramide and diethylenephosphoramide, compounds with nitrogen-mustard-like activity. Cancer. 1953; 6(1): 142−8. 【5.4.137】

チオテパ

製造販売承認申請

CTD 第１部

1.6　外国における使用状況等

大日本住友製薬株式会社

1. 外国における使用状況等に関する資料

リサイオ点滴静注液 100mg は海外で承認されていない。

チオテパを有効成分として含有する製剤として、欧米では Tepadina®が承認・販売されている。このうち、「小児悪性固形腫瘍における自家造血幹細胞移植の前治療」に対して投与可能な効能・効果で承認・販売している国を下表に示す。なお、凍結乾燥注射剤の Tepadina®は、溶液製剤であるリサイオ点滴静注液 100mg とは異なる製剤である。

「小児悪性固形腫瘍における自家造血幹細胞移植の前治療」を含む効能・効果における Tepadina®の承認・販売国（2018 年 10 月現在）

国名	
オーストリア	*
ベルギー	*
ブルガリア	*
クロアチア	*
キプロス	*
チェコ共和国	*
デンマーク	*
エストニア	*
フィンランド	*
フランス	*
ドイツ	*
ギリシャ	*
オランダ	*
ハンガリー	*
アイスランド	*
アイルランド	*
イタリア	*
ラトビア	*
リトアニア	*
ルクセンブルク	*
マルタ共和国	*
ノルウェー	*
ポーランド	*
ポルトガル	*
ルーマニア	*
スロバキア	*
スロベニア	*
スペイン	*
スウェーデン	*
イギリス	*
ロシア	
スイス	
香港	

国名
イスラエル
インド

＊：EMA より中央審査方式で承認取得後、ADIENNE Pharma&Biotech 社（ADIENNE 社）が地域代理店を置いている国

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 15 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 15 mg thiotepa.
After reconstitution with 1.5 ml of water for injections, each ml of solution contains 10 mg thiotepa (10 mg/ml).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
White crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TEPADINA is indicated, in combination with other chemotherapy medicinal products:
- with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients;
- when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.

4.2 Posology and method of administration

TEPADINA administration must be supervised by a physician experienced in conditioning treatment prior to haematopoietic progenitor cell transplantation.

Posology

TEPADINA is administered at different doses, in combination with other chemotherapeutic medicinal products, in patients with haematological diseases or solid tumours prior to HPCT.

TEPADINA posology is reported, in adult and paediatric patients, according to the type of HPCT (autologous or allogeneic) and disease.

Adults

AUTOLOGOUS HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 300 mg/m^2/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m^2 (24.32 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA
The recommended dose ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 300 mg/m^2/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m^2 (24.32 mg/kg), during the time of the entire conditioning treatment.
CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA
The recommended dose is 185 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 2 consecutive days before autologous HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
MULTIPLE MYELOMA
The recommended dose ranges from 150 mg/m^2/day (4.05 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.

Solid tumours

The recommended dose in solid tumours ranges from 120 mg/m^2/day (3.24 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) divided in one or two daily infusions, administered from 2 up to 5 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 800 mg/m^2 (21.62 mg/kg), during the time of the entire conditioning treatment.
BREAST CANCER
The recommended dose ranges from 120 mg/m^2/day (3.24 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered from 3 up to 5 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 800 mg/m^2 (21.62 mg/kg), during the time of the entire conditioning treatment.
CNS TUMOURS
The recommended dose ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) divided in one or two daily infusions, administered from 3 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.
OVARIAN CANCER
The recommended dose is 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered in 2 consecutive days before autologous HPCT, without exceeding the total maximum cumulative dose of 500 mg/m^2 (13.51 mg/kg), during the time of the entire conditioning treatment.
GERM CELL TUMOURS
The recommended dose ranges from 150 mg/m^2/day (4.05 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.

ALLOGENEIC HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 185 mg/m^2/day (5 mg/kg/day) to 481 mg/m^2/day (13 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 3 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 555 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA
The recommended dose in lymphoma is 370 mg/m^2/day (10 mg/kg/day) divided in two daily infusions before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
MULTIPLE MYELOMA
The recommended dose is 185 mg/m^2/day (5 mg/kg/day) as a single daily infusion before allogeneic HPCT, without exceeding the total maximum cumulative dose of 185 mg/m^2 (5 mg/kg), during the time of the entire conditioning treatment.
LEUKAEMIA
The recommended dose ranges from 185 mg/m^2/day (5 mg/kg/day) to 481 mg/m^2/day (13 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 2 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 555 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
THALASSEMIA
The recommended dose is 370 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

Paediatric population

AUTOLOGOUS HPCT

Solid tumours

The recommended dose in solid tumours ranges from 150 mg/m^2/day (6 mg/kg/day) to 350 mg/m^2/day (14 mg/kg/day) as a single daily infusion, administered from 2 up to 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 1050 mg/m^2 (42 mg/kg), during the time of the entire conditioning treatment.
CNS TUMOURS
The recommended dose ranges from 250 mg/m^2/day (10 mg/kg/day) to 350 mg/m^2/day (14 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 1050 mg/m^2 (42 mg/kg), during the time of the entire conditioning treatment.

ALLOGENEIC HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m^2/day (5 mg/kg/day) to 250 mg/m^2/day (10 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 3 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 375 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
LEUKAEMIA
The recommended dose is 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
THALASSEMIA
The recommended dose ranges from 200 mg/m^2/day (8 mg/kg/day) to 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

REFRACTORY CYTOPENIA
The recommended dose is 125 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before allogeneic HPCT, without exceeding the total maximum cumulative dose of 375 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
GENETIC DISEASES
The recommended dose is 125 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 2 consecutive days before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
SICKLE CELL ANAEMIA
The recommended dose is 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

Special populations

Renal impairment
Studies in renally impaired patients have not been conducted. As thiotepa and its metabolites are poorly excreted in the urine, dose modification is not recommended in patients with mild or moderate renal insufficiency. However, caution is recommended (see sections 4.4 and 5.2).

Hepatic impairment
Thiotepa has not been studied in patients with hepatic impairment. Since thiotepa is mainly metabolized through the liver, caution needs to be exercised when thiotepa is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. Dose modification is not recommended for transient alterations of hepatic parameters (see section 4.4).

Elderly
The administration of thiotepa has not been specifically investigated in elderly patients. However, in clinical studies, a proportion of patients over the age of 65 received the same cumulative dose as the other patients. No dose adjustment was deemed necessary.

Method of administration

TEPADINA must be administered by a qualified healthcare professional as a 2-4 hours intravenous infusion via a central venous catheter.
Each TEPADINA vial must be reconstituted with 1.5 ml of sterile water for injection. The total volume of reconstituted vials to be administered should be further diluted in 500 ml of sodium chloride 9 mg/ml (0.9%) solution for injection prior to administration (1,000 ml if the dose is higher than 500 mg). In children, if the dose is lower than 250 mg, an appropriate volume of sodium chloride 9 mg/ml (0.9%) solution for injection may be used in order to obtain a final TEPADINA concentration between 0.5 and 1 mg/ml. For instructions on reconstitution and further dilution prior to administration, see section 6.6.

Precautions to be taken before handling or administering the medicinal product
Topical reactions associated with accidental exposure to thiotepa may occur. Therefore, the use of gloves is recommended in preparing the solution for infusion. If thiotepa solution accidentally contacts the skin, the skin must be immediately thoroughly washed with soap and water. If thiotepa accidentally contacts mucous membranes, they must be flushed thoroughly with water (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance.
Pregnancy and lactation (see section 4.6).
Concomitant use with yellow fever vaccine and with live virus and bacterial vaccines (see section 4.5).

4.4 Special warnings and precautions for use

The consequence of treatment with thiotepa at the recommended dose and schedule is profound myelosuppression, occurring in all patients. Severe granulocytopenia, thrombocytopenia, anaemia or any combination thereof may develop. Frequent complete blood counts, including differential white blood cell counts, and platelet counts need to be performed during the treatment and until recovery is achieved. Platelet and red blood cell support, as well as the use of growth factors such as Granulocyte-colony stimulating factor (G-CSF), should be employed as medically indicated. Daily white blood cell counts and platelet counts are recommended during therapy with thiotepa and after transplant for at least 30 days.

Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) should be considered for the prevention and management of infections during the neutropenic period.

Thiotepa has not been studied in patients with hepatic impairment. Since thiotepa is mainly metabolized through the liver, caution needs to be observed when thiotepa is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. When treating such patients it is recommended that serum transaminase, alkaline phosphatase and bilirubin are monitored regularly following transplant, for early detection of hepatotoxicity.

Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or prior progenitor cell transplant may be at an increased risk of hepatic veno-occlusive disease (see section 4.8).

Caution must be used in patients with history of cardiac diseases, and cardiac function must be monitored regularly in patients receiving thiotepa.

Caution must be used in patients with history of renal diseases and periodic monitoring of renal function should be considered during therapy with thiotepa.

Thiotepa might induce pulmonary toxicity that may be additive to the effects produced by other cytotoxic agents (busulfan, fludarabine and cyclophosphamide) (see section 4.8).

Previous brain irradiation or craniospinal irradiation may contribute to severe toxic reactions (e.g. encephalopathy).

The increased risk of a secondary malignancy with thiotepa, a known carcinogen in humans, must be explained to the patient.

Concomitant use with live attenuated vaccines (except yellow fever vaccines), phenytoin and fosphenytoin is not recommended (see section 4.5).

Thiotepa must not be concurrently administered with cyclophosphamide when both medicinal products are present in the same conditioning treatment. TEPADINA must be delivered after the completion of any cyclophosphamide infusion (see section 4.5).

During the concomitant use of thiotepa and inhibitors of CYP2B6 or CYP3A4, patients should be carefully monitored clinically (see section 4.5).

As most alkylating agents, thiotepa might impair male or female fertility. Male patients should seek for sperm cryopreservation before therapy is started and should not father a child while treated and during the year after cessation of treatment (see section 4.6).

4.5 Interactions with other medicinal products and other forms of interaction

Specific interactions with thiotepa
Live virus and bacterial vaccines must not be administered to a patient receiving an immunosuppressive chemotherapeutic agent and at least three months must elapse between discontinuation of therapy and vaccination.

Thiotepa appears to be metabolised via CYP2B6 and CYP3A4. Co-administration with inhibitors of CYP2B6 (for example clopidogrel and ticlopidine) or CYP3A4 (for example azole antifungals, macrolides like erythromycin, clarithromycin, telithromycin, and protease inhibitors) may increase the plasma concentrations of thiotepa and potentially decrease the concentrations of the active metabolite TEPA. Co-administration of inducers of cytochrome P450 (such as rifampicin, carbamazepine, phenobarbital) may increase the metabolism of thiotepa leading to increased plasma concentrations of the active metabolite. Therefore, during the concomitant use of thiotepa and these medicinal products, patients should be carefully monitored clinically.

Thiotepa is a weak inhibitor for CYP2B6, and may thereby potentially increase plasma concentrations of substances metabolised via CYP2B6, such as ifosfamide, tamoxifen, bupropion, efavirenz and cyclophosphamide. CYP2B6 catalyzes the metabolic conversion of cyclophosphamide to its active form 4-hydroxycyclophosphamide (4-OHCP) and co-administration of thiotepa may therefore lead to decreased concentrations of the active 4-OHCP. Therefore, a clinical monitoring should be exercised during the concomitant use of thiotepa and these medicinal products.

Contraindications of concomitant use
Yellow fever vaccine: risk of fatal generalized vaccine-induced disease.

More generally, live virus and bacterial vaccines must not be administered to a patient receiving an immunosuppressive chemotherapeutic agent and at least three months must elapse between discontinuation of therapy and vaccination.

Concomitant use not recommended
Live attenuated vaccines (except yellow fever): risk of systemic, possibly fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

An inactivated virus vaccine should be used instead, whenever possible (poliomyelitis).

Phenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicinal product or risk of toxicity enhancement and loss of efficacy of the cytotoxic medicinal product due to increased hepatic metabolism by phenytoin.

Concomitant use to take into consideration
Ciclosporine, tacrolimus: excessive immunosuppression with risk of lymphoproliferation.

Alkylating chemotherapeutic agents, including thiotepa, inhibit plasma pseudocholinesterase by 35% to 70%. The action of succinyl-choline can be prolonged by 5 to 15 minutes.

Thiotepa must not be concurrently administered with cyclophosphamide when both medicinal products are present in the same conditioning treatment. TEPADINA must be delivered after the completion of any cyclophosphamide infusion.

The concomitant use of thiotepa and other myelosuppressive or myelotoxic agents (i.e. cyclophosphamide, melphalan, busulfan, fludarabine, treosulfan) may potentiate the risk of haematologic adverse reactions due to overlapping toxicity profiles of these medicinal products.

Interaction common to all cytotoxics
Due to the increase of thrombotic risk in case of malignancy, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulation state during malignancy, and the potential interaction between oral anticoagulants and anticancer chemotherapy require, if it is decided to treat the patient with oral anticoagulants, to increase the frequency of the INR (International Normalised Ratio) monitoring.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential have to use effective contraception during treatment and a pregnancy test should be performed before treatment is started.

Pregnancy
There are no data on the use of thiotepa during pregnancy. In pre-clinical studies thiotepa, as most alkylating agents, has been shown to cause embryofoetal lethality and teratogenicity (see section 5.3). Therefore, thiotepa is contraindicated during pregnancy.

Breast-feeding
It is unknown whether thiotepa is excreted in human milk. Due to its pharmacological properties and its potential toxicity for breast-fed newborns/infants, breast-feeding is contraindicated during treatment with thiotepa.

Fertility
As most alkylating agents, thiotepa might impair male and female fertility.
Male patients should seek for sperm cryopreservation before therapy is started and should not father a child while treated and during the year after cessation of treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

TEPADINA may have major influence on the ability to drive and use machines. It is likely that certain adverse reactions of thiotepa like dizziness, headache and blurred vision could affect these functions.

4.8 Undesirable effects

Summary of the safety profile

The safety of thiotepa has been examined through a review of adverse events reported in published data from clinical trials. In these studies, a total of 6,588 adult patients and 902 paediatric patients received thiotepa for conditioning treatment prior to haematopoietic progenitor cell transplantation.

Serious toxicities involving the haematologic, hepatic and respiratory systems were considered as expected consequences of the conditioning regimen and transplant process. These include infection and Graft-versus host disease (GvHD) which, although not directly related, were the major causes of morbidity and mortality, especially in allogeneic HPCT.
The most frequently adverse reactions reported in the different conditioning treatments including thiotepa are: infections, cytopenia, acute GvHD and chronic GvHD, gastrointestinal disorders, haemorrhagic cystitis, mucosal inflammation.

Leukoencephalopathy
Cases of leukoencephalopathy have been observed following treatment with thiotepa in adult and paediatric patients with multiple previous chemotherapies, including methotrexate and radiotherapy. Some cases had a fatal outcome.

Tabulated list of adverse reactions

Adults

The adverse reactions considered at least possibly related to conditioning treatment including thiotepa, reported in adult patients as more than an isolated case, are listed below by system organ class and by frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies 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) very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	**Very common**	**Common**	**Uncommon**	**Not known**
Infections and infestations	Infection susceptibility increased Sepsis		Toxic shock syndrome	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Treatment related second malignancy		
Blood and lymphatic system disorders	Leukopenia Thrombocytopenia Febrile neutropenia Anaemia Pancytopenia Granulocytopenia			
Immune system disorders	Acute graft versus host disease Chronic graft versus host disease	Hypersensitivity		
Endocrine disorders		Hypopituitarism		
Metabolism and nutrition disorders	Anorexia Decreased appetite Hyperglycaemia			
Psychiatric disorders	Confusional state Mental status changes	Anxiety	Delirium Nervousness Hallucination Agitation	
Nervous system disorders	Dizziness Headache Vision blurred Encephalopathy Convulsion Paraesthesia	Intracranial aneurysm Extrapyramidal disorder Cognitive disorder Cerebral haemorrhage		Leukoencephalopathy
Eye disorders	Conjunctivitis	Cataract		
Ear and labyrinth disorders	Hearing impaired Ototoxicity Tinnitus			

Cardiac disorders	Arrhythmia	Tachycardia Cardiac failure	Cardiomyopathy Myocarditis	
Vascular disorders	Lymphoedema Hypertension	Haemorrhage Embolism		
Respiratory, thoracic and mediastinal disorders	Idiopathic pneumonia syndrome Epistaxis	Pulmonary oedema Cough Pneumonitis	Hypoxia	
Gastrointestinal disorders	Nausea Stomatitis Oesophagitis Vomiting Diarrhoea Dyspepsia Abdominal pain Enteritis Colitis	Constipation Gastrointestinal perforation Ileus	Gastrointestinal ulcer	
Hepatobiliary disorders	Venoocclusive liver disease Hepatomegaly Jaundice			
Skin and subcutaneous tissue disorders	Rash Pruritus Alopecia	Erythema	Pigmentation disorder Erythrodermic psoriasis	Severe toxic skin reactions including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Back pain Myalgia Arthralgia			
Renal and urinary disorders	Cystitis haemorrhagic	Dysuria Oliguria Renal failure Cystitis Haematuria		
Reproductive system and breast disorders	Azoospermia Amenorrhoea Vaginal haemorrhage	Menopausal symptoms Infertility female Infertility male		
General disorders and administration site conditions	Pyrexia Asthenia Chills Generalised oedema Injection site inflammation Injection site pain Mucosal inflammation	Multi-organ failure Pain		

Investigation	Weight increased Blood bilirubin increased Transaminases increased Blood amylase increased	Blood creatinine increased Blood urea increased Gamma-glutamyltransferase increased Blood alkaline phosphatase increased Aspartate aminotransferase increased		

Paediatric population

The adverse reactions considered at least possibly related to conditioning treatment including thiotepa, reported in paediatric patients as more than an isolated case, are listed below by system organ class and by frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies 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) very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	**Very common**	**Common**	**Not known**
Infections and infestations	Infection susceptibility increased Sepsis	Thrombocytopenic purpura	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Treatment related second malignancy	
Blood and lymphatic system disorders	Thrombocytopenia Febrile neutropenia Anaemia Pancytopenia Granulocytopenia		
Immune system disorders	Acute graft versus host disease Chronic graft versus host disease		
Endocrine disorders	Hypopituitarism Hypogonadism Hypothyroidism		
Metabolism and nutrition disorders	Anorexia Hyperglycaemia		
Psychiatric disorders	Mental status changes	Mental disorder due to a general medical condition	

Nervous system disorders	Headache Encephalopathy Convulsion Cerebral haemorrhage Memory impairment Paresis	Ataxia	Leukoencephalopathy
Ear and labyrinth disorders	Hearing impaired		
Cardiac disorders	Cardiac arrest	Cardiovascular insufficiency Cardiac failure	
Vascular disorders	Haemorrhage	Hypertension	
Respiratory, thoracic and mediastinal disorders	Pneumonitis	Idiopathic pneumonia syndrome Pulmunary haemorrage Pulmonary oedema Epistaxis Hypoxia Respiratory arrest	Pulmonary arterial hypertension
Gastrointestinal disorders	Nausea Stomatitis Vomiting Diarrhoea Abdominal pain	Enteritis Intestinal obstruction	
Hepatobiliary disorders	Venoocclusive liver disease	Liver failure	
Skin and subcutaneous tissue disorders	Rash Erythema Desquamation Pigmentation disorder		Severe toxic skin reactions including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Growth retardation		
Renal and urinary disorders	Bladder disorders	Renal failure Cystitis haemorrhagic	
General disorders and administration site conditions	Pyrexia Mucosal inflammation Pain Multi-organ failure		

Investigation	Blood bilirubin increased Transaminases increased Blood creatinine increased Aspartate aminotransferase increased Alanine aminotransferase increased	Blood urea increased Blood electrolytes abnormal Prothrombin time ratio increased	

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

4.9 Overdose

There is no experience with overdoses of thiotepa. The most important adverse reactions expected in case of overdose is myeloablation and pancytopenia.
There is no known antidote for thiotepa.
The haematological status needs to be closely monitored and vigorous supportive measures instituted as medically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Alkylating Agents, ATC code: L01AC01

Mechanism of action
Thiotepa is a polyfunctional cytotoxic agent related chemically and pharmacologically to the nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylene imine radicals that, as in the case of irradiation therapy, disrupt the bonds of DNA, e.g. by alkylation of guanine at the N-7, breaking the linkage between the purine base and the sugar and liberating alkylated guanine.

Clinical safety and efficacy
The conditioning treatment must provide cytoreduction and ideally disease eradication. Thiotepa has marrow ablation as its dose-limiting toxicity, allowing significant dose escalation with the infusion of autologous HPCT. In allogeneic HPCT, the conditioning treatment must be sufficiently immunosuppressive and myeloablative to overcome host rejection of the graft. Due to its highly myeloablative characteristics, thiotepa enhances recipient immunosuppression and myeloablation, thus strengthening engraftment; this compensates for the loss of the GvHD-related GvL effects. As alkylating agent, thiotepa produces the most profound inhibition of tumour cell growth *in vitro* with the smallest increase in medicinal product concentration. Due to its lack of extramedullary toxicity despite dose escalation beyond myelotoxic doses, thiotepa has been used for decades in combination with other chemotherapy medicinal products prior to autologous and allogeneic HPCT.
The results of published clinical studies supporting the efficacy of thiotepa are summarised:

Autologous HPCT

Haematological diseases

Engraftment: Conditioning treatments including thiotepa have proved to be myeloablative.

Disease Free Survival (DFS): An estimated 43% at five years has been reported, confirming that conditioning treatments containing thiotepa following autologous HPCT are effective therapeutic strategies for treating patients with haematological diseases.

Relapse: In all conditioning treatments containing thiotepa, relapse rates at more than 1 year have been reported as being 60% or lower, which was considered by the physicians as the threshold to prove efficacy. In some of the conditioning treatments evaluated, relapse rates lower than 60% have also been reported at 5 years.

Overall Survival (OS): OS ranged from 29% to 87% with a follow-up ranging from 22 up to 63 months.

Regimen Related Mortality (RRM) and *Transplant Related Mortality (TRM)*: RRM values ranging from 2.5% to 29% have been reported. TRM values ranged from 0% to 21% at 1 year, confirming the safety of the conditioning treatment including thiotepa for autologous HPCT in adult patients with haematological diseases.

Solid tumours

Engraftment: Conditioning treatments including thiotepa have proved to be myeloablative.

Disease Free Survival (DFS): Percentages reported with follow-up periods of more than 1 year confirm that conditioning treatments containing thiotepa following autologous HPCT are effective choices for treating patients with solid tumours.

Relapse: In all conditioning treatments containing thiotepa, relapse rates at more than 1 year have been reported as being lower than 60%, which was considered by the physicians as the threshold to prove efficacy. In some cases, relapse rates of 35% and of 45% have been reported at 5 years and 6 years respectively.

Overall Survival: OS ranged from 30% to 87% with a follow-up ranging from 11.7 up to 87 months.

Regimen Related Mortality (RRM) and *Transplant Related Mortality (TRM)*: RRM values ranging from 0% to 2% have been reported. TRM values ranged from 0% to 7.4% confirming the safety of the conditioning treatment including thiotepa for autologous HPCT in adult patients with solid tumours.

Allogeneic HPCT

Haematological diseases

Engraftment: Engraftment has been achieved (92%-100%) in all reported conditioning treatments and it was considered to occur at the expected time. Therefore it can be concluded that conditioning treatments including thiotepa are myeloablative.

GvHD (graft versus host disease): all conditioning treatments evaluated assured a low incidence of acute GvHD grade III-IV (from 4% to 24%).

D*isease Free Survival (DFS):* Percentages reported with follow-up periods of more than 1 year and up to 5 years confirm that conditioning treatments containing thiotepa following allogeneic HPCT are effective choices for treating patients with haematological diseases.

Relapse: In all conditioning treatments containing thiotepa, relapse rates at more than 1 year have been reported as being lower than 40% (which was considered by the physicians as the threshold to prove efficacy). In some cases, relapse rates lower than 40% have also been reported at 5 years and 10 years.

Overall Survival: OS ranged from 31% to 81% with a follow-up ranging from 7.3 up to 120 months.

Regimen Related Mortality (RRM) and *Transplant Related Mortality* (*TRM)*: low values have been reported, confirming the safety of the conditioning treatments including thiotepa for allogeneic HPCT in adult patients with haematological diseases.

Paediatric population

Autologous HPCT

Solid tumours

Engraftment: It has been achieved with all reported conditioning regimens including thiotepa.

Disease Free Survival (DFS): With a follow-up of 36 to 57 months, DFS ranged from 46% to 70% in the reported studies. Considering that all patients were treated for high risk solid tumours, DFS results confirm that conditioning treatments containing thiotepa following autologous HPCT are effective therapeutic strategies for treating paediatric patients with solid tumours.

Relapse: In all the reported conditioning regimens containing thiotepa, relapse rates at 12 to 57 months ranged from 33% to 57%. Considering that all patients suffer of recurrence or poor prognosis solid tumours, these rates support the efficacy of conditioning regimens based on thiotepa.
Overall Survival (OS): OS ranged from 17% to 84% with a follow-up ranging from 12.3 up to 99.6 months.
Regimen Related Mortality (RRM) and *Transplant Related Mortality (TRM)*: RRM values ranging from 0% to 26.7% have been reported. TRM values ranged from 0% to 18% confirming the safety of the conditioning treatments including thiotepa for autologous HPCT in paediatric patients with solid tumours.

Allogeneic HPCT
Haematological diseases
Engraftment: It has been achieved with all evaluated conditioning regimens including thiotepa with a success rate of 96% - 100%. The haematological recovery is in the expected time.
Disease Free Survival (DFS): Percentages of 40% - 75% with follow-up of more than 1 year have been reported. DFS results confirm that conditioning treatment containing thiotepa following allogeneic HPCT are effective therapeutic strategies for treating paediatric patients with haematological diseases.
Relapse: In all the reported conditioning regimens containing thiotepa, the relapse rate was in the range of 15% - 44%. These data support the efficacy of conditioning regimens based on thiotepa in all haematological diseases.
Overall Survival (OS): OS ranged from 50% to 100% with a follow-up ranging from 9.4 up to 121 months.
Regimen Related Mortality (RRM) and *Transplant Related Mortality (TRM)*: RRM values ranging from 0% to 2.5% have been reported. TRM values ranged from 0% to 30% confirming the safety of the conditioning treatment including thiotepa for allogeneic HPCT in paediatric patients with haematological diseases.

5.2 Pharmacokinetic properties

Absorption
Thiotepa is unreliably absorbed from the gastrointestinal tract: acid instability prevents thiotepa from being administered orally.

Distribution
Thiotepa is a highly lipophilic compound. After intravenous administration, plasma concentrations of the active substance fit a two compartment model with a rapid distribution phase. The volume of distribution of thiotepa is large and it has been reported as ranging from 40.8 l/m^2 to 75 l/m^2, indicating distribution to total body water. The apparent volume of distribution of thiotepa appears independent of the administered dose. The fraction unbound to proteins in plasma is 70-90%; insignificant binding of thiotepa to gamma globulin and minimal albumin binding (10-30%) has been reported.
After intravenous administration, CSF medicinal product exposure is nearly equivalent to that achieved in plasma; the mean ratio of AUC in CSF to plasma for thiotepa is 0.93. CSF and plasma concentrations of TEPA, the first reported active metabolite of thiotepa, exceed the concentrations of the parent compound.

Biotransformation
Thiotepa undergoes rapid and extensive hepatic metabolism and metabolites could be detected in urine within 1 hour after infusion. The metabolites are active alkylating agents but the role they play in the antitumor activity of thiotepa remains to be elucidated. Thiotepa undergoes oxidative desulphuration via the cytochrome P450 CYP2B and CYP3A isoenzyme families to the major and active metabolite TEPA (triethylenephosphoramide). The total excreted amount of thiotepa and its identified metabolites accounts for 54-100% of the total alkylating activity, indicating the presence of other alkylating metabolites. During conversion of GSH conjugates to N-acetylcysteine conjugates, GSH, cysteinylglycine, and cysteine conjugates are formed. These metabolites are not found in urine, and, if formed, are probably excreted in bile or as intermediate metabolites rapidly converted into thiotepa-mercapturate.

Elimination
The total clearance of thiotepa ranged from 11.4 to 23.2 l/h/m^2. The elimination half-life varied from 1.5 to 4.1 hours. The identified metabolites TEPA, monochlorotepa and thiotepa-mercapturate are all excreted in the urine. Urinary excretion of thiotepa and TEPA is nearly complete after 6 and 8 hours respectively. The mean urinary recovery of thiotepa and its metabolites is 0.5% for the unchanged medicinal product and monochlorotepa, and 11% for TEPA and thiotepa-mercapturate.

Linearity/non-linearity
There is no clear evidence of saturation of metabolic clearance mechanisms at high doses of thiotepa.

Special populations

Paediatric population
The pharmacokinetics of high dose thiotepa in children between 2 and 12 years of age do not appear to vary from those reported in children receiving 75 mg/m^2 or adults receiving similar doses.

Renal impairment
The effects of renal impairment on thiotepa elimination have not been assessed.

Hepatic impairment
The effects of hepatic impairment on thiotepa metabolism and elimination have not been assessed.

5.3 Preclinical safety data

No conventional acute and repeat dose toxicity studies were performed.
Thiotepa was shown to be genotoxic *in vitro* and *in vivo*, and carcinogenic in mice and rats.
Thiotepa was shown to impair fertility and interfere with spermatogenesis in male mice, and to impair ovarian function in female mice. It was teratogenic in mice and in rats, and foeto-lethal in rabbits. These effects were seen at doses lower than those used in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

TEPADINA is unstable in acid medium.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
18 months.

After reconstitution
Chemical and physical in-use stability after reconstitution has been demonstrated for 8 hours when stored at 2°C-8°C.

After dilution
Chemical and physical in-use stability after dilution has been demonstrated for 24 hours when stored at 2°C-8°C and for 4 hours when stored at 25°C.

From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than the above mentioned conditions when dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened vial
Store and transport refrigerated (2°C – 8°C).
Do not freeze.

After reconstitution and dilution
For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I clear glass vial with a bromobutyl stopper, containing 15 mg thiotepa.
Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Preparation of TEPADINA
Procedures for proper handling and disposal of anticancer medicinal products must be considered. All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood.
As with other cytotoxic compounds, caution needs to be exercised in handling and preparation of TEPADINA solutions to avoid accidental contact with skin or mucous membranes. Topical reactions associated with accidental exposure to thiotepa may occur. In fact, the use of gloves is recommended in preparing the solution for infusion. If thiotepa solution accidentally contacts the skin, the skin must be immediately and thoroughly washed with soap and water. If thiotepa accidentally contacts mucous membranes, they must be flushed thoroughly with water.

Reconstitution
TEPADINA must be reconstituted with 1.5 ml of sterile water for injection.
Using a syringe fitted with a needle, aseptically withdraw 1.5 ml of sterile water for injection.
Inject the content of the syringe into the vial through the rubber stopper.
Remove the syringe and the needle and mix manually by repeated inversions.
Only colourless solutions, without any particulate matter, must be used. Reconstituted solutions may occasionally show opalescence; such solutions can still be administered.

Further dilution in the infusion bag
The reconstituted solution is hypotonic and must be further diluted prior to administration with 500 ml sodium chloride 9 mg/ml (0.9%) solution for injection (1000 ml if the dose is higher than 500 mg) or with an appropriate volume of sodium chloride 9 mg/ml (0.9%) in order to obtain a final TEPADINA concentration between 0.5 and 1 mg/ml.

Administration
TEPADINA infusion solution should be inspected visually for particulate matter prior to administration. Solutions containing a precipitate should be discarded.
Prior to and following each infusion, the indwelling catheter line should be flushed with approximately 5 ml sodium chloride 9 mg/ml (0.9%) solution for injection.
The infusion solution must be administered to patients using an infusion set equipped with a 0.2 µm in-line filter. Filtering does not alter solution potency.

Disposal
TEPADINA is for single use only.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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adienne@adienne.com

8. MARKETING AUTHORISATION NUMBER

EU/1/10/622/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 100 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 100 mg thiotepa.
After reconstitution with 10 ml of water for injections, each ml of solution contains 10 mg thiotepa (10 mg/ml).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
White crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TEPADINA is indicated, in combination with other chemotherapy medicinal products:
- with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients;
- when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.

4.2 Posology and method of administration

TEPADINA administration must be supervised by a physician experienced in conditioning treatment prior to haematopoietic progenitor cell transplantation.

Posology

TEPADINA is administered at different doses, in combination with other chemotherapeutic medicinal products, in patients with haematological diseases or solid tumours prior to HPCT.

TEPADINA posology is reported, in adult and paediatric patients, according to the type of HPCT (autologous or allogeneic) and disease.

Adults

AUTOLOGOUS HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 300 mg/m^2/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m^2 (24.32 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA
The recommended dose ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 300 mg/m^2/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m^2 (24.32 mg/kg), during the time of the entire conditioning treatment.
CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA
The recommended dose is 185 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 2 consecutive days before autologous HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
MULTIPLE MYELOMA
The recommended dose ranges from 150 mg/m^2/day (4.05 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.

Solid tumours

The recommended dose in solid tumours ranges from 120 mg/m^2/day (3.24 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) divided in one or two daily infusions, administered from 2 up to 5 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 800 mg/m^2 (21.62 mg/kg), during the time of the entire conditioning treatment.
BREAST CANCER
The recommended dose ranges from 120 mg/m^2/day (3.24 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered from 3 up to 5 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 800 mg/m^2 (21.62 mg/kg), during the time of the entire conditioning treatment.
CNS TUMOURS
The recommended dose ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) divided in one or two daily infusions, administered from 3 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.
OVARIAN CANCER
The recommended dose is 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered in 2 consecutive days before autologous HPCT, without exceeding the total maximum cumulative dose of 500 mg/m^2 (13.51 mg/kg), during the time of the entire conditioning treatment.
GERM CELL TUMOURS
The recommended dose ranges from 150 mg/m^2/day (4.05 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.

ALLOGENEIC HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 185 mg/m^2/day (5 mg/kg/day) to 481 mg/m^2/day (13 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 3 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 555 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA
The recommended dose in lymphoma is 370 mg/m^2/day (10 mg/kg/day) divided in two daily infusions before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
MULTIPLE MYELOMA
The recommended dose is 185 mg/m^2/day (5 mg/kg/day) as a single daily infusion before allogeneic HPCT, without exceeding the total maximum cumulative dose of 185 mg/m^2 (5 mg/kg), during the time of the entire conditioning treatment.
LEUKAEMIA
The recommended dose ranges from 185 mg/m^2/day (5 mg/kg/day) to 481 mg/m^2/day (13 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 2 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 555 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
THALASSEMIA
The recommended dose is 370 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

Paediatric population

AUTOLOGOUS HPCT

Solid tumours

The recommended dose in solid tumours ranges from 150 mg/m^2/day (6 mg/kg/day) to 350 mg/m^2/day (14 mg/kg/day) as a single daily infusion, administered from 2 up to 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 1050 mg/m^2 (42 mg/kg), during the time of the entire conditioning treatment.
CNS TUMOURS
The recommended dose ranges from 250 mg/m^2/day (10 mg/kg/day) to 350 mg/m^2/day (14 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 1050 mg/m^2 (42 mg/kg), during the time of the entire conditioning treatment.

ALLOGENEIC HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m^2/day (5 mg/kg/day) to 250 mg/m^2/day (10 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 3 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 375 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
LEUKAEMIA
The recommended dose is 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
THALASSEMIA
The recommended dose ranges from 200 mg/m^2/day (8 mg/kg/day) to 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

REFRACTORY CYTOPENIA
The recommended dose is 125 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before allogeneic HPCT, without exceeding the total maximum cumulative dose of 375 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
GENETIC DISEASES
The recommended dose is 125 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 2 consecutive days before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
SICKLE CELL ANAEMIA
The recommended dose is 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

Special populations

Renal impairment
Studies in renally impaired patients have not been conducted. As thiotepa and its metabolites are poorly excreted in the urine, dose modification is not recommended in patients with mild or moderate renal insufficiency. However, caution is recommended (see sections 4.4 and 5.2).

Hepatic impairment
Thiotepa has not been studied in patients with hepatic impairment. Since thiotepa is mainly metabolized through the liver, caution needs to be exercised when thiotepa is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. Dose modification is not recommended for transient alterations of hepatic parameters (see section 4.4).

Elderly
The administration of thiotepa has not been specifically investigated in elderly patients. However, in clinical studies, a proportion of patients over the age of 65 received the same cumulative dose as the other patients. No dose adjustment was deemed necessary.

Method of administration
TEPADINA must be administered by a qualified healthcare professional as a 2-4 hours intravenous infusion via a central venous catheter.
Each TEPADINA vial must be reconstituted with 10 ml of sterile water for injection. The total volume of reconstituted vials to be administered should be further diluted in 500 ml of sodium chloride 9 mg/ml (0.9%) solution for injection prior to administration (1000 ml if the dose is higher than 500 mg). In children, if the dose is lower than 250 mg, an appropriate volume of sodium chloride 9 mg/ml (0.9%) solution for injection may be used in order to obtain a final TEPADINA concentration between 0.5 and 1 mg/ml. For instructions on reconstitution and further dilution prior to administration, see section 6.6.

Precautions to be taken before handling or administering the medicinal product
Topical reactions associated with accidental exposure to thiotepa may occur. Therefore, the use of gloves is recommended in preparing the solution for infusion. If thiotepa solution accidentally contacts the skin, the skin must be immediately thoroughly washed with soap and water. If thiotepa accidentally contacts mucous membranes, they must be flushed thoroughly with water (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance.
Pregnancy and lactation (see section 4.6).
Concomitant use with yellow fever vaccine and with live virus and bacterial vaccines (see section 4.5).

4.4 Special warnings and precautions for use

The consequence of treatment with thiotepa at the recommended dose and schedule is profound myelosuppression, occurring in all patients. Severe granulocytopenia, thrombocytopenia, anaemia or any combination thereof may develop. Frequent complete blood counts, including differential white blood cell counts, and platelet counts need to be performed during the treatment and until recovery is achieved. Platelet and red blood cell support, as well as the use of growth factors such as Granulocyte-colony stimulating factor (G-CSF), should be employed as medically indicated. Daily white blood cell counts and platelet counts are recommended during therapy with thiotepa and after transplant for at least 30 days.

Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) should be considered for the prevention and management of infections during the neutropenic period.

Thiotepa has not been studied in patients with hepatic impairment. Since thiotepa is mainly metabolized through the liver, caution needs to be observed when thiotepa is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. When treating such patients it is recommended that serum transaminase, alkaline phosphatase and bilirubin are monitored regularly following transplant, for early detection of hepatotoxicity.

Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or prior progenitor cell transplant may be at an increased risk of hepatic veno-occlusive disease (see section 4.8).

Caution must be used in patients with history of cardiac diseases, and cardiac function must be monitored regularly in patients receiving thiotepa.

Caution must be used in patients with history of renal diseases and periodic monitoring of renal function should be considered during therapy with thiotepa.

Thiotepa might induce pulmonary toxicity that may be additive to the effects produced by other cytotoxic agents (busulfan, fludarabine and cyclophosphamide) (see section 4.8).

Previous brain irradiation or craniospinal irradiation may contribute to severe toxic reactions (e.g. encephalopathy).

The increased risk of a secondary malignancy with thiotepa, a known carcinogen in humans, must be explained to the patient.

Concomitant use with live attenuated vaccines (except yellow fever vaccines), phenytoin and fosphenytoin is not recommended (see section 4.5).

Thiotepa must not be concurrently administered with cyclophosphamide when both medicinal products are present in the same conditioning treatment. TEPADINA must be delivered after the completion of any cyclophosphamide infusion (see section 4.5).

During the concomitant use of thiotepa and inhibitors of CYP2B6 or CYP3A4, patients should be carefully monitored clinically (see section 4.5).

As most alkylating agents, thiotepa might impair male or female fertility. Male patients should seek for sperm cryopreservation before therapy is started and should not father a child while treated and during the year after cessation of treatment (see section 4.6).

4.5 Interactions with other medicinal products and other forms of interaction

Specific interactions with thiotepa
Live virus and bacterial vaccines must not be administered to a patient receiving an immunosuppressive chemotherapeutic agent and at least three months must elapse between discontinuation of therapy and vaccination.

Thiotepa appears to be metabolised via CYP2B6 and CYP3A4. Co-administration with inhibitors of CYP2B6 (for example clopidogrel and ticlopidine) or CYP3A4 (for example azole antifungals, macrolides like erythromycin, clarithromycin, telithromycin, and protease inhibitors) may increase the plasma concentrations of thiotepa and potentially decrease the concentrations of the active metabolite TEPA. Co-administration of inducers of cytochrome P450 (such as rifampicin, carbamazepine, phenobarbital) may increase the metabolism of thiotepa leading to increased plasma concentrations of the active metabolite. Therefore, during the concomitant use of thiotepa and these medicinal products, patients should be carefully monitored clinically.

Thiotepa is a weak inhibitor for CYP2B6, and may thereby potentially increase plasma concentrations of substances metabolised via CYP2B6, such as ifosfamide, tamoxifen, bupropion, efavirenz and cyclophosphamide. CYP2B6 catalyzes the metabolic conversion of cyclophosphamide to its active form 4-hydroxycyclophosphamide (4-OHCP) and co-administration of thiotepa may therefore lead to decreased concentrations of the active 4-OHCP. Therefore, a clinical monitoring should be exercised during the concomitant use of thiotepa and these medicinal products.

Contraindications of concomitant use
Yellow fever vaccine: risk of fatal generalized vaccine-induced disease.

More generally, live virus and bacterial vaccines must not be administered to a patient receiving an immunosuppressive chemotherapeutic agent and at least three months must elapse between discontinuation of therapy and vaccination.

Concomitant use not recommended
Live attenuated vaccines (except yellow fever): risk of systemic, possibly fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

An inactivated virus vaccine should be used instead, whenever possible (poliomyelitis).

Phenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicinal product or risk of toxicity enhancement and loss of efficacy of the cytotoxic medicinal product due to increased hepatic metabolism by phenytoin.

Concomitant use to take into consideration
Ciclosporine, tacrolimus: excessive immunosuppression with risk of lymphoproliferation.

Alkylating chemotherapeutic agents, including thiotepa, inhibit plasma pseudocholinesterase by 35% to 70%. The action of succinyl-choline can be prolonged by 5 to 15 minutes.

Thiotepa must not be concurrently administered with cyclophosphamide when both medicinal products are present in the same conditioning treatment. TEPADINA must be delivered after the completion of any cyclophosphamide infusion.

The concomitant use of thiotepa and other myelosuppressive or myelotoxic agents (i.e. cyclophosphamide, melphalan, busulfan, fludarabine, treosulfan) may potentiate the risk of haematologic adverse reactions due to overlapping toxicity profiles of these medicinal products.

Interaction common to all cytotoxics
Due to the increase of thrombotic risk in case of malignancy, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulation state during malignancy, and the potential interaction between oral anticoagulants and anticancer chemotherapy require, if it is decided to treat the patient with oral anticoagulants, to increase the frequency of the INR (International Normalised Ratio) monitoring.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential have to use effective contraception during treatment and a pregnancy test should be performed before treatment is started.

Pregnancy
There are no data on the use of thiotepa during pregnancy. In pre-clinical studies thiotepa, as most alkylating agents, has been shown to cause embryofoetal lethality and teratogenicity (see section 5.3). Therefore, thiotepa is contraindicated during pregnancy.

Breast-feeding
It is unknown whether thiotepa is excreted in human milk. Due to its pharmacological properties and its potential toxicity for breast-fed newborns/ infants, breast-feeding is contraindicated during treatment with thiotepa.

Fertility
As most alkylating agents, thiotepa might impair male and female fertility.
Male patients should seek for sperm cryopreservation before therapy is started and should not father a child while treated and during the year after cessation of treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

TEPADINA may have major influence on the ability to drive and use machines. It is likely that certain adverse reactions of thiotepa like dizziness, headache and blurred vision could affect these functions.

4.8 Undesirable effects

Summary of the safety profile

The safety of thiotepa has been examined through a review of adverse events reported in published data from clinical trials. In these studies, a total of 6,588 adult patients and 902 paediatric patients received thiotepa for conditioning treatment prior to haematopoietic progenitor cell transplantation.

Serious toxicities involving the haematologic, hepatic and respiratory systems were considered as expected consequences of the conditioning regimen and transplant process. These include infection and Graft-versus host disease (GvHD) which, although not directly related, were the major causes of morbidity and mortality, especially in allogeneic HPCT.
The most frequently adverse reactions reported in the different conditioning treatments including thiotepa are: infections, cytopenia, acute GvHD and chronic GvHD, gastrointestinal disorders, haemorrhagic cystitis, mucosal inflammation.

Leukoencephalopathy
Cases of leukoencephalopathy have been observed following treatment with thiotepa in adult and paediatric patients with multiple previous chemotherapies, including methotrexate and radiotherapy. Some cases had a fatal outcome.

Tabulated list of adverse reactions

Adults

The adverse reactions considered at least possibly related to conditioning treatment including thiotepa, reported in adult patients as more than an isolated case, are listed below by system organ class and by frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies 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) very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	**Very common**	**Common**	**Uncommon**	**Not known**
Infections and infestations	Infection susceptibility increased Sepsis		Toxic shock syndrome	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Treatment related second malignancy		
Blood and lymphatic system disorders	Leukopenia Thrombocytopenia Febrile neutropenia Anaemia Pancytopenia Granulocytopenia			
Immune system disorders	Acute graft versus host disease Chronic graft versus host disease	Hypersensitivity		
Endocrine disorders		Hypopituitarism		
Metabolism and nutrition disorders	Anorexia Decreased appetite Hyperglycaemia			
Psychiatric disorders	Confusional state Mental status changes	Anxiety	Delirium Nervousness Hallucination Agitation	
Nervous system disorders	Dizziness Headache Vision blurred Encephalopathy Convulsion Paraesthesia	Intracranial aneurysm Extrapyramidal disorder Cognitive disorder Cerebral haemorrhage		Leukoencephalopathy
Eye disorders	Conjunctivitis	Cataract		
Ear and labyrinth disorders	Hearing impaired Ototoxicity Tinnitus			

Cardiac disorders	Arrhythmia	Tachycardia Cardiac failure	Cardiomyopathy Myocarditis	
Vascular disorders	Lymphoedema Hypertension	Haemorrhage Embolism		
Respiratory, thoracic and mediastinal disorders	Idiopathic pneumonia syndrome Epistaxis	Pulmonary oedema Cough Pneumonitis	Hypoxia	
Gastrointestinal disorders	Nausea Stomatitis Oesophagitis Vomiting Diarrhoea Dyspepsia Abdominal pain Enteritis Colitis	Constipation Gastrointestinal perforation Ileus	Gastrointestinal ulcer	
Hepatobiliary disorders	Venoocclusive liver disease Hepatomegaly Jaundice			
Skin and subcutaneous tissue disorders	Rash Pruritus Alopecia	Erythema	Pigmentation disorder Erythrodermic psoriasis	Severe toxic skin reactions including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Back pain Myalgia Arthralgia			
Renal and urinary disorders	Cystitis haemorrhagic	Dysuria Oliguria Renal failure Cystitis Haematuria		
Reproductive system and breast disorders	Azoospermia Amenorrhoea Vaginal haemorrhage	Menopausal symptoms Infertility female Infertility male		
General disorders and administration site conditions	Pyrexia Asthenia Chills Generalised oedema Injection site inflammation Injection site pain Mucosal inflammation	Multi-organ failure Pain		

Investigation	Weight increased Blood bilirubin increased Transaminases increased Blood amylase increased	Blood creatinine increased Blood urea increased Gamma-glutamyltransferase increased Blood alkaline phosphatase increased Aspartate aminotransferase increased		

Paediatric population

The adverse reactions considered at least possibly related to conditioning treatment including thiotepa, reported in paediatric patients as more than an isolated case, are listed below by system organ class and by frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies 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) very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	**Very common**	**Common**	**Not known**
Infections and infestations	Infection susceptibility increased Sepsis	Thrombocytopenic purpura	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Treatment related second malignancy	
Blood and lymphatic system disorders	Thrombocytopenia Febrile neutropenia Anaemia Pancytopenia Granulocytopenia		
Immune system disorders	Acute graft versus host disease Chronic graft versus host disease		
Endocrine disorders	Hypopituitarism Hypogonadism Hypothyroidism		
Metabolism and nutrition disorders	Anorexia Hyperglycaemia		
Psychiatric disorders	Mental status changes	Mental disorder due to a general medical condition	

Nervous system disorders	Headache Encephalopathy Convulsion Cerebral haemorrhage Memory impairment Paresis	Ataxia	Leukoencephalopathy
Ear and labyrinth disorders	Hearing impaired		
Cardiac disorders	Cardiac arrest	Cardiovascular insufficiency Cardiac failure	
Vascular disorders	Haemorrhage	Hypertension	
Respiratory, thoracic and mediastinal disorders	Pneumonitis	Idiopathic pneumonia syndrome Pulmunary haemorrage Pulmonary oedema Epistaxis Hypoxia Respiratory arrest	Pulmonary arterial hypertension
Gastrointestinal disorders	Nausea Stomatitis Vomiting Diarrhoea Abdominal pain	Enteritis Intestinal obstruction	
Hepatobiliary disorders	Venoocclusive liver disease	Liver failure	
Skin and subcutaneous tissue disorders	Rash Erythema Desquamation Pigmentation disorder		Severe toxic skin reactions including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Growth retardation		
Renal and urinary disorders	Bladder disorders	Renal failure Cystitis haemorrhagic	
General disorders and administration site conditions	Pyrexia Mucosal inflammation Pain Multi-organ failure		

Investigation	Blood bilirubin increased Transaminases increased Blood creatinine increased Aspartate aminotransferase increased Alanine aminotransferase increased	Blood urea increased Blood electrolytes abnormal Prothrombin time ratio increased	

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

4.9 Overdose

There is no experience with overdoses of thiotepa. The most important adverse reactions expected in case of overdose is myeloablation and pancytopenia.
There is no known antidote for thiotepa.

The haematological status needs to be closely monitored and vigorous supportive measures instituted as medically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Alkylating Agents, ATC code: L01AC01

Mechanism of action
Thiotepa is a polyfunctional cytotoxic agent related chemically and pharmacologically to the nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylene imine radicals that, as in the case of irradiation therapy, disrupt the bonds of DNA, e.g. by alkylation of guanine at the N-7, breaking the linkage between the purine base and the sugar and liberating alkylated guanine.

Clinical safety and efficacy
The conditioning treatment must provide cytoreduction and ideally disease eradication. Thiotepa has marrow ablation as its dose-limiting toxicity, allowing significant dose escalation with the infusion of autologous HPCT. In allogeneic HPCT, the conditioning treatment must be sufficiently immunosuppressive and myeloablative to overcome host rejection of the graft. Due to its highly myeloablative characteristics, thiotepa enhances recipient immunosuppression and myeloablation, thus strengthening engraftment; this compensates for the loss of the GvHD-related GvL effects. As alkylating agent, thiotepa produces the most profound inhibition of tumour cell growth *in vitro* with the smallest increase in medicinal product concentration. Due to its lack of extramedullary toxicity despite dose escalation beyond myelotoxic doses, thiotepa has been used for decades in combination with other chemotherapy medicinal products prior to autologous and allogeneic HPCT.
The results of published clinical studies supporting the efficacy of thiotepa are summarised:

Autologous HPCT

Haematological diseases

Engraftment: Conditioning treatments including thiotepa have proved to be myeloablative.

Disease Free Survival (DFS): An estimated 43% at five years has been reported, confirming that conditioning treatments containing thiotepa following autologous HPCT are effective therapeutic strategies for treating patients with haematological diseases.

Relapse: In all conditioning treatments containing thiotepa, relapse rates at more than 1 year have been reported as being 60% or lower, which was considered by the physicians as the threshold to prove efficacy. In some of the conditioning treatments evaluated, relapse rates lower than 60% have also been reported at 5 years.

Overall Survival (OS): OS ranged from 29% to 87% with a follow-up ranging from 22 up to 63 months.

Regimen Related Mortality (RRM) and *Transplant Related Mortality TRM* : RRM values ranging from 2.5% to 29% have been reported. TRM values ranged from 0% to 21% at 1 year, confirming the safety of the conditioning treatment including thiotepa for autologous HPCT in adult patients with haematological diseases.

Solid tumours

Engraftment: Conditioning treatments including thiotepa have proved to be myeloablative.

Disease Free Survival (DFS): Percentages reported with follow-up periods of more than 1 year confirm that conditioning treatments containing thiotepa following autologous HPCT are effective choices for treating patients with solid tumours.

Relapse: In all conditioning treatments containing thiotepa, relapse rates at more than 1 year have been reported as being lower than 60%, which was considered by the physicians as the threshold to prove efficacy. In some cases, relapse rates of 35% and of 45% have been reported at 5 years and 6 years respectively.

Overall Survival: OS ranged from 30% to 87% with a follow-up ranging from 11.7 up to 87 months.

Regimen Related Mortality (RRM) and *Transplant Related Mortality (TRM)*: RRM values ranging from 0% to 2% have been reported. TRM values ranged from 0% to 7.4% confirming the safety of the conditioning treatment including thiotepa for autologous HPCT in adult patients with solid tumours.

Allogeneic HPCT

Haematological diseases

Engraftment: Engraftment has been achieved (92%-100%) in all reported conditioning treatments and it was considered to occur at the expected time. Therefore it can be concluded that conditioning treatments including thiotepa are myeloablative.

GvHD (graft versus host disease): all conditioning treatments evaluated assured a low incidence of acute GvHD grade III-IV (from 4% to 24%).

D*isease Free Survival (DFS):* Percentages reported with follow-up periods of more than 1 year and up to 5 years confirm that conditioning treatments containing thiotepa following allogeneic HPCT are effective choices for treating patients with haematological diseases.

Relapse: In all conditioning treatments containing thiotepa, relapse rates at more than 1 year have been reported as being lower than 40% (which was considered by the physicians as the threshold to prove efficacy). In some cases, relapse rates lower than 40% have also been reported at 5 years and 10 years.

Overall Survival: OS ranged from 31% to 81% with a follow-up ranging from 7.3 up to 120 months.

Regimen Related Mortality (RRM) and *Transplant Related Mortality* (*TRM)*: low values have been reported, confirming the safety of the conditioning treatments including thiotepa for allogeneic HPCT in adult patients with haematological diseases.

Paediatric population

Autologous HPCT

Solid tumours

Engraftment: It has been achieved with all reported conditioning regimens including thiotepa.

Disease Free Survival (DFS): With a follow-up of 36 to 57 months, DFS ranged from 46% to 70% in the reported studies. Considering that all patients were treated for high risk solid tumours, DFS results confirm that conditioning treatments containing thiotepa following autologous HPCT are effective therapeutic strategies for treating paediatric patients with solid tumours.

Relapse: In all the reported conditioning regimens containing thiotepa, relapse rates at 12 to 57 months ranged from 33% to 57%. Considering that all patients suffer of recurrence or poor prognosis solid tumours, these rates support the efficacy of conditioning regimens based on thiotepa.
Overall Survival (OS): OS ranged from 17% to 84% with a follow-up ranging from 12.3 up to 99.6 months.
Regimen Related Mortality (RRM) and *Transplant Related Mortality (TRM)*: RRM values ranging from 0% to 26.7% have been reported. TRM values ranged from 0% to 18% confirming the safety of the conditioning treatments including thiotepa for autologous HPCT in paediatric patients with solid tumours.

Allogeneic HPCT
Haematological diseases
Engraftment: It has been achieved with all evaluated conditioning regimens including thiotepa with a success rate of 96% - 100%. The haematological recovery is in the expected time.
Disease Free Survival (DFS): Percentages of 40% - 75% with follow-up of more than 1 year have been reported. DFS results confirm that conditioning treatment containing thiotepa following allogeneic HPCT are effective therapeutic strategies for treating paediatric patients with haematological diseases.
Relapse: In all the reported conditioning regimens containing thiotepa, the relapse rate was in the range of 15% - 44%. These data support the efficacy of conditioning regimens based on thiotepa in all haematological diseases.
Overall Survival (OS): OS ranged from 50% to 100% with a follow-up ranging from 9.4 up to 121 months.
Regimen Related Mortality (RRM) and *Transplant Related Mortality (TRM)*: RRM values ranging from 0% to 2.5% have been reported. TRM values ranged from 0% to 30% confirming the safety of the conditioning treatment including thiotepa for allogeneic HPCT in paediatric patients with haematological diseases.

5.2 Pharmacokinetic properties

Absorption
Thiotepa is unreliably absorbed from the gastrointestinal tract: acid instability prevents thiotepa from being administered orally.

Distribution
Thiotepa is a highly lipophilic compound. After intravenous administration, plasma concentrations of the active substance fit a two compartment model with a rapid distribution phase. The volume of distribution of thiotepa is large and it has been reported as ranging from 40.8 l/m^2 to 75 l/m^2, indicating distribution to total body water. The apparent volume of distribution of thiotepa appears independent of the administered dose. The fraction unbound to proteins in plasma is 70-90%; insignificant binding of thiotepa to gamma globulin and minimal albumin binding (10-30%) has been reported.
After intravenous administration, CSF medicinal product exposure is nearly equivalent to that achieved in plasma; the mean ratio of AUC in CSF to plasma for thiotepa is 0.93. CSF and plasma concentrations of TEPA, the first reported active metabolite of thiotepa, exceed the concentrations of the parent compound.

Biotransformation
Thiotepa undergoes rapid and extensive hepatic metabolism and metabolites could be detected in urine within 1 hour after infusion. The metabolites are active alkylating agents but the role they play in the antitumor activity of thiotepa remains to be elucidated. Thiotepa undergoes oxidative desulphuration via the cytochrome P450 CYP2B and CYP3A isoenzyme families to the major and active metabolite TEPA (triethylenephosphoramide). The total excreted amount of thiotepa and its identified metabolites accounts for 54-100% of the total alkylating activity, indicating the presence of other alkylating metabolites. During conversion of GSH conjugates to N-acetylcysteine conjugates, GSH, cysteinylglycine, and cysteine conjugates are formed. These metabolites are not found in urine, and, if formed, are probably excreted in bile or as intermediate metabolites rapidly converted into thiotepa-mercapturate.

Elimination
The total clearance of thiotepa ranged from 11.4 to 23.2 l/h/m^2. The elimination half-life varied from 1.5 to 4.1 hours. The identified metabolites TEPA, monochlorotepa and thiotepa-mercapturate are all excreted in the urine. Urinary excretion of thiotepa and TEPA is nearly complete after 6 and 8 hours respectively. The mean urinary recovery of thiotepa and its metabolites is 0.5% for the unchanged medicinal product and monochlorotepa, and 11% for TEPA and thiotepa-mercapturate.

Linearity /non linearity
There is no clear evidence of saturation of metabolic clearance mechanisms at high doses of thiotepa.

Special populations

Paediatric population
The pharmacokinetics of high dose thiotepa in children between 2 and 12 years of age do not appear to vary from those reported in children receiving 75 mg/m^2 or adults receiving similar doses.

Renal impairment
The effects of renal impairment on thiotepa elimination have not been assessed.

Hepatic impairment
The effects of hepatic impairment on thiotepa metabolism and elimination have not been assessed.

5.3 Preclinical safety data

No conventional acute and repeat dose toxicity studies were performed.
Thiotepa was shown to be genotoxic *in vitro* and *in vivo*, and carcinogenic in mice and rats.
Thiotepa was shown to impair fertility and interfere with spermatogenesis in male mice, and to impair ovarian function in female mice. It was teratogenic in mice and in rats, and foeto-lethal in rabbits.
These effects were seen at doses lower than those used in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

TEPADINA is unstable in acid medium.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
18 months.

After reconstitution
Chemical and physical in-use stability after reconstitution has been demonstrated for 8 hours when stored at 2°C-8°C.

After dilution
Chemical and physical in-use stability after dilution has been demonstrated for 24 hours when stored at 2°C -8°C and for 4 hours when stored at 25°C.

From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than the above mentioned conditions when dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened vial
Store and transport refrigerated (2°C – 8°C).
Do not freeze.

After reconstitution and dilution
For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I clear glass vial with a bromobutyl stopper, containing 100 mg thiotepa.
Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Preparation of TEPADINA
Procedures for proper handling and disposal of anticancer medicinal products must be considered. All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood.
As with other cytotoxic compounds, caution needs to be exercised in handling and preparation of TEPADINA solutions to avoid accidental contact with skin or mucous membranes. Topical reactions associated with accidental exposure to thiotepa may occur. In fact, the use of gloves is recommended in preparing the solution for infusion. If thiotepa solution accidentally contacts the skin, the skin must be immediately and thoroughly washed with soap and water. If thiotepa accidentally contacts mucous membranes, they must be flushed thoroughly with water.

Reconstitution
TEPADINA must be reconstituted with 10 ml of sterile water for injection.
Using a syringe fitted with a needle, aseptically withdraw 10 ml of sterile water for injection.
Inject the content of the syringe into the vial through the rubber stopper.
Remove the syringe and the needle and mix manually by repeated inversions.
Only colourless solutions, without any particulate matter, must be used. Reconstituted solutions may occasionally show opalescence; such solutions can still be administered.

Further dilution in the infusion bag
The reconstituted solution is hypotonic and must be further diluted prior to administration with 500 ml sodium chloride 9 mg/ml (0.9%) solution for injection (1000 ml if the dose is higher than 500 mg) or with an appropriate volume of sodium chloride 9 mg/ml (0.9%) in order to obtain a final TEPADINA concentration between 0.5 and 1 mg/ml.

Administration
TEPADINA infusion solution should be inspected visually for particulate matter prior to administration. Solutions containing a precipitate should be discarded.
Prior to and following each infusion, the indwelling catheter line should be flushed with approximately 5 ml sodium chloride 9 mg/ml (0.9%) solution for injection.
The infusion solution must be administered to patients using an infusion set equipped with a 0.2 μm in-line filter. Filtering does not alter solution potency.

Disposal
TEPADINA is for single use only.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

EU/1/10/622/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

RIEMSER Pharma GmbH
Bahnhofstraße 44b
D-17489 Greifswald
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 15 mg powder for concentrate for solution for infusion
Thiotepa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 15 mg thiotepa. After reconstitution with 1.5 ml of water for injection, each ml contains 10 mg thiotepa.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use, after reconstitution and dilution.

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
After reconstitution, use within 8 hours when stored in a refrigerator.
After dilution, use within 24 hours when stored in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated (2°C-8°C). Do not freeze.

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/622/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TEPADINA 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL

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

TEPADINA 15 mg powder for concentrate for solution for infusion
Thiotepa
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

15 mg

6. OTHER

ADIENNE S.r.l. S.U.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 100 mg powder for concentrate for solution for infusion
Thiotepa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 100 mg thiotepa. After reconstitution with 10 ml of water for injection, each ml contains 10 mg thiotepa.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use, after reconstitution and dilution.

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
After reconstitution, use within 8 hours when stored in a refrigerator.
After dilution, use within 24 hours when stored in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated (2°C-8°C). Do not freeze.

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/622/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TEPADINA 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}]
SN: {number}
NN: {number} [

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

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

TEPADINA 100 mg powder for concentrate for solution for infusion
Thiotepa
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg

6. OTHER

ADIENNE S.r.l. S.U.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

TEPADINA 15 mg powder for concentrate for solution for infusion
thiotepa

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

What is in this leaflet

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

1. What TEPADINA is and what it is used for

TEPADINA contains the active substance thiotepa, which belongs to a group of medicines called alkylating agents.

TEPADINA is used to prepare patients for bone marrow transplantation. It works by destroying bone marrow cells. This enables the transplantation of new bone marrow cells (haematopoietic progenitor cells), which in turn enable the body to produce healthy blood cells.
TEPADINA can be used in adults and children and adolescents.

2. What you need to know before you use TEPADINA

Do not use TEPADINA
- if you are allergic to thiotepa,
- if you are pregnant or think you may be pregnant,
- if you are breast-feeding,
- if you are receiving yellow fever vaccination, live virus and bacterial vaccines.

Warning and precautions
You should tell your doctor if you have:
- liver or kidney problems,
- heart or lung problems,
- seizures/fits (epilepsy) or have had them in the past (if treated with phenytoin or fosphenytoin).

Because TEPADINA destroys bone marrow cells responsible for producing blood cells, regular blood tests will be taken during treatment to check your blood cell counts.

In order to prevent and manage infections, you will be given anti-infectives.

TEPADINA may cause another type of cancer in the future. Your doctor will discuss this risk with you.

Other medicines and TEPADINA
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
You must tell your doctor if you are pregnant or you think you may be pregnant before you receive TEPADINA. You must not use TEPADINA during pregnancy.

Both women and men using TEPADINA must use effective contraceptive methods during treatment.

It is not known whether this medicinal product is excreted in breast milk. As a precautionary measure, women must not breast-feed during treatment with TEPADINA.

TEPADINA can impair male and female fertility. Male patients should seek for sperm preservation before therapy is started and should not father a child while treated and during the year after cessation of treatment.

Driving and using machines
It is likely that certain adverse reactions of thiotepa like dizziness, headache and blurred vision could affect your ability to drive and use machines.

3. How to use TEPADINA

Your doctor will calculate the dose according to your body surface or weight and your disease.

How TEPADINA is given
TEPADINA is administered by a qualified healthcare professional as an intravenous infusion (drip in a vein) after dilution of the individual vial. Each infusion will last 2-4 hours.

Frequency of administration
You will receive your infusions every 12 or 24 hours. The duration of treatment can last up to 5 days. Frequency of administration and duration of treatment depend on your disease.

4. Possible side effects

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

The most serious side effects of TEPADINA therapy or the transplant procedure may include
- decrease in circulating blood cell counts (intended effect of the medicine to prepare you for your transplant infusion)
- infection
- liver disorders including blocking of a liver vein
- the graft attacks your body (graft versus host disease)
- respiratory complications

Your doctor will monitor your blood counts and liver enzymes regularly to detect and manage these events.

Side effects of TEPADINA may occur with certain frequencies, which are defined as follows:

Very common side effects (may affect more than 1 in 10 people)
- increased susceptibility to infection
- whole-body inflammatory state (sepsis)
- decreased counts of white blood cells, platelets and red blood cells (anaemia)
- the transplanted cells attack your body (graft versus host disease)
- dizziness, headache, blurred vision
- uncontrolled shaking of the body (convulsion)
- sensation of tingling, pricking or numbness (paraesthesia)
- partial loss of movement
- cardiac arrest
- nausea, vomiting, diarrhoea
- inflammation of the mucosa of the mouth (mucositis)
- irritated stomach, gullet, intestine
- inflammation of the colon
- anorexia, decreased appetite
- high glucose in the blood
- skin rash, itching, shedding
- skin colour disorder (do not confuse with jaundice - see below)
- redness of the skin (erythema)
- hair loss
- back and abdominal pain, pain
- muscle and joint pain
- abnormal electrical activity in the heart (arrhythmia)
- inflammation of lung tissue
- enlarged liver
- altered organ function
- blocking of a liver vein (Veno-Occlusive Disease, VOD)
- yellowing of the skin and eyes (jaundice)
- hearing impaired
- lymphatic obstruction
- high blood pressure
- increased liver, renal and digestive enzymes
- abnormal blood electrolytes
- weight gain
- fever, general weakness, chills
- bleeding (haemorrhage)
- nasal bleeding
- general swelling due to fluid retention (oedema)
- pain or inflammation at the injection site
- eye infection (conjunctivitis)
- decreased sperm cell count
- vaginal bleeding
- absence of menstrual periods (amenorrhea)
- memory loss
- delaying in weight and height increase
- bladder disfunction
- underproduction of testosterone
- insufficient production of thyroid hormone
- deficient activity of the pituitary gland
- confusional state

Common side effects (may affect up to 1 in 10 people)
- anxiety, confusion
- abnormal bulging outward of one of the arteries in the brain (intracranial aneurysm)
- creatinine elevated
- allergic reactions
- occlusion of a blood vessel (embolism)
- heart rhythm disorder
- heart inability
- cardiovascular inability
- oxygen deficiency
- fluid accumulation in the lungs (pulmonary oedema)
- pulmonary bleeding
- respiratory arrest
- blood in the urine (haematuria) and moderate renal insufficiency
- inflammation of the urinary bladder
- discomfort in urination and decrease in urine output (disuria and oliguria)
- increase in the amount of nitrogen components in the blood stream (BUN increase)
- cataract
- inability of the liver
- cerebral haemorrhage
- cough
- constipation and upset stomach
- obstruction of the bowel
- perforation of stomach
- changes in muscle tone
- gross lack of coordination of muscle movements
- bruises due to a low platelet count
- menopausal symptoms
- cancer (second primary malignancies)
- abnormal brain function
- male and female infertility

Uncommon side effects (may affect up to 1 in 100 people)
- inflammation and exfoliation of the skin (erythrodermic psoriasis)
- delirium, nervousness, hallucination, agitation
- gastrointestinal ulcer
- inflammation of the muscular tissue of the heart (myocarditis)
- abnormal heart condition (cardiomyopathy)

Not known: frequency cannot be estimated from the available data
- increased blood pressure in the arteries (blood vessels) of the lungs (pulmonary arterial hypertension)
- severe skin damage (e.g. severe lesions, bullae, etc.) potentially involving the full body surface which can be even life-threatening
- damage to a component of the brain (the so called white matter) which can be even life-threatening (leukoencephalopathy).

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 TEPADINA

Keep out of the sight and reach of children.

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

Store and transport refrigerated (2°C-8°C).
Do not freeze.

After reconstitution the product is stable for 8 hours when stored at 2°C -8°C.

After dilution the product is stable for 24 hours when stored at 2°C -8°C and for 4 hours when stored at 25°C. From a microbiological point of view, the product should be used immediately.

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

6. Contents of the pack and other information

What TEPADINA contains
- The active substance is thiotepa. One vial contains 15 mg thiotepa. After reconstitution, each ml contains 10 mg thiotepa (10 mg/ml).
- TEPADINA does not contain any other ingredients.

What TEPADINA looks like and contents of the pack
TEPADINA is a white crystalline powder supplied in a glass vial containing 15 mg thiotepa.
Each carton contains 1 vial.

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This leaflet was last revised in

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

The following information is intended for healthcare professionals only.

PREPARATION GUIDE

TEPADINA 15 mg powder for concentrate for solution for infusion
Thiotepa

Read this guide prior to the preparation and administration of TEPADINA.

1. PRESENTATION

TEPADINA is supplied as 15 mg powder for concentrate for solution for infusion.
TEPADINA must be reconstituted and diluted prior to administration.

2. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

General
Procedures for proper handling and disposal of anticancer medicinal products should be considered. All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood.
As with other cytotoxic compounds, caution need to be exercised in handling and preparation of TEPADINA solutions to avoid accidental contact with skin or mucous membranes. Topical reactions associated with accidental exposure to thiotepa may occur. In fact, the use of gloves is recommended in preparing the solution for infusion. If thiotepa solution accidentally contacts the skin, immediately the skin must be thoroughly washed with soap and water. If thiotepa accidentally contacts mucous membranes, they must be flushed thoroughly with water.

Calculation of dose of TEPADINA
TEPADINA is administered at different doses in combination with other chemotherapeutic medicinal products in patients prior to conventional haematopoietic progenitor cell transplantation (HPCT) for haematological diseases or solid tumours.
TEPADINA posology is reported, in adult and paediatric patients, according to the type of HPCT (autologous or allogeneic) and disease.

Posology in adults

AUTOLOGOUS HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 300 mg/m^2/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m^2 (24.32 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA
The recommended dose ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 300 mg/m^2/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m^2 (24.32 mg/kg), during the time of the entire conditioning treatment.
CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA
The recommended dose is 185 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 2 consecutive days before autologous HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA
The recommended dose ranges from 150 mg/m^2/day (4.05 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.

Solid tumours

The recommended dose in solid tumours ranges from 120 mg/m^2/day (3.24 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) divided in one or two daily infusions, administered from 2 up to 5 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 800 mg/m^2 (21.62 mg/kg), during the time of the entire conditioning treatment.
BREAST CANCER
The recommended dose ranges from 120 mg/m^2/day (3.24 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered from 3 up to 5 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 800 mg/m^2 (21.62 mg/kg), during the time of the entire conditioning treatment.
CNS TUMOURS
The recommended dose ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) divided in one or two daily infusions, administered from 3 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.
OVARIAN CANCER
The recommended dose is 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered in 2 consecutive days before autologous HPCT, without exceeding the total maximum cumulative dose of 500 mg/m^2 (13.51 mg/kg), during the time of the entire conditioning treatment.
GERM CELL TUMOURS
The recommended dose ranges from 150 mg/m^2/day (4.05 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.

ALLOGENEIC HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 185 mg/m^2/day (5 mg/kg/day) to 481 mg/m^2/day (13 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 3 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 555 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
LYMPHOMA
The recommended dose in lymphoma is 370 mg/m^2/day (10 mg/kg/day) divided in two daily infusions before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
MULTIPLE MYELOMA
The recommended dose is 185 mg/m^2/day (5 mg/kg/day) as a single daily infusion before allogeneic HPCT, without exceeding the total maximum cumulative dose of 185 mg/m^2 (5 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA
The recommended dose ranges from 185 mg/m^2/day (5 mg/kg/day) to 481 mg/m^2/day (13 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 2 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 555 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
THALASSEMIA
The recommended dose is 370 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

Posology in paediatric patients

AUTOLOGOUS HPCT

Solid tumours

The recommended dose in solid tumours ranges from 150 mg/m^2/day (6 mg/kg/day) to 350 mg/m^2/day (14 mg/kg/day) as a single daily infusion, administered from 2 up to 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 1050 mg/m^2 (42 mg/kg), during the time of the entire conditioning treatment.
CNS TUMOURS
The recommended dose ranges from 250 mg/m^2/day (10 mg/kg/day) to 350 mg/m^2/day (14 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 1050 mg/m^2 (42 mg/kg), during the time of the entire conditioning treatment.

ALLOGENEIC HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m^2/day (5 mg/kg/day) to 250 mg/m^2/day (10 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 3 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 375 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
LEUKAEMIA
The recommended dose is 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
THALASSEMIA
The recommended dose ranges from 200 mg/m^2/day (8 mg/kg/day) to 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
REFRACTORY CYTOPENIA
The recommended dose is 125 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before allogeneic HPCT, without exceeding the total maximum cumulative dose of 375 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
GENETIC DISEASES
The recommended dose is 125 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 2 consecutive days before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

SICKLE CELL ANAEMIA
The recommended dose is 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

Reconstitution
TEPADINA must be reconstituted with 1.5 ml of sterile water for injections.
Using a syringe fitted with a needle, aseptically withdraw 1.5 ml of sterile water for injections.
Inject the content of the syringe into the vial through the rubber stopper.
Remove the syringe and the needle and mix manually by repeated inversions.
Only colourless solutions, without any particulate matter, must be used. Reconstituted solutions may occasionally show opalescence; such solutions can still be administered.

Further dilution in the infusion bag
The reconstituted solution is hypotonic and must be further diluted prior to administration with 500 ml sodium chloride 9 mg/ml (0.9%) solution for injection (1000 ml if the dose is higher than 500 mg) or with an appropriate volume of sodium chloride 9 mg/ml (0.9%) in order to obtain a final TEPADINA concentration between 0.5 and 1 mg/ml.

Administration
TEPADINA infusion solution should be inspected visually for particulate matter prior to administration. Solutions containing a precipitate should be discarded.

The infusion solution must be administered to patients using an infusion set equipped with a 0.2 µm in-line filter. Filtering does not alter solution potency.

TEPADINA should be aseptically administered as a 2-4 hours infusion under room temperature (about 25°C) and normal light conditions.

Prior to and following each infusion, the indwelling catheter line should be flushed with approximately 5 ml sodium chloride 9 mg/ml (0.9%) solution for injection.

Disposal
TEPADINA is for single use only.
Any unused product or waste material should be disposed of in accordance with local requirements

Package leaflet: Information for the user

TEPADINA 100 mg powder for concentrate for solution for infusion
thiotepa

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

What is in this leaflet:

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

1. What TEPADINA is and what it is used for

TEPADINA contains the active substance thiotepa, which belongs to a group of medicines called alkylating agents.

TEPADINA is used to prepare patients for bone marrow transplantation. It works by destroying bone marrow cells. This enables the transplantation of new bone marrow cells (haematopoietic progenitor cells), which in turn enable the body to produce healthy blood cells.
TEPADINA can be used in adults and children and adolescents.

2. What you need to know before you use TEPADINA

Do not use TEPADINA
- if you are allergic to thiotepa,
- if you are pregnant or think you may be pregnant,
- if you are breast-feeding,
- if you are receiving yellow fever vaccination, live virus and bacterial vaccines.

Warning and precautions
You should tell your doctor if you have:
- liver or kidney problems,
- heart or lung problems,
- seizures/fits (epilepsy) or have had them in the past (if treated with phenytoin or fosphenytoin).

Because TEPADINA destroys bone marrow cells responsible for producing blood cells, regular blood tests will be taken during treatment to check your blood cell counts.

In order to prevent and manage infections, you will be given anti-infectives.

TEPADINA may cause another type of cancer in the future. Your doctor will discuss this risk with you.

Other medicines and TEPADINA
Tell your doctor if you are taking, have recently taken or might take any other medicines

Pregnancy, breast-feeding and fertility
You must tell your doctor if you are pregnant or you think you may be pregnant before you receive TEPADINA. You must not use TEPADINA during pregnancy.

Both women and men using TEPADINA must use effective contraceptive methods during treatment.

It is not known whether this medicinal product is excreted in breast milk. As a precautionary measure, women must not breast-feed during treatment with TEPADINA.

TEPADINA can impair male and female fertility. Male patients should seek for sperm preservation before therapy is started and should not father a child while treated and during the year after cessation of treatment.

Driving and using machines
It is likely that certain adverse events of thiotepa like dizziness, headache and blurred vision could affect your ability to drive and use machines.

3. How to use TEPADINA

Your doctor will calculate the dose according to your body surface or weight and your disease.

How TEPADINA is given
TEPADINA is administered by a qualified healthcare professional as an intravenous infusion (drip in a vein) after dilution of the individual vial. Each infusion will last 2-4 hours.

Frequency of administration
You will receive your infusions every 12 or 24 hours. The duration of treatment can last up to 5 days. Frequency of administration and duration of treatment depend on your disease.

4. Possible side effects

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

The most serious side effects of TEPADINA therapy or the transplant procedure may include
- decrease in circulating blood cell counts (intended effect of the medicine to prepare you for your transplant infusion)
- infection
- liver disorders including blocking of a liver vein
- the graft attacks your body (graft versus host disease)
- respiratory complications

Your doctor will monitor your blood counts and liver enzymes regularly to detect and manage these events.

Side effects of TEPADINA may occur with certain frequencies, which are defined as follows:

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

- increased susceptibility to infection
- whole-body inflammatory state (sepsis)
- decreased counts of white blood cells, platelets and red blood cells (anaemia)
- the transplanted cells attack your body (graft versus host disease)
- dizziness, headache, blurred vision
- uncontrolled shaking of the body (convulsion)
- sensation of tingling, pricking or numbness (paraesthesia)
- partial loss of movement
- cardiac arrest
- nausea, vomiting, diarrhoea
- inflammation of the mucosa of the mouth (mucositis)
- irritated stomach, gullet, intestine
- inflammation of the colon
- anorexia, decreased appetite
- high glucose in the blood
- skin rash, itching, shedding
- skin colour disorder (do not confuse with jaundice - see below)
- redness of the skin (erythema)
- hair loss
- back and abdominal pain, pain
- muscle and joint pain
- abnormal electrical activity in the heart (arrhythmia)
- inflammation of lung tissue
- enlarged liver
- altered organ function
- blocking of a liver vein (Veno-Occlusive Disease, VOD)
- yellowing of the skin and eyes (jaundice)
- hearing impaired
- lymphatic obstruction
- high blood pressure
- increased liver, renal and digestive enzymes
- abnormal blood electrolytes
- weight gain
- fever, general weakness, chills
- bleeding (haemorrhage)
- nasal bleeding
- general swelling due to fluid retention (oedema)
- pain or inflammation at the injection site
- eye infection (conjunctivitis)
- decreased sperm cell count
- vaginal bleeding
- absence of menstrual periods (amenorrhea)
- memory loss
- delaying in weight and height increase
- bladder disfunction
- underproduction of testosterone
- insufficient production of thyroid hormone
- deficient activity of the pituitary gland
- confusional state

Common side effects (may affect up to 1 in 10 people)
- anxiety, confusion
- abnormal bulging outward of one of the arteries in the brain (intracranial aneurysm)
- creatinine elevated
- allergic reactions
- occlusion of a blood vessel (embolism)
- heart rhythm disorder
- heart inability
- cardiovascular inability
- oxygen deficiency
- fluid accumulation in the lungs (pulmonary oedema)
- pulmonary bleeding
- respiratory arrest
- blood in the urine (haematuria) and moderate renal insufficiency
- inflammation of the urinary bladder
- discomfort in urination and decrease in urine output (disuria and oliguria)
- increase in the amount of nitrogen components in the blood stream (BUN increase)
- cataract
- inability of the liver
- cerebral haemorrhage
- cough
- constipation and upset stomach
- obstruction of the bowel
- perforation of stomach
- changes in muscle tone
- gross lack of coordination of muscle movements
- bruises due to a low platelet count
- menopausal symptoms
- cancer (second primary malignancies)
- abnormal brain function
- male and female infertility

Uncommon side effects (may affect up to 1 in 100 people)
- inflammation and exfoliation of the skin (erythrodermic psoriasis)
- delirium, nervousness, hallucination, agitation
- gastrointestinal ulcer
- inflammation of the muscular tissue of the heart (myocarditis)
- abnormal heart condition (cardiomyopathy)

Not known: frequency cannot be estimated from the available data
- increased blood pressure in the arteries (blood vessels) of the lungs (pulmonary arterial hypertension)
- severe skin damage (e.g. severe lesions, bullae, etc.) potentially involving the full body surface which can be even life-threatening
- damage to a component of the brain (the so called white matter) which can be even life-threatening (leukoencephalopathy).

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 TEPADINA

Keep out of the sight and reach of children.

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

Store and transport refrigerated (2°C-8°C).
Do not freeze.

After reconstitution the product is stable for 8 hours when stored at 2°C -8°C.

After dilution the product is stable for 24 hours when stored at 2°C -8°C and for 4 hours when stored at 25°C. From a microbiological point of view, the product should be used immediately.

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

6. Contents of the pack and other information

What TEPADINA contains
- The active substance is thiotepa. One vial contains 100 mg thiotepa. After reconstitution, each ml contains 10 mg thiotepa (10 mg/ml).
- TEPADINA does not contain any other ingredients.

What TEPADINA looks like and contents of the pack
TEPADINA is a white crystalline powder supplied in a glass vial containing 100 mg thiotepa.
Each carton contains 1 vial.

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This leaflet was last revised in:

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

The following information is intended for healthcare professionals only.

PREPARATION GUIDE

TEPADINA 100 mg powder for concentrate for solution for infusion
Thiotepa

Read this guide prior to the preparation and administration of TEPADINA.

1. PRESENTATION

TEPADINA is supplied as 100 mg powder for concentrate for solution for infusion.
TEPADINA must be reconstituted and diluted prior to administration.

2. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

General
Procedures for proper handling and disposal of anticancer medicinal products should be considered. All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood.
As with other cytotoxic compounds, caution need to be exercised in handling and preparation of TEPADINA solutions to avoid accidental contact with skin or mucous membranes. Topical reactions associated with accidental exposure to thiotepa may occur. In fact, the use of gloves is recommended in preparing the solution for infusion. If thiotepa solution accidentally contacts the skin, immediately the skin must be thoroughly washed with soap and water. If thiotepa accidentally contacts mucous membranes, they must be flushed thoroughly with water.

Calculation of dose of TEPADINA
TEPADINA is administered at different doses in combination with other chemotherapeutic medicinal products in patients prior to conventional haematopoietic progenitor cell transplantation (HPCT) for haematological diseases or solid tumours.
TEPADINA posology is reported, in adult and paediatric patients, according to the type of HPCT (autologous or allogeneic) and disease.

Posology in adults

AUTOLOGOUS HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 300 mg/m^2/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m^2 (24.32 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA
The recommended dose ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 300 mg/m^2/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m^2 (24.32 mg/kg), during the time of the entire conditioning treatment.

CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA
The recommended dose is 185 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 2 consecutive days before autologous HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
MULTIPLE MYELOMA
The recommended dose ranges from 150 mg/m^2/day (4.05 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.

Solid tumours

The recommended dose in solid tumours ranges from 120 mg/m^2/day (3.24 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) divided in one or two daily infusions, administered from 2 up to 5 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 800 mg/m^2 (21.62 mg/kg), during the time of the entire conditioning treatment.
BREAST CANCER
The recommended dose ranges from 120 mg/m^2/day (3.24 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered from 3 up to 5 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 800 mg/m^2 (21.62 mg/kg), during the time of the entire conditioning treatment.
CNS TUMOURS
The recommended dose ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) divided in one or two daily infusions, administered from 3 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.
OVARIAN CANCER
The recommended dose is 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered in 2 consecutive days before autologous HPCT, without exceeding the total maximum cumulative dose of 500 mg/m^2 (13.51 mg/kg), during the time of the entire conditioning treatment.
GERM CELL TUMOURS
The recommended dose ranges from 150 mg/m^2/day (4.05 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.

ALLOGENEIC HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 185 mg/m^2/day (5 mg/kg/day) to 481 mg/m^2/day (13 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 3 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 555 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
LYMPHOMA
The recommended dose in lymphoma is 370 mg/m^2/day (10 mg/kg/day) divided in two daily infusions before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA
The recommended dose is 185 mg/m^2/day (5 mg/kg/day) as a single daily infusion before allogeneic HPCT, without exceeding the total maximum cumulative dose of 185 mg/m^2 (5 mg/kg), during the time of the entire conditioning treatment.
LEUKAEMIA
The recommended dose ranges from 185 mg/m^2/day (5 mg/kg/day) to 481 mg/m^2/day (13 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 2 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 555 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
THALASSEMIA
The recommended dose is 370 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

Posology in paediatric patients

AUTOLOGOUS HPCT

Solid tumours

The recommended dose in solid tumours ranges from 150 mg/m^2/day (6 mg/kg/day) to 350 mg/m^2/day (14 mg/kg/day) as a single daily infusion, administered from 2 up to 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 1050 mg/m^2 (42 mg/kg), during the time of the entire conditioning treatment.
CNS TUMOURS
The recommended dose ranges from 250 mg/m^2/day (10 mg/kg/day) to 350 mg/m^2/day (14 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 1050 mg/m^2 (42 mg/kg), during the time of the entire conditioning treatment.

ALLOGENEIC HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m^2/day (5 mg/kg/day) to 250 mg/m^2/day (10 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 3 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 375 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
LEUKAEMIA
The recommended dose is 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
THALASSEMIA
The recommended dose ranges from 200 mg/m^2/day (8 mg/kg/day) to 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
REFRACTORY CYTOPENIA
The recommended dose is 125 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before allogeneic HPCT, without exceeding the total maximum cumulative dose of 375 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.

GENETIC DISEASES
The recommended dose is 125 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 2 consecutive days before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.
SICKLE CELL ANAEMIA
The recommended dose is 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

Reconstitution
TEPADINA must be reconstituted with 10 ml of sterile water for injections.
Using a syringe fitted with a needle, aseptically withdraw 10 ml of sterile water for injections.
Inject the content of the syringe into the vial through the rubber stopper.
Remove the syringe and the needle and mix manually by repeated inversions.
Only colourless solutions, without any particulate matter, must be used. Reconstituted solutions may occasionally show opalescence; such solutions can still be administered.

Further dilution in the infusion bag
The reconstituted solution is hypotonic and must be further diluted prior to administration with 500 ml sodium chloride 9 mg/ml (0.9%) solution for injection (1000 ml if the dose is higher than 500 mg) or with an appropriate volume of sodium chloride 9 mg/ml (0.9%) in order to obtain a final TEPADINA concentration between 0.5 and 1 mg/ml.

Administration
TEPADINA infusion solution should be inspected visually for particulate matter prior to administration. Solutions containing a precipitate should be discarded.

The infusion solution must be administered to patients using an infusion set equipped with a 0.2 µm in-line filter. Filtering does not alter solution potency.

TEPADINA should be aseptically administered as a 2-4 hours infusion under room temperature (about 25°C) and normal light conditions.

Prior to and following each infusion, the indwelling catheter line should be flushed with approximately 5 ml sodium chloride 9 mg/ml (0.9%) solution for injection.

Disposal
TEPADINA is for single use only.
Any unused product or waste material should be disposed of in accordance with local requirements.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TEPADINA® (thiotepa) for injection, for intravenous, intracavitary, or intravesical use.

Initial U.S. Approval: 1959

WARNING: SEVERE MYELOSUPPRESSION, CARCINOGENICITY

See full prescribing information for complete boxed warning.

- **May cause severe marrow suppression or ablation with resulting infection or bleeding. Monitor hematologic laboratory parameters *[see Warnings and Precautions (5.1)]***
- **Potentially carcinogenic in humans *[see Warnings and Precautions (5.7)]***

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

TEPADINA (thiotepa) is an alkylating drug indicated:

- To reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor (stem) cell transplantation (HSCT) for pediatric patients with class 3 beta-thalassemia. (1.1, 14)
- For treatment of adenocarcinoma of the breast or ovary. (1.2)
- For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities. (1.3)
- For treatment of superficial papillary carcinoma of the urinary bladder. (1.4)

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

- The recommended dose of TEPADINA for class 3 beta-thalassemia is two administrations of 5 mg/kg given intravenously approximately 12 hours apart on Day -6 before allogeneic HSCT in conjunction with high-dose busulfan and cyclophosphamide. (2.1)
- The recommended dose of TEPADINA for treatment of adenocarcinoma of the breast or ovary is 0.3 to 0.4 mg/kg intravenously. (2.1)
- The recommended dose of TEPADINA for treatment of malignant effusions is 0.6 to 0.8 mg/kg intracavitary. (2.1)
- The recommended dose of TEPADINA for treatment of superficial papillary carcinoma of the urinary bladder is 60 mg in 30 to 60 mL of Sodium Chloride Injection into the bladder by catheter. (2.1)

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

- For injection: 15 mg, lyophilized white powder in single-dose vial for reconstitution. (3)
- For injection: 100 mg, lyophilized white powder in single-dose vial for reconstitution. (3)

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

- Hypersensitivity to the active substance. (4)
- Concomitant use with live or attenuated vaccines. (4)

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

- Cutaneous toxicity: Cleanse skin at least twice daily through 48 hours after the last dose of TEPADINA. (5.3)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to avoid pregnancy. (5.8)

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

The most common adverse reactions (incidence greater than 10%) were neutropenia, anemia, thrombocytopenia, elevated alanine aminotransferase, elevated aspartate aminotransferase, elevated bilirubin, mucositis, cytomegalovirus infection, hemorrhage, diarrhea, hematuria and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ADIENNE at 844-668-3940 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Lactation: Breastfeeding is not recommended. (8.2)
- Moderate or severe renal impairment: Monitor patients more frequently for toxicity. (8.6, 12.2)
- Moderate or severe hepatic impairment: Monitor patients more frequently for toxicity. (8.7, 12.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 01/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Class 3 beta-Thalassemia
- 1.2 Adenocarcinoma of the Breast or Ovary
- 1.3 Malignant Effusions
- 1.4 Superficial Papillary Carcinoma of the Urinary Bladder

2 DOSAGE AND ADMINISTRATION
- 2.1 Recommended Dosage
- 2.2 Preparation Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Myelosuppression
- 5.2 Hypersensitivity
- 5.3 Cutaneous Toxicity
- 5.4 Concomitant Use of Live and Attenuated Vaccines
- 5.5 Hepatic Veno-Occlusive Disease
- 5.6 Central Nervous System Toxicity
- 5.7 Carcinogenicity
- 5.8 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS
- 7.1 Effect of Cytochrome CYP3A Inhibitors and Inducers
- 7.2 Effect of TEPADINA on Cytochrome CYP2B6 Substrates

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING
- 16.1 How Supplied
- 16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: SEVERE MYELOSUPPRESSION, CARCINOGENICITY

- **TEPADINA may cause severe marrow suppression, and high doses may cause marrow ablation with resulting infection or bleeding. Monitor hematologic laboratory parameters. Hematopoietic progenitor (stem) cell transplantation (HSCT) is required to prevent potentially fatal complications of the prolonged myelosuppression after high doses of TEPADINA *[see Warnings and Precautions (5.1)]***
- **TEPADINA should be considered potentially carcinogenic in humans *[see Warnings and Precautions (5.7)]***

1 INDICATIONS AND USAGE

1.1 Class 3 Beta-Thalassemia

TEPADINA is indicated to reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor (stem) cell transplantation (HSCT) for pediatric patients with class 3 beta-thalassemia *[see Clinical Studies (14)]*.

1.2 Adenocarcinoma of the Breast or Ovary

TEPADINA is indicated for treatment of adenocarcinoma of the breast or ovary.

1.3 Malignant Effusions

TEPADINA is indicated for controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities.

1.4 Superficial Papillary Carcinoma of the Urinary Bladder

TEPADINA is indicated for treatment of superficial papillary carcinoma of the urinary bladder.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Class 3 Beta-Thalassemia

The recommended dose of TEPADINA in pediatric patients is two administrations of 5 mg/kg given intravenously approximately 12 hours apart on Day -6 before allogeneic HSCT in conjunction with high-dose busulfan and cyclophosphamide as outlined in Table 1. See Prescribing Information for cyclophosphamide and busulfan for information on these drugs.

Table 1: Dosage Regimen For Allogeneic HSCT In Pediatric Patients With Class 3 Beta-Thalassemia

	Day prior to transplantation										
Treatment	**Day -10**	**Day -9**	**Day -8**	**Day -7**	**Day -6**	**Day -5**	**Day -4**	**Day -3**	**Day -2**	**Day -1**	**Day 0**
Busulfan IV weight-based dose *	▲	▲	▲	▲							
TEPADINA IV 5 mg/kg twice					▲						
Cyclophosphamide IV 40 mg/kg/day						▲	▲	▲	▲		
Stem cell Infusion											▲

*Busulfan IV weight-based dose: 1.0 mg/kg every 6 hours for patients less than 9 kg; 1.2 mg/kg every 6 hours for patients 9 to 16 kg; 1.1 mg/kg every 6 hours for patients 16.1 to 23 kg; 0.95 mg/kg every 6 hours for patients 23.1 to 34 kg; 0.8 mg/kg every 6 hours for patients more than 34 kg.

Infuse TEPADINA via a central venous catheter over 3 hours using an infusion set equipped with a 0.2 micron in-line filter. Prior to and following each infusion, flush the catheter with approximately 5 ml sodium chloride 0.9% solution for injection.

TEPADINA is excreted through the skin of patients receiving high-dose therapy. Take precautions to prevent skin toxicity [*see Warnings and Precautions (5.3)*].

Adenocarcinoma of the Breast or Ovary

The recommended dose of TEPADINA for treatment of adenocarcinoma of the breast or ovary is 0.3 to 0.4 mg/kg intravenously. Doses should be given at 1 to 4 week intervals. Initially the higher dose in the given range is commonly administered. The maintenance dose should be adjusted weekly on the basis of pretreatment control blood counts and subsequent blood counts. Maintenance doses should not be administered more frequently than weekly.

Malignant Effusions

The recommended dose of TEPADINA for treatment of malignant effusions is 0.6 to 0.8 mg/kg intracavitary. Administration is usually effected through the same tubing which is used to remove the fluid from the cavity involved. Doses should be given at 1 to 4 week intervals. Initially the higher dose in the given range is commonly administered. The maintenance dose should be adjusted weekly on the basis of pretreatment control blood counts and subsequent blood counts. Maintenance doses should not be administered more frequently than weekly.

Superficial Papillary Carcinoma of the Urinary Bladder

The recommended dose of TEPADINA for treatment of superficial papillary carcinoma of the urinary bladder is 60 mg in 30 to 60 mL of Sodium Chloride Injection into the bladder by catheter. The solution should be retained for 2 hours. If the patient finds it impossible to retain 60 mL for 2 hours, the dose may be given in a volume of 30 mL. The patient may be repositioned every 15 minutes for maximum area contact. The usual course of treatment is once a week for 4 weeks. The course may be repeated if necessary, but second and third courses must be given with caution since bone-marrow depression may be increased.

2.2 Preparation Instructions

TEPADINA is a cytotoxic drug. Follow applicable special handling and disposal procedures[1].

Reconstitution

Reconstitute TEPADINA 15 mg with 1.5 ml of sterile water for injection. Using a syringe fitted with a needle, aseptically withdraw 1.5 ml of sterile water for injection. Inject the content of the syringe into the vial through the rubber stopper. Remove the syringe and needle, and mix manually by repeated inversions.

Reconstitute TEPADINA 100 mg with 10 ml of sterile water for injection. Using a syringe fitted with a needle, aseptically withdraw 10 ml of sterile water for injection. Inject the content of the syringe into the vial through the rubber stopper. Remove the syringe and needle, and mix manually by repeated inversions.

The reconstituted solution is hypotonic and must be diluted in saline prior to administration. Reconstituted solutions, free of visible particulate matter, may occasionally show opalescence; such solutions can still be used for further dilution.

If not used immediately after reconstitution, the product is stable for 8 hours when stored at 2°C to 8°C (36° to 46°F).

Dilution in the infusion bag

Prior to administration, dilute the reconstituted solution further with an appropriate volume of sodium chloride 0.9% solution for injection to obtain a final TEPADINA concentration between 0.5 and 1 mg/mL. Dilute TEPADINA as recommended in Table 2.

Table 2: Dilution of TEPADINA in the infusion bag

Calculated TEPADINA Dose	Dilution Volume (Sodium Chloride 0.9% solution for injection)
Less than 250 mg	Appropriate volume to obtain a final concentration of 0.5 to 1 mg/mL
250 mg to 500 mg	500 mL or appropriate volume to obtain a final concentration of 0.5 to 1 mg/mL
Greater than 500 mg	1000 mL or appropriate volume to obtain a final concentration of 0.5 to 1 mg/mL

After dilution the product is stable for 24 hours when stored at 2°C to 8°C (36° to 46°F) and for 4 hours when stored at 25°C (77°F). From a microbiological point of view, the product should be used immediately.

Inspect the diluted solution visually for particulate matter and discoloration prior to administration. Use TEPADINA diluted solutions only if free of visible particulate matter. Filter using a 0.2 micron filter prior to administration. Filtering does not alter solution potency

3 DOSAGE FORMS AND STRENGTHS

- For injection, 15 mg, lyophilized white powder in single-dose vial for reconstitution
- For injection, 100 mg, lyophilized white powder in single-dose vial for reconstitution

4 CONTRAINDICATIONS

TEPADINA is contraindicated in:

- Patients with severe hypersensitivity to thiotepa *[see Warnings and Precautions (5.2)]*
- Concomitant use with live or attenuated vaccines *[see Warnings and Precautions (5.4)]*

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

The consequence of treatment with high doses of TEPADINA together with other chemotherapy at the recommended dose and schedule in the preparative regimen for class 3 beta- thalassemia is profound myelosuppression occurring in all patients. Do not begin the preparative regimen if a stem cell donor is not available. Monitor complete blood counts, and provide supportive care for infections, anemia and thrombocytopenia until there is adequate hematopoietic recovery.

For patients receiving TEPADINA for treatment of adenocarcinoma of the breast, adenocarcinoma of the ovary, malignant effusions and superficial papillary carcinoma of the urinary bladder, if the bone marrow has been compromised by prior irradiation or chemotherapy, or is recovering from chemotherapy, the risk of severe myelosuppression with TEPADINA may be increased. Perform periodic complete blood counts during the course of treatment with TEPADINA. Provide supportive care for infections, bleeding, and symptomatic anemia *[see Adverse Reactions (6.1)]*.

5.2 Hypersensitivity

Clinically significant hypersensitivity reactions, including anaphylaxis, have occurred following administration of TEPADINA. If anaphylactic or other clinically significant allergic reaction occurs, discontinue treatment with TEPADINA, initiate appropriate therapy, and monitor until signs and symptoms resolve *[see Contraindications (4), Adverse Reactions (6.1)]*.

5.3 Cutaneous Toxicity

TEPADINA and/or its active metabolites may be excreted in part via skin patients receiving high-dose therapy. Treatment with TEPADINA may cause skin discoloration, pruritus, blistering, desquamation, and peeling that may be more severe in the groin, axillae, skin folds, in the neck area, and under dressings. Instruct patients to shower or bathe with water at least twice daily through 48 hours after administration of TEPADINA. Change occlusive dressing and clean the covered skin at least twice daily through 48 hours after administration of TEPADINA. Change bed sheets daily during treatment.

Skin reactions associated with accidental exposure to TEPADINA may also occur. Wash the skin thoroughly with soap and water in case TEPADINA solution contacts the skin. Flush mucous membranes in case of TEPADINA contact with mucous membranes.

5.4 Concomitant Use of Live and Attenuated Vaccines

Do not administer live or attenuated viral or bacterial vaccines to a patient treated with TEPADINA until the immunosuppressive effects have resolved.

5.5 Hepatic Veno-Occlusive Disease

Hepatic veno-occlusive disease may occur in patients who have received high-dose TEPADINA in conjunction with busulfan and cyclophosphamide *[see Adverse Reactions (6.1)]*. Monitor by physical examination, serum transaminases and bilirubin daily through BMT Day +28, and provide supportive care to patients who develop hepatic veno-occlusive disease.

5.6 Central Nervous System Toxicity

Fatal encephalopathy has occurred in patients treated with high doses of thiotepa. Other central nervous system toxicities, such as headache, apathy, psychomotor retardation, disorientation, confusion, amnesia, hallucinations, drowsiness, somnolence, seizures, coma, inappropriate behaviour and forgetfulness have been reported to occur in a dose-dependent manner during or shortly after administration of high-dose thiotepa. In pediatric patients treated with TEPADINA at the recommended dose in combination with busulfan and cyclophosphamide, 8% developed central nervous system toxicity (seizures and intracranial hemorrhage). Do not exceed the recommended dose of TEPADINA. If severe or life-threatening central nervous system toxicity occurs, discontinue administration of TEPADINA and provide supportive care.

5.7 Carcinogenicity

Like many alkylating agents, thiotepa has been reported to be carcinogenic when administered to laboratory animals *[see Nonclinical Toxicity (13.1)]*. Carcinogenicity is shown most clearly in studies using mice, but there is some evidence of carcinogenicity in man. There is an increased risk of a secondary malignancy with use of TEPADINA.

5.8 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, TEPADINA can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of TEPADINA in pregnant women. Thiotepa given by the intraperitoneal (IP) route was teratogenic in mice at doses $\geq$ 1 mg/kg (3.2 mg/m^2), approximately 8-fold less than the maximum recommended human therapeutic dose (0.8 mg/kg, 27 mg/m^2), based on body-surface area. Thiotepa given by the IP route was teratogenic in rats at doses $\geq$ 3 mg/kg (21 mg/m^2), approximately equal to the maximum recommended human

therapeutic dose, based on body-surface area. Thiotepa was lethal to rabbit fetuses at a dose of 3 mg/kg (41 mg/m^2), approximately two times the maximum recommended human therapeutic dose based on body-surface area.

Advise pregnant women of the potential risk to the fetus [*see Use in Specific Populations (8.1, 8.3)*]. Advise females of reproductive potential to use highly effective contraception during and after treatment with TEPADINA for at least 6 months after therapy. Advise males of reproductive potential to use effective contraception during and after treatment with TEPADINA for at least 1 year after therapy [*see Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression [*see Warnings and Precautions (5.1)*]
- Infection [*see Warnings and Precautions (5.1)*]
- Hypersensitivity [*see Warnings and Precautions (5.2)*]
- Cutaneous Toxicity [*see Warnings and Precautions (5.3)*]
- Hepatic Veno-Occlusive Disease [*see Warnings and Precautions (5.5)*]
- Central Nervous System Toxicity [*see Warnings and Precautions (5.6)]*
- Carcinogenicity [*see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

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

Adverse Reactions With the Preparative Regimen for Class 3 Beta-Thalassemia

The safety of TEPADINA was evaluated by retrospective analysis of 76 pediatric patients with class 3 beta-thalassemia who underwent allogeneic hematopoietic progenitor (stem) cell transplantation (HSCT) using busulfan and cyclophosphamide with TEPADINA (n=25) or without TEPADINA (n=51) [*see Clinical Studies (14)*]. Adverse reactions were abstracted retrospectively from the medical records.

Serious adverse events that occurred in the TEPADINA-treated and control cohort were, respectively: gastrointestinal hemorrhage (4% vs 2%), pneumonia (4% vs 0), seizure (4% vs 2%), subarachnoid hemorrhage (4% vs 0) and veno-occlusive disease (4% vs 2%). By 90 days after HSCT, grades 2 to 4 acute graft-versus-host disease was observed in 7 (28%) patients in the TEPADINA cohort and in 13 (26%) patients in the control cohort. By 1-year after transplantation, chronic graft-versus-host disease was observed in 8 (35%) of 23 evaluable patients in the TEPADINA cohort, and 7 (14%) of 49 evaluable patients in the control cohort.

Adverse reactions occurring in at least 5% of patients treated with TEPADINA from start of the preparative regimen through 30 days after transplantation are shown in Table 3.

Table 3: Common Adverse Reactions (>5%) Occurring Through 30 Days After Transplantation In Patients With Class 3 Beta-Thalassemia Using Busulfan And Cyclophosphamide With Or Without TEPADINA in the Preparative Regimen

	Preparative Regimen of Busulfan and Cyclophosphamide			
	With TEPADINA N=25 patients (%)		Without TEPADINA N=51 patients (%)	
Adverse Reaction	**Any Grade**	**Grade 3-5[1]**	**Any Grade**	**Grade 3-5[1]**
Mucositis[2]	16 (64%)	4 (16%)	22 (43%)	1 (2%)
Cytomegalovirus Infection	12 (48%)	0	15 (29%)	0
Hemorrhage[3]	7 (28%)	2 (8%)	12 (24%)	3 (6%)
Diarrhea	6 (24%)	0	7 (14%)	2 (4%)
Hematuria[4]	5 (20%)	0	10 (20%)	3 (6%)
Rash[5]	3 (12%)	0	11 (22%)	0
Intracranial Hemorrhage[6]	2 (8%)	1 (4%)	0	0
Pseudomonas Infection	2 (8%)	0	0	0

[1]Severe, life-threatening or fatal
[2]Mucositis includes mouth hemorrhage, mucosal inflammation and stomatitis
[3]Hemorrhage includes all hemorrhage terms
[4]Hematuria includes cystitis hemorrhagic and hematuria
[5]Rash includes dermatitis exfoliative, palmar erythema, rash, rash maculo-papular, rash pruritic and skin toxicity
[6]Hemorrhage Intracranial includes hemorrhage intracranial and subarachnoid hemorrhage

All patients in the TEPADINA-treated and control cohorts developed profound cytopenias, including neutropenia, anemia, thrombocytopenia. Table 4 shows the selected chemistry abnormalities that occurred from start of the preparative regimen through 30 days after transplantation.

Table 4: Selected Laboratory Abnormalities Occurring Through 30 Days After Transplantation In Patients With Class 3 Beta-Thalassemia Using Busulfan And Cyclophosphamide With Or Without TEPADINA in the Preparative Regimen

	Preparative Regimen of Busulfan and Cyclophosphamide			
	With TEPADINA N=25 patients (%)		Without TEPADINA N=51 patients (%)	
Adverse Reaction	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Elevated alanine aminotransferase	22 (88%)	6 (24%)	49 (96%)	14 (27%)
Elevated aspartate aminotransferase	20 (80%)	4 (16%)	45 (88%)	9 (18%)
Elevated total bilirubin	20 (80%)	4 (16%)	39 (77%)	2 (4%)

Adverse Reactions with Treatment of adenocarcinoma of the breast, adenocarcinoma of the ovary, malignant effusions and superficial papillary carcinoma of the urinary bladder

Gastrointestinal: Nausea, vomiting, abdominal pain, anorexia.

General: Fatigue, weakness. Febrile reaction and discharge from a subcutaneous lesion may occur as the result of breakdown of tumor tissue.

Hypersensitivity Reactions: Allergic reactions - rash, urticaria, laryngeal edema, asthma, anaphylactic shock, wheezing.

Local Reactions: Contact dermatitis, pain at the injection site.

Neurologic: Dizziness, headache, blurred vision.

Renal: Dysuria, urinary retention, chemical cystitis or hemorrhagic cystitis.

Reproductive: Amenorrhea, interference with spermatogenesis.

Respiratory: Prolonged apnea has been reported when succinylcholine was administered prior to surgery, following combined use of thiotepa and other anticancer agents. It was theorized that this was caused by decrease of pseudocholinesterase activity caused by the anticancer drugs.

Skin: Dermatitis, alopecia. Skin depigmentation has been reported following topical use.

Special Senses: Conjunctivitis.

6.2 Postmarketing Experience

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.

The following adverse reactions have been identified during post approval use of TEPADINA in preparative regimens prior to allogeneic or autologous hematopoietic progenitor (stem) cell transplantation (HSCT) in adult and pediatric patients.

Blood and lymphatic system disorders: Febrile bone marrow aplasia.

Cardiac disorders: Bradycardia, cardiac failure congestive, cardio-respiratory arrest, pericardial effusion, pericarditis, right ventricular hypertrophy.

Congenital, familial and genetic disorders: Aplasia.

Ear and labyrinth disorders: Deafness.

Eye disorders: Blindness, eyelid ptosis, papilledema, strabismus.

Gastrointestinal disorders: Ascites, dysphagia, enterocolitis, gastritis, palatal disorder.

General disorders and administration site conditions: Device related infection, gait disturbance, malaise, multi-organ failure, pain.

Hepatobiliary disorders: Hepatomegaly.

Immune system disorders: Bone marrow transplant rejection, immunosuppression.

Infections and infestations: Acute sinusitis, bronchopulmonary aspergillosis, candida sepsis, enterococcal infection, Epstein-Barr virus infection, Escherichia sepsis, Fusarium infection, gastroenteritis, infection, lower respiratory tract infection fungal, lower respiratory tract infection viral, parainfluenza virus infection, Pneumonia legionella, relapsing fever, respiratory tract infection, sepsis, septic shock, Staphylococcal bacteremia, Staphylococcal infection, systemic candida, urinary tract infection.

Injury, poisoning and procedural complications: Refractoriness to platelet transfusion, subdural hematoma.

Investigations: Coagulation test abnormal, hemoglobin decreased, Klebsiella test positive, nuclear magnetic resonance imaging brain abnormal, transaminases increased, weight increased.

Metabolism and nutrition disorders: Hyponatremia.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): Breast cancer metastatic, central nervous system lymphoma, leukemia recurrent, lymphoma, malignant neoplasm progression, metastatic neoplasm, post transplant lymphoproliferative disorder.

Nervous system disorders: Aphasia, brain injury, bulbar palsy, central nervous system lesion, cerebral microangiopathy, cerebral ventricle dilatation, cerebrovascular accident, cognitive disorder, convulsion, coordination abnormal, encephalitis, encephalopathy, hemiplegia, hypotonia, leukoencephalopathy, memory impairment, motor dysfunction, neurotoxicity, quadriparesis, speech disorder, tremor, VIIth nerve paralysis, white matter lesion.

Psychiatric disorders: Delirium, depression, disorientation, suicidal ideation.

Renal and urinary disorders: Renal failure, nephropathy toxic.

Respiratory, thoracic and mediastinal disorders: Acute respiratory distress, aspiration, dyspnea exertional, interstitial lung disease, lung disorder, pneumonitis, pulmonary arteriopathy, pulmonary sepsis, pulmonary veno-occlusive disease, respiratory distress, respiratory failure, pulmonary hypertension.

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome and toxic epidermal necrolysis.

Vascular disorders: Capillary leak syndrome.

7 DRUG INTERACTIONS

7.1 Effect of Cytochrome CYP3A Inhibitors and Inducers

In vitro studies suggest that thiotepa is metabolized by CYP3A4 and CYP2B6 to its active metabolite TEPA. Avoid coadministration of strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, ritonavir) and strong CYP3A4 inducers (e.g., rifampin, phenytoin) with TEPADINA due to the potential effects on efficacy and toxicity *[see Clinical Pharmacology (12.2)]*. Consider alternative medications with no or minimal potential to inhibit or induce CYP3A4. If concomitant use of strong CYP3A4 modulators cannot be avoided, closely monitor for adverse drug reactions.

7.2 Effect of TEPADINA on Cytochrome CYP2B6 Substrates

In vitro studies suggest that thiotepa inhibits CYP2B6. TEPADINA may increase the exposure of drugs that are substrates of CYP2B6 in patients; however, the clinical relevance of this *in vitro* interaction is unknown *[see Clinical Pharmacology (12.2)]*.

The administration of thiotepa with cyclophosphamide in patients reduces the conversion of cyclophosphamide to the active metabolite, 4-hydroxycyclophosphamide; the effect appears sequence dependent with a greater reduction in the conversion to 4-hydroxycyclophosphamide when thiotepa is administered 1.5 hours prior to the intravenous administration of cyclophosphamide compared to administration of thiotepa after intravenous cyclophosphamide *[see Clinical Pharmacology (12.2)]*. The reduction in 4-hydroxycyclophosphamide levels may potentially reduce efficacy of cyclophosphamide treatment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TEPADINA can cause fetal harm when administered to a pregnant woman based on findings from animals and the drug's mechanism of action [*see Clinical Pharmacology (12.1)*]. Limited available data with TEPADINA use in pregnant women are insufficient to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of thiotepa to pregnant mice and rats during organogenesis produced teratogenic effects (neural tube defects and malformations of the skeletal system of the fetus) at doses approximately 0.125 and 1 times, respectively, the maximum recommended human daily dose on a mg/m^2 basis. Thiotepa was lethal to rabbit fetuses at approximately 2 times the maximum recommended human therapeutic dose based on body-surface area *[see Data]*. Consider the benefits and risks of TEPADINA for the mother and possible risks to the fetus when prescribing TEPADINA to a pregnant woman.

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

Data

Animal Data

Thiotepa given by the IP route in mice at doses ≥ 1 mg/kg (3.2 mg/m^2), approximately 8-fold less than the maximum recommended human therapeutic dose based on body-surface area, and in rats at doses ≥ 3 mg/kg (21 mg/m^2), approximately equal to the maximum recommended human therapeutic dose based on body-surface area, resulted in various malformations including neural tube defects, omphalocele, renal agenesis, atresia ani, limb and digit defects, cleft palate, micrognathia, other skeletal anomalies in the skull, vertebrae and ribs, and reduced skeletal ossification. Thiotepa was lethal to rabbit fetuses at a dose of 3 mg/kg (41 mg/m^2), approximately 2 times the maximum recommended human therapeutic dose based on body-surface area.

8.2 Lactation

Risk Summary

There is no information regarding the presence of thiotepa in human milk, the effects on the breastfed infant, or the effects on milk production.

Because of the potential for serious adverse reactions, including the potential for tumorigenicity shown for thiotepa in animal studies, advise patients not to breastfeed during TEPADINA treatment.

8.3 Females and Males of Reproductive Potential

Pregnancy testing

TEPADINA can cause fetal harm when administered to a pregnant female. Verify the pregnancy status of females of reproductive potential prior to initiating TEPADINA therapy.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy during TEPADINA treatment and for at least 6 months after the final dose of TEPADINA. Advise females to immediately report pregnancy *[see Use in Specific Populations (8.1)]*.

Males

TEPADINA may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during TEPADINA treatment and for at least 1 year after the final dose of TEPADINA [*see Nonclinical Toxicology (13.1)*].

Infertility

Based on nonclinical findings, male and female fertility may be compromised by treatment with TEPADINA. Inform male patients about the possibility of sperm conservation before the start of therapy *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of TEPADINA for prevention of graft rejection in pediatric patients undergoing allogeneic HSCT for class 3 beta-thalassemia was established in one prospective study and one retrospective study [*see Clinical Studies (14)*] that included 1 infant (1 month to 1 year), 23 children (2 to 11 years) and 13 adolescents (12 to 16 years) who received TEPADINA as part of their preparative regimen. Safety and effectiveness of TEPADINA in neonates have not been established.

Safety and effectiveness of TEPADINA for treatment of adenocarcinoma of the breast, adenocarcinoma of the ovary, malignant effusions and superficial papillary carcinoma of the urinary bladder in pediatric patients have not been established.

8.5 Geriatric Use

The safety and effectiveness of TEPADINA as a preparative regimen prior to allogeneic hematopoietic progenitor (stem) cell transplantation (HSCT) for patients with class 3 beta-thalassemia have not been established in geriatric patients. Clinical studies of TEPADINA for this indication did not include subjects aged 65 and over.

Clinical studies of TEPADINA for treatment of adenocarcinoma of the breast, adenocarcinoma of the ovary, malignant effusions and superficial papillary carcinoma of the urinary bladder did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of

decreasing hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

In patients with moderate (creatinine clearance (CLcr) of 30 mL/min to 59 mL/min) renal impairment, decreased renal excretion may result in increased plasma levels of thiotepa and TEPA *[see Clinical Pharmacology (12.2)]*. This may result in increased toxicity. Monitor patients with moderate to severe (CLcr < 30 mL/min) renal impairment for signs and symptoms of toxicity following treatment with TEPADINA for an extended period of time.

8.7 Hepatic Impairment

Thiotepa is extensively metabolized in the liver. Patients with moderate (bilirubin levels greater than 1.5 times to 3 times the upper limit of normal and any AST) hepatic impairment may have increased plasma levels of thiotepa [*see Clinical Pharmacology (12.2)*]. This may result in toxicity. Monitor patients with moderate to severe (bilirubin levels greater than 3 times upper limit of normal and any AST) hepatic impairment for signs and symptoms of toxicity following treatment with TEPADINA for an extended period of time.

10 OVERDOSE

There is no experience with overdoses of thiotepa. The most important adverse reactions expected in case of overdose are myeloablation and pancytopenia *[see Nonclinical Toxicology (13.2)]*. There is no known antidote for thiotepa. Monitor the hematological status closely and provide vigorous supportive measures as medically indicated.

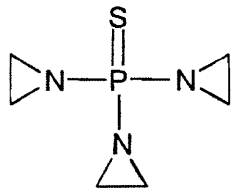
11 DESCRIPTION

TEPADINA (thiotepa) is an alkylating agent. TEPADINA (thiotepa) for injection is supplied as a non-pyrogenic, sterile lyophilized white powder for intravenous, intracavitary, or intravesical use after reconstitution and dilution.

TEPADINA is available in a single-dose vial containing:

- 15 mg thiotepa. After reconstitution with 1.5 ml of water for injection, each ml contains 10 mg thiotepa.
- 100 mg thiotepa. After reconstitution with 10 ml of water for injection, each ml contains 10 mg thiotepa.

Thiotepa is a synthetic product with antitumor activity. The chemical name for thiotepa is Tris(1-aziridinyl)phosphine sulfide. Thiotepa has the following structural formula:



Thiotepa has the molecular formula $C_6H_{12}N_3PS$, and a molecular weight of 189.23, and it appears as fine, white crystalline flakes, with a melting range of 52°C to 57°C. It is soluble in water and organic solvents. When reconstituted with sterile water for injection, the resulting solution has a pH of approximately 5.5 to 7.5. Thiotepa is unstable in acid medium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Thiotepa is a cytotoxic agent of the polyfunctional type, related chemically and pharmacologically to the nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethyleneimine radicals which, like irradiation, disrupt the bonds of DNA. One of the principle bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guanines.

12.2 Pharmacokinetics

Absorption

Thiotepa reached maximal concentrations close to the end infusion following an intravenous infusion.

Distribution

The binding of thiotepa to plasma proteins is approximately 10% to 20%. The mean volume of distribution (% coefficient of variation) of thiotepa was 30 L/m^2 (44%) or 1.2 L/kg (47%) following a single intravenous infusion of TEPADINA at a dose of 5 mg/kg over 3 hours in pediatric population. In adults administered intravenous thiotepa between 20 mg to 250 mg/m^2 as an intravenous bolus or infusion up to 4 hours, the mean volume of distribution of thiotepa ranged from 1.0 L/kg (30%) to 1.9 L/kg (17%).

Elimination

Following a single intravenous infusion over 3 hours of TEPADINA at a dose of 5 mg/kg in pediatric population, the estimated mean (% coefficient of variation) clearance of thiotepa was 0.58 L/hr/kg (60%) or 13.8 L/hr/m^2 (52%). The mean terminal elimination half-life was 1.7 hours (64%) for thiotepa and 4 hours (29%) for its major active metabolite, N,N',N''-triethylenephosphoramide (TEPA) in pediatric population. In adults administered intravenous thiotepa between 20 mg to 250 mg/m^2 as an intravenous bolus or infusion up to 4 hours, the mean thiotepa clearance ranged from 14.6 L/hr/m^2 (23%) to 27.9 L/hr/m^2 (69%). In adult population, the mean terminal elimination half-life ranged from 1.4 hours (7%) to 3.7 hours (14%) for thiotepa and from 4.9 hours to 17.6 hours (20%) for TEPA.

Metabolism
Thiotepa undergoes hepatic metabolism. *In vitro* data suggests that CYP3A4 and CYP2B6 may be responsible for the metabolism of thiotepa to TEPA, a major active metabolite.

Excretion
In adult and pediatric patients, urinary excretion of thiotepa accounted for less than 2% of the dose and TEPA accounted for 11% or less of the dose.

Specific Populations

Hepatic Impairment
The clearance of thiotepa following a single TEPADINA dose of 5 mg/kg in pediatric population with mild hepatic impairment was similar to the clearance observed in patients with normal liver function administered thiotepa.
The exposure (as measured by area under the curve (AUC)) of thiotepa increased by 1.6-fold and 1.8-fold following administration of multiple thiotepa doses of 7 mg/kg administered every 2 days with cyclophosphamide in two adult patients who had liver metastases with moderate hepatic impairment compared to the exposure observed in one patient with normal hepatic function. The effect of severe hepatic impairment on thiotepa exposure is unknown.

Renal Impairment

The exposure (as measured by AUC) of thiotepa increased by 1.4-fold and TEPA increased by 2.6-fold following administration of multiple doses of 120 mg/m^2/day in one patient with moderate renal impairment (CLcr = 38 mL/min) administered cyclophosphamide plus thiotepa plus carboplatin, compared to exposure of thiotepa in patients with normal renal function. The effects of severe renal impairment or end-stage renal disease on thiotepa exposure are unknown.

Drug Interactions

The clinical relevance of *in vitro* inhibition of the cytochrome P450 enzymes described below is unknown, but it cannot be excluded that the systemic exposure of thiotepa or medicinal products that are substrates for these enzymes may be affected with concomitant administration with TEPADINA.

Effect of Cytochrome P450 Modulators on Thiotepa

In vitro data demonstrates that CYP3A4 and CYP2B6 inhibitors decrease the metabolism of thiotepa *[see Drug Interactions (7.1)]*.

Effect of Thiotepa on Cytochrome P450 2B6

In vitro data demonstrates that thiotepa inhibits CYP2B6.

Effect of Thiotepa on Cyclophosphamide

The administration of thiotepa 1.5 hours prior to intravenous cyclophosphamide in patients administered cyclophosphamide plus thiotepa plus carboplatin decreased the AUC of 4-hydroxycyclophosphamide by 26% and maximal concentrations of 4-hydroxycyclophosphamide by 62%, compared to administration of cyclophosphamide prior to thiotepa.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In mice, repeated intraperitoneal (IP) administration of thiotepa (1.15 or 2.3 mg/kg three times per week for 52 or 43 weeks, respectively) produced a significant increase in the combined incidence of squamous-cell carcinomas of the skin, preputial gland, and ear canal, and combined incidence of lymphoma and lymphocytic leukemia. In other studies in mice, repeated IP administration of thiotepa (4 or 8 mg/kg three times per week for 4 weeks followed by a 20 week observation period or 1.8 mg/kg three times per week for 4 weeks followed by a 35 week observation period) resulted in an increased incidence of lung tumors. In rats, repeated IP administration of thiotepa (0.7 or 1.4 mg/kg three times per week for 52 or 34 weeks, respectively) produced significant increases in the incidence of squamous-cell carcinomas of the skin or ear canal, combined hematopoietic neoplasms, and uterine adenocarcinomas. Thiotepa given intravenously (IV) to rats (1 mg/kg once per week for 52 weeks) produced an increased incidence of malignant tumors (abdominal cavity sarcoma, lymphosarcoma myelosis, seminoma, fibrosarcoma, salivary gland hemangioendothelioma, mammary sarcoma, pheochromocytoma) and benign tumors.

The lowest reported carcinogenic dose in mice (1.15 mg/kg, 3.68 mg/m^2) is approximately 7-fold less than the maximum recommended human therapeutic dose based on body-surface area. The lowest reported carcinogenic dose in rats (0.7 mg/kg, 4.9 mg/m^2) is approximately 6-fold less than the maximum recommended human therapeutic dose based on body-surface area.

Thiotepa was mutagenic in *in vitro* assays in *Salmonella typhimurium, E coli*, Chinese hamster lung and human lymphocytes. Chromosomal aberrations and sister chromatid exchanges were observed *in vitro* with thiotepa in bean root tips, human lymphocytes, Chinese hamster lung, and monkey lymphocytes.

Mutations were observed with oral thiotepa in mouse at doses > 2.5 mg/kg (8 mg/m^2). The mouse micronucleus test was

positive with intraperitoneal administration of > 1 mg/kg (3.2 mg/m^2). Other positive *in vivo* chromosomal aberration or mutation assays included *Drosophila melanogaster*, Chinese hamster marrow, murine marrow, monkey lymphocyte, and murine germ cell.

Thiotepa impaired fertility in male mice at oral or intraperitoneal doses ≥ 0.7 mg/kg (2.24 mg/m^2), approximately 12-fold less than the maximum recommended human therapeutic dose based on body-surface area. Thiotepa (0.5 mg) inhibited implantation in female rats when instilled into the uterine cavity. Thiotepa interfered with spermatogenesis in mice at IP doses ≥ 0.5 mg/kg (1.6 mg/m^2), approximately 17-fold less than the maximum recommended human therapeutic dose based on body-surface area. Thiotepa interfered with spermatogenesis in hamsters at an IP dose of 1 mg/kg (4.1 mg/m^2), approximately 7-fold less than the maximum recommended human therapeutic dose based on body-surface area.

14 CLINICAL STUDIES

TEPADINA was evaluated in a retrospective study of pediatric patients with class 3 beta-thalassemia who underwent allogeneic hematopoietic progenitor (stem) cell transplantation (HSCT) from a human leukocyte antigen (HLA)-identical sibling donor. Twenty-five patients (10 male and 15 female) of median age 10 years (range, 5-16 years) were treated with intravenous busulfan at weight-based dosing from Day -10 to Day -7 pretransplant [*see Table 1*]), intravenous TEPADINA 5 mg/kg twice on Day -6, intravenous cyclophosphamide 40 mg/kg/day on Day -5 to Day -2, and marrow infusion on Day 0. All patients had also received precytoreduction with hydroxyurea, azathioprine and fludarabine prior to start of the preparative regimen.

Efficacy was based on the incidence of graft rejection (primary or late rejection). The incidence of graft rejection in these 25 patients using TEPADINA was 0% (95% CI: [0, 0.12]). Of the 51 patients who received the same preparative regimen, historically, without TEPADINA, the incidence of graft rejection reported was 25.5% (95% CI: [0.13, 0.37]).

15 REFERENCES

1. OSHA Hazardous Drugs. OSHA. [Accessed from http://www.osha.gov/SLTC/hazardousdrugs/index.html].

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TEPADINA is supplied as Unit carton with one single-dose Type I clear glass vial with a bromobutyl stopper.

TEPADINA 15 mg
One vial contains 15 mg thiotepa (*NDC 53964-001-01).*

TEPADINA 100 mg
One vial contains 100 mg thiotepa (*NDC 53964-002-02*).

16.2 Storage and Handling

TEPADINA vials must be stored and transported refrigerated at 2°C to 8°C (36° to 46°F). Do not freeze.

TEPADINA is a cytotoxic drug. Follow applicable special handling and disposal procedures[1].

17 PATIENT COUNSELING INFORMATION

Hypersensitivity
Counsel patients on the signs and symptoms of hypersensitivity and to seek immediate emergency assistance if they develop any of these signs and symptoms *[see Warnings and Precautions (5.2)]*.

Myelosuppression
Inform patients of the possibility of developing low blood cell counts and the need for hematopoietic progenitor cell infusion. Instruct patients to immediately report to their healthcare provider if bleeding or fever occurs *[see Warnings and Precautions (5.1)]*.

Females and Males of Reproductive Potential
TEPADINA can cause fetal harm. Advise females receiving TEPADINA to avoid pregnancy during TEPADINA treatment and for at least 6 months after the final dose of TEPADINA *[see Warnings and Precautions (5.8)]*.

Advise males with female sexual partners of reproductive potential to use effective contraception during TEPADINA treatment and for at least 1 year after the final dose of TEPADINA *[see Use in Specific Populations (8.3)]*.

Advise females to report pregnancy immediately *[see Warnings and Precautions (5.8)]*.

Advise patients that TEPADINA can produce infertility. Inform male patients about the possibility of sperm conservation before the start of therapy *[see Use in Specific Populations (8.3)]*.

Lactation
Advise patients to avoid breastfeeding while receiving TEPADINA *[see Use in Specific Populations (8.2)]*.

Secondary malignancies
Inform patients that TEPADINA can increase the risk of secondary malignancy *[see Warnings and Precautions (5.7)]*.

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Revision Date: 01/2017

チオテパ

製造販売承認申請

CTD 第１部

1.7　同種同効品一覧

大日本住友製薬株式会社

1. 同種同効品一覧表

本剤の同種同効品として、アルキル化剤であり、国内で自家造血幹細胞移植の前治療への適応を有する注射用ブスルファン、注射用シクロホスファミド水和物、注射用メルファランについて記載した。

一般的名称	注射用チオテパ	注射用ブスルファン	注射用シクロホスファミド水和物	注射用メルファラン
販売名	リサイオ®点滴静注液 100mg	ブスルフェクス®点滴静注用 60mg	注射用エンドキサン®100mg 注射用エンドキサン®500mg	アルケラン®静注用 50mg
会社名	大日本住友製薬株式会社	大塚製薬株式会社	塩野義製薬株式会社	アスペンジャパン株式会社
効能・効果	小児悪性固形腫瘍における自家造血幹細胞移植の前治療	1. 同種造血幹細胞移植の前治療 2. ユーイング肉腫ファミリー腫瘍、神経芽細胞腫における自家造血幹細胞移植の前治療	1. 下記疾患の自覚的並びに他覚的症状の緩解 多発性骨髄腫、悪性リンパ腫、肺癌、乳癌、急性白血病、真性多血症、子宮頸癌、子宮体癌、卵巣癌、神経腫瘍（神経芽腫、網膜芽腫）、骨腫瘍 ただし、下記の疾患については、他の抗悪性腫瘍剤と併用することが必要である。 慢性リンパ性白血病、慢性骨髄性白血病、咽頭癌、胃癌、膵癌、肝癌、結腸癌、睾丸腫瘍、絨毛性疾患（絨毛癌、破壊胞状奇胎、胞状奇胎）、横紋筋肉腫、悪性黒色腫 2. 以下の悪性腫瘍に対する他の抗悪性腫瘍剤との併用療法 乳癌（手術可能例における術前、あるいは術後化学療法） 3. 褐色細胞腫	下記疾患における造血幹細胞移植時の前処置 白血病、悪性リンパ腫、多発性骨髄腫、小児固形腫瘍

一般的名称	注射用チオテパ	注射用ブスルファン	注射用シクロホスファミド水和物	注射用メルファラン
効能・効果（続き）			4. 下記疾患における造血幹細胞移植の前治療 急性白血病、慢性骨髄性白血病、骨髄異形成症候群、重症再生不良性貧血、悪性リンパ腫、遺伝性疾患（免疫不全、先天性代謝障害及び先天性血液疾患：Fanconi 貧血、Wiskott-Aldrich 症候群、Hunter 病等） 5. 治療抵抗性の下記リウマチ性疾患 全身性エリテマトーデス、全身性血管炎（顕微鏡的多発血管炎、ヴェゲナ肉芽腫症、結節性多発動脈炎、Churg-Strauss 症候群、大動脈炎症候群等）、多発性筋炎/皮膚筋炎、強皮症、混合性結合組織病、及び血管炎を伴う難治性リウマチ性疾患	
添付文書改訂日	—	2018 年 9 月改訂	2015 年 6 月改訂	2017 年 2 月改訂

※※2018年9月改訂（——部分、第13版）
※2016年6月改訂（-----部分、第12版）

日本標準商品分類番号
87 4213

造血幹細胞移植前治療薬

劇薬、処方箋医薬品
注意－医師等の処方箋により使用すること

ブスルフェクス®点滴静注用60mg
注射用ブスルファン
Busulfex® injection 60mg

	ブスルフェクス点滴静注用60mg
承認番号	21800AMY10108
薬価収載	2009年3月
販売開始	2009年3月
国際誕生	1999年2月
効能追加	2006年10月

貯　法：2～8℃に保存
使用期限：製造後2年(外箱等に表示)
注意事項：〔取扱い上の注意〕の項参照

TD110X2B04

〔警　告〕
1. 造血幹細胞移植の前治療に本剤を投与する場合には、緊急時に十分対応できる医療施設において、造血幹細胞移植に十分な知識と経験をもつ医師のもとで、適切と判断される患者にのみ実施すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。
2. 本剤を小児に投与する場合には、小児のがん化学療法に十分な知識と経験をもつ医師のもとで実施すること。
3. 本剤の使用にあたっては、本剤及び併用薬剤の添付文書を熟読し、慎重に患者を選択すること（〔禁忌〕、「1. 慎重投与」、「2. 重要な基本的注意」の項参照）。

〔禁　忌（次の患者には投与しないこと）〕
1. 重症感染症を合併している患者[感染症が増悪し致命的となることがある]
2. 本剤の成分に対し過敏症の既往歴のある患者
3. 妊婦又は妊娠している可能性のある婦人（「6. 妊婦、産婦、授乳婦等への投与」の項参照）

〔組成・性状〕

販売名	有効成分	添加物	性状
ブスルフェクス点滴静注用60mg	1バイアル10mL中 ブスルファン 60mg	ポリエチレングリコール400 6.67mL *N,N*-ジメチルアセトアミド 3.33mL	本剤は、無色澄明の液である。

〔効能・効果〕
1. 同種造血幹細胞移植の前治療
2. ユーイング肉腫ファミリー腫瘍、神経芽細胞腫における自家造血幹細胞移植の前治療

※※〔用法・用量〕
他の抗悪性腫瘍薬との併用において、成人にはA法又はB法、小児にはC法を使用する。なお、患者の状態により適宜減量する。

成人	A法：ブスルファンとして1回0.8mg/kgを2時間かけて点滴静注する。本剤は6時間毎に1日4回、4日間投与する。 B法：ブスルファンとして1回3.2mg/kgを3時間かけて点滴静注する。本剤は1日1回、4日間投与する。
小児	C法：ブスルファンとして以下の体重別の投与量を2時間かけて点滴静注する。本剤は6時間毎に1日4回、4日間投与する。

実体重	本剤投与量〔mg/kg〕
9kg未満	1.0
9kg以上16kg未満	1.2
16kg以上23kg以下	1.1
23kg超34kg以下	0.95
34kg超	0.8

《用法・用量に関連する使用上の注意》
1. シクロホスファミド、メルファラン又はフルダラビンとの併用以外での有効性及び安全性は確立されていない（〔臨床成績〕の項参照）。
2. 肥満患者(BMIが25以上)では投与量が過多にならないように、標準体重から換算した投与量を考慮すること。
3. 薬液が血管外に漏れると組織障害を起こすおそれがあるので、中心静脈より投与すること（「9. 適用上の注意」の項参照）。

＜注射液の調製法及び投与法＞
本剤を10倍量の生理食塩液又は5%ブドウ糖液に添加し、十分に混和して使用すること。なお、本剤は室温(約25℃)で用時調製し、希釈後に混濁又は結晶が認められる場合には使用しないこと。
希釈後は、安定性が低下するので、室温においては希釈調製から8時間以内に投与を終了すること。投与に際しては、中心静脈カテーテルを留置して投与すること。また、他の注射剤との配合又は混注は行わないこと（「9. 適用上の注意」及び〔取扱い上の注意〕の項参照）。

※※〔使用上の注意〕
1. 慎重投与(次の患者には慎重に投与すること)
(1)肝機能障害のある患者（「2. 重要な基本的注意」の項参照）
(2)腎機能障害のある患者[腎機能障害が増悪するおそれがある]
(3)心機能障害のある患者[心機能障害が増悪するおそれがある]
(4)肺障害のある患者[肺障害が増悪するおそれがある]
(5)感染症を合併している患者[感染症が増悪し致命的となることがある]
(6)高齢者（「5. 高齢者への投与」の項参照）

2. 重要な基本的注意
(1)本剤の使用にあたっては、患者の状態及び臓器機能(心、肺、肝、腎等)を十分検討し、造血幹細胞移植を実施可能と判断される患者にのみ投与し、以下の事項について特に注意すること。
1) 本剤の投与中は心電図、血圧及び尿量等のモニターを行うこと。また、投与後は定期的に臨床検査(血液検査、肝機能検査、腎機能検査等)及び尿量のモニター等を行うこと。
2) 本剤の投与後は患者の状態を十分に観察し、致命的な感染症の発現を抑制するため、抗菌剤投与等の感染症対策を行い、適切な無菌管理を行うこと。
3) 本剤の投与後は輸血及び造血因子の投与等適切な支持療法を行うこと。
(2)本剤の投与により痙攣を起こす可能性があるため、あらかじめ抗痙攣薬の使用を考慮するなどの適切な措置を講ずること。
(3)本剤を使用する場合には、静脈閉塞性肝疾患の発現に注意すること。静脈閉塞性肝疾患の症状としてあらわれる体重増加、肝腫大又は肝の圧痛、腹水、黄疸等に注意すること（「4. 副作用」の項参照）。
(4)本剤をB法で使用する際には、関連文献（「医療上の必要性の高い未承認薬・適応外薬検討会議　公知申請への該当性に係る報告書：ブスルファン(新用法・用量の追加)[1]」等）を熟読すること。

3. 相互作用
併用注意(併用に注意すること)

薬剤名等	臨床症状・措置方法	機序・危険因子
イトラコナゾール[2]	本剤の血漿中濃度が上昇し、本剤の作用が増強することがある。	機序は不明であるが、本剤の血漿中濃度を上昇させることがある。
メトロニダゾール[3]	本剤の血漿中濃度が上昇し、本剤の作用が増強することがある。	機序は不明であるが、本剤の血漿中濃度を上昇させることがある。

4. 副作用

● 国内臨床試験

国内臨床試験において、安全性評価対象29例(同種移植27例、自家移植2例)中、副作用は全ての被験者に認められた。主な副作用は口内炎・舌炎24例(82.8%)、悪心23例(79.3%)、嘔吐19例(65.5%)、食欲不振19例(65.5%)、下痢・軟便19例(65.5%)、倦怠感15例(51.7%)であった。重症度がGrade3以上で、発現頻度が5%以上であった副作用は、食欲不振14例(48.3%)、悪心10例(34.5%)、γ-GTP上昇9例(31.0%)、ALT(GPT)上昇6例(20.7%)、発熱性好中球減少症5例(17.2%)、口内炎・舌炎4例(13.8%)、嘔吐3例(10.3%)、血糖上昇3例(10.3%)、血清カリウム低下3例(10.3%)、血圧上昇2例(6.9%)、下痢・軟便2例(6.9%)、血清アルブミン低下2例(6.9%)、発熱2例(6.9%)であった。

● 海外臨床試験(成人)

成人を対象とした海外臨床試験において、安全性評価対象103例(同種移植61例、自家移植42例)中、副作用は全ての被験者に認められた。同種移植において、主な副作用は悪心57例(93.4%)、口内炎・舌炎57例(93.4%)、嘔吐54例(88.5%)、食欲不振40例(65.6%)、下痢・軟便39例(63.9%)、血清マグネシウム低下32例(52.5%)であった。重症度がGrade3以上で、発現頻度が5%以上であった副作用は、食欲不振24例(39.3%)、ビリルビン上昇18例(29.5%)、口内炎・舌炎16例(26.2%)、血糖上昇5例(8.2%)、静脈閉塞性肝疾患4例(6.6%)、ALT(GPT)上昇4例(6.6%)、悪心4例(6.6%)であった。一方、自家移植において、主な副作用は悪心39例(92.9%)、口内炎・舌炎36例(85.7%)、嘔吐35例(83.3%)、下痢・軟便25例(59.5%)、発熱24例(57.1%)であった。重症度がGrade3以上で、発現頻度が5%以上であった副作用は、食欲不振7例(16.7%)、ビリルビン上昇4例(9.5%)、口内炎・舌炎4例(9.5%)であった。

● 海外臨床試験(小児)

小児を対象とした海外臨床試験において、安全性評価対象55例(同種移植28例、自家移植27例)中、副作用は46例(83.6%)に認められた。同種移植において、28例中19例(67.9%)に副作用が認められ、主な副作用は口内炎・舌炎13例(46.4%)、ALT(GPT)上昇9例(32.1%)、食欲不振9例(32.1%)、AST(GOT)上昇8例(28.6%)、γ-GTP上昇8例(28.6%)、嘔吐6例(21.4%)であった。重症度がGrade3以上で、発現頻度が5%以上であった副作用は、食欲不振9例(32.1%)、γ-GTP上昇5例(17.9%)、ALT(GPT)上昇4例(14.3%)、発熱性好中球減少症4例(14.3%)、肝腫大3例(10.7%)、口内炎・舌炎3例(10.7%)であった。一方、自家移植において、27例中27例(100%)に副作用が認められ、主な副作用は口内炎・舌炎27例(100%)、嘔吐19例(70.4%)、食欲不振18例(66.7%)、下痢・軟便16例(59.3%)、AST(GOT)上昇15例(55.6%)、ALT(GPT)上昇14例(51.9%)、腹痛14例(51.9%)、発熱13例(48.1%)、γ-GTP上昇9例(33.3%)、発熱性好中球減少症8例(29.6%)、悪心6例(22.2%)、腹水6例(22.2%)であった。重症度がGrade3以上で、発現頻度が5%以上であった副作用は、口内炎・舌炎21例(77.8%)、食欲不振18例(66.7%)、発熱性好中球減少症8例(29.6%)、発熱8例(29.6%)、下痢・軟便7例(25.9%)、肝腫大5例(18.5%)、腹痛4例(14.8%)、AST(GOT)上昇2例(7.4%)、ビリルビン上昇2例(7.4%)、胸水2例(7.4%)、嘔吐2例(7.4%)、吐血2例(7.4%)であった。なお、移植合併症に関する検討において、静脈閉塞性肝疾患が同種移植で2例(7.1%)及び自家移植で4例(14.8%)に発現した。また、有害事象として、同種移植28例のうち14例(50.0%)に移植片対宿主病が発現した。

(1)重大な副作用

1) 静脈閉塞性肝疾患(7.5%)

静脈閉塞性肝疾患があらわれることがあるので、観察を十分に行い、異常が認められた場合には適切な処置を行うこと。

2) 感染症及び出血等

本剤投与後は重度の骨髄抑制状態となり、その結果感染症(22.5%)及び出血(頻度不明)等を引き起こし、致命的となることがあるので、本剤の投与後は患者の状態を十分に把握して適切な処置を行うこと。

3) ショック、アナフィラキシー(頻度不明)

ショック、アナフィラキシーがあらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

4) 痙攣(頻度不明)

ブスルファンは髄液移行性が高く、あらかじめ抗痙攣薬が投与されていない場合は10%以上の患者で痙攣が起こるとの報告がある[4]。国内及び海外臨床試験(成人)ではあらかじめフェニトインが投与され、132例中1例に痙攣が発現した。海外臨床試験(小児)ではあらかじめベンゾジアゼピン系の抗痙攣薬が投与され、55例中2例に痙攣が発現した。

5) 肺胞出血・喀血、間質性肺炎、呼吸不全、急性呼吸窮迫症候群(5%未満)

肺胞出血・喀血、間質性肺炎、呼吸不全、急性呼吸窮迫症候群があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

6) 心筋症(頻度不明)

心筋症があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

7) 胃腸障害

口内炎・舌炎(84.0%)、嘔吐(71.1%)、悪心(68.4%)、食欲不振(56.1%)、下痢・軟便(54.5%)が高頻度にあらわれるので、観察を十分に行い、異常が認められた場合には適切な処置を行うこと。

(2)その他の副作用

次のような症状があらわれた場合には、観察を十分に行い、異常が認められた場合には、適切な処置を行うこと。

1) 国内

種類/頻度	20%以上	5～20%未満	5%未満
肝臓	ALP上昇、ALT(GPT)上昇、AST(GOT)上昇、LDH上昇、γ-GTP上昇、肝機能異常	ビリルビン上昇	
血液		APTT延長、FDP上昇、発熱性好中球減少症	アンチトロンビンIII低下、血栓性微小血管症、血中フィブリノゲン上昇、白血球増多
免疫	移植片対宿主病	免疫グロブリン低下	生着症候群、骨髄移植拒絶反応
呼吸器	咽喉頭疼痛	咽喉頭不快感、咳嗽、鼻出血、鼻漏	咽頭紅斑、胸水、上気道炎、嗄声
循環器		血圧上昇	徐脈
消化器	腹痛	口腔内痛、痔核、消化不良、腹部不快感、肛門周囲の異常	マロリー・ワイス症候群、胃酸過多、胃前庭部毛細血管拡張症、口内乾燥、歯肉出血、出血性胃炎、舌苔、腸炎、腹部膨満
精神・神経系	頭痛	めまい	情動不安
腎臓・泌尿器		血清クレアチニン上昇、血尿、出血性膀胱炎、蛋白尿、膀胱炎	BUN上昇、BUN低下、腎機能障害、前立腺炎、排尿困難
皮膚	脱毛	瘙痒症、紅斑、色素沈着、発疹	皮下出血、皮脂欠乏症、皮膚落屑

種類/頻度	20%以上	5～20%未満	5%未満
代謝	血清アルブミン低下、血清総蛋白低下、血糖上昇	血清カリウム低下、血清カルシウム低下、血清ナトリウム低下、血清マグネシウム低下、血清リン上昇、血清リン低下	トリグリセリド上昇、血清カリウム上昇、血清クロル上昇、血清クロル低下、血清ナトリウム上昇、電解質失調
筋骨格		関節痛、頸部痛、四肢痛、背部痛	顎痛、筋痛
感覚器	味覚異常	口内異常感	
眼			角膜炎、眼瘙痒、眼球乾燥、眼充血、眼瞼炎、結膜炎、羞明
その他	倦怠感、発熱	CRP上昇、体重減少、浮腫	ほてり・潮紅、圧迫感、胸痛、胸部不快感、灼熱感、体重増加、白血球Al-P上昇

2) 海外(成人)
①同種移植

種類/頻度	20%以上	5～20%未満	5%未満
肝臓	ALT(GPT)上昇、ビリルビン上昇	Al-P上昇、AST(GOT)上昇、黄疸	LDH上昇、肝腫大、門脈圧亢進症
血液			APTT延長、プロトロンビン時間延長、凝血異常、血中フィブリノゲン低下、脾腫
免疫		移植片対宿主病	
呼吸器		ラ音、咽喉頭疼痛	咳嗽、呼吸音減弱、呼吸困難、鼻乾燥、鼻出血、鼻閉、鼻漏、副鼻腔うっ血、副鼻腔不快感、無気肺、嚥下性肺炎
循環器			血圧低下、心拡大、起立性低血圧
消化器	腹痛	肛門周囲の異常、便秘、腹部膨満、消化不良	しゃっくり、胃腸出血、鼓腸、口腔内痛、口腔粘膜出血、口内水疱、痔核、食道炎、食道痛、食道不快感、舌苔、唾液過多、腸雑音異常、直腸出血、吐血、腹水、腹部不快感、嚥下障害
精神・神経系	頭痛	不眠症、情動不安	めまい、肝性脳症、激越、錯乱状態、失見当識、振戦、脳出血、譫妄
腎臓・泌尿器		乏尿、血清クレアチニン上昇	BUN上昇、血尿、出血性膀胱炎、腎機能障害、多尿、尿意切迫、排尿困難、膀胱痛
皮膚		皮下出血、発疹、脱毛	瘙痒症、紅斑、皮膚乾燥、皮膚障害
代謝	血清カリウム低下、血清カルシウム低下、血清マグネシウム低下、血糖上昇	体液貯留、血清リン低下	血清アルブミン低下、血清カリウム上昇、血清ナトリウム低下、脱水
筋骨格			関節痛、筋痛、筋痙攣、骨痛、四肢痛、背部痛
感覚器			口内異常感、耳痛、耳鳴、味覚異常
眼			強膜浮腫、結膜出血、霧視

種類/頻度	20%以上	5～20%未満	5%未満
その他	倦怠感、発熱	浮腫、脱力、体重減少	ほてり・潮紅、悪寒、灼熱感、体重増加、粘膜過形成、不正子宮出血、冷感、膣出血

②自家移植

種類/頻度	20%以上	5～20%未満	5%未満
肝臓		ALT(GPT)上昇、ビリルビン上昇	Al-P上昇、AST(GOT)上昇、黄疸
呼吸器		咽喉頭疼痛、咽頭紅斑、鼻閉	咽喉乾燥、呼吸音減弱、呼吸困難、鼻出血
循環器		頻脈	起立性低血圧、血圧低下
消化器		消化不良、腹痛、肛門周囲の異常	しゃっくり、胃炎、口腔粘膜出血、痔核、食道炎、舌苔、唾液過多、腹水、腹部膨満、便秘、嚥下障害
精神・神経系		めまい、情動不安、頭痛	しびれ感、悪夢、不眠症
腎臓・泌尿器		血清クレアチニン上昇	血尿、排尿困難、乏尿
皮膚		脱毛、発疹、皮下出血	紅斑
代謝	血清マグネシウム低下	血清カリウム低下、血清カルシウム低下、血清リン低下、血糖上昇	血清アルブミン低下、血清ナトリウム低下、血清リン上昇、血清総蛋白低下、体液貯留、尿酸上昇
筋骨格			関節痛、顔面痛、筋痛
眼			霧視
その他	倦怠感、発熱	ほてり・潮紅、脱力、浮腫	悪寒、体重減少、体重増加

3) 海外(小児)
①同種移植

種類/頻度	20%以上	5～20%未満	5%未満
肝臓	ALT(GPT)上昇、AST(GOT)上昇、γ-GTP上昇	Al-P上昇、ビリルビン上昇、肝腫大	
血液		発熱性好中球減少症	脾腫
消化器		腹水、腹痛	メレナ、直腸炎、吐血、膵炎
精神・神経系			めまい
腎臓・泌尿器			出血性膀胱炎
皮膚			紅斑、発疹
その他		体重増加、脱力	倦怠感、発熱

②自家移植

種類/頻度	20%以上	5～20%未満	5%未満
肝臓	ALT(GPT)上昇、AST(GOT)上昇、γ-GTP上昇	ビリルビン上昇、肝腫大	黄疸、肝臓痛、門脈狭窄
血液	発熱性好中球減少症		有熱性骨髄無形成、脾腫
呼吸器		胸水、鼻出血	呼吸困難、頻呼吸
循環器			頻脈
消化器	腹水、腹痛	直腸炎、吐血	胃炎、鼓腸、蛋白漏出性胃腸症、裂肛
精神・神経系		情動不安	
腎臓・泌尿器			血尿、尿閉、乏尿
皮膚		紅斑、色素沈着、皮膚落屑	発疹、皮下出血
代謝			血清アルブミン低下、血清カリウム低下、血清ナトリウム低下、血清マグネシウム低下
筋骨格			殿部痛
感覚器			耳痛
その他	発熱	倦怠感、体重増加、脱力、浮腫	悪寒、疼痛

5. 高齢者への投与
高齢者への投与の有効性・安全性は確立していない(使用経験がない)。

6. 妊婦、産婦、授乳婦等への投与
(1)妊婦又は妊娠している可能性のある婦人には投与しないこと[動物実験(マウス、ラット、ウサギ)で胎児あるいは出生児において筋骨格系の異常、性腺の発育障害、体重・体長の減少及び生殖機能への影響が認められたとの報告がある[5]]。
(2)授乳婦に投与する場合には授乳を中止させること[授乳中の投与に関する安全性は確立していない]。

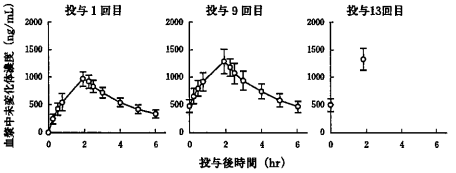
7. 小児等への投与
小児55例(年齢0～18歳未満)を対象とした海外臨床試験において、小児に特徴的な副作用と考えられる症状等は認められなかった(「4. 副作用」の項参照)。本剤を前治療薬として用いた造血幹細胞移植を小児に施行するにあたっては、歯牙形成不全を含む成長障害等[6,7]の可能性を十分に考慮した上で行うこと。

8. 過量投与
本剤の過量投与に関する情報は乏しく、本剤に対する解毒剤あるいは過量投与に対する確立された処置方法はないため、用法・用量に定められている投与量を超えて投与しないこと。なお、ブスルファンは透析により除去可能であるとの報告があることから、過量投与の場合透析を考慮すること[8]。

9. 適用上の注意
(1)**投与経路**
直接末梢静脈に投与すると薬液の漏出による局所の組織障害を起こすことがあるので、必ず中心静脈からの点滴静脈内投与とし、皮下、筋肉内には投与しないこと。
(2)**調製時**
1) 本剤は10倍量の生理食塩液又は5%ブドウ糖液に添加し、十分に混和して使用すること。
2) 本剤は室温(約25℃)で用時調製し、調製から8時間以内に投与を終了すること。
3) 調製後に混濁又は結晶が認められる場合は使用しないこと。
4) ポリカーボネート製の容器・シリンジ等及びポリエーテルスルホン製のシリンジフィルターは使用しないこと。
(3)**投与時**
1) 他の注射剤との配合又は混注は行わないこと。
2) 中心静脈カテーテルを留置して投与すること。
3) インラインフィルターを用いて、又は点滴用セットにフィルターを装着して本剤を投与する場合は、ポリエーテルスルホン製、ポリスルホン製又はポリエステル製のフィルターのものを使用すること。
4) ポリカーボネート製の三方活栓や延長チューブ等を使用した場合、そのコネクター部分にひび割れが発生し、血液及び薬液漏れ、空気混入等の可能性があるので注意すること。
(4)**投与速度**
本剤の投与においては希釈調製された全量が1回2時間(A法及びC法)又は1回3時間(B法)で投与されるよう、持続注入ポンプを用いて点滴静脈注射すること(急速静脈内投与を行わないこと)。

10. その他の注意
(1)ブスルファンは、遺伝毒性が報告されている[5]。
(2)添加物である*N,N*-ジメチルアセトアミド(DMA)については、海外臨床試験において、肝トランスアミナーゼの上昇を伴う肝毒性及び幻覚等の神経毒性が報告されている[9]。また、ラットでのDMA 2g/kgの単回腹腔内投与、1g/kgの経皮投与において胎児への催奇形性が認められたとの報告がある[10]。
(3)ブスルファン投与により、動物実験において雄ラットの不妊の誘発、精子形成阻害、また、マウスの卵母細胞の減少が認められたとの報告がある[5]。
(4)ブスルファン投与により、動物実験(マウス、ラット)においてがん原性が示唆されたとの報告がある[11]。また、ブスルファンを投与した患者に二次発がんが認められたとの報告がある[11]。

※※〔薬物動態〕
※
1. 血漿中濃度
(1)**国内臨床試験**
悪性腫瘍患者に、1回0.8mg/kgの用量で6時間毎に1日4回、4日間静脈内投与したときの血漿中未変化体濃度は、投与時間の経過とともに上昇し、投与終了直前でC_{max}が観察され、投与終了後速やかに減少した。



血漿中ブスルファン濃度の推移(平均値±標準偏差)

薬物動態パラメータは以下のとおりであり、反復投与による薬物動態の変動はみられなかった。他の報告においても、同様の薬物動態パラメータの値が示されている[12,13]。

ブスルファンの薬物動態パラメータ(平均値±標準偏差)

投与回数	例数	C_{max} (ng/mL)	$t_{1/2}$ (hr)	AUC*1 (μmol·min/L)	CL/ABW*2 (mL/min/kg)	V_z/ABW (L/kg)
1回目	29	994±123	2.66±0.40	1171±220	2.66±0.44	0.60±0.05
9回目	28*3	1311±192	2.86±0.38	1242±206	2.46±0.37	0.60±0.07

*1　投与1回目は$AUC_{0\infty}$を、投与9回目はAUC_{ss}をそれぞれ示す。
*2　ABWは実体重を示す。
*3　投与9回目のC_{max}については29例である。

(2)**海外臨床試験(小児)**
悪性腫瘍又は非悪性腫瘍患者に、1回0.8～1.2mg/kgの用量で6時間毎に1日4回、4日間静脈内投与したときの血漿中未変化体濃度を用いて算出した薬物動態パラメータは以下のとおりである。反復投与による薬物動態の変動はみられなかった[14]。

ブスルファンの薬物動態パラメータ(平均値±標準偏差)

体重	投与量 (mg/kg)	例数	投与回数	$t_{1/2}$ (hr)	AUC (μmol·min/L)	CL/ABW*1 (mL/min/kg)	V_z/ABW*2 (L/kg)
体重< 9kg	1.0	8	1回目	2.08±0.242	1132±263	3.74±0.734	0.68±0.182
			9回目	2.36±0.357	1270±253	3.30±0.559	0.68±0.182
			13回目	2.35±0.263	1292±375	3.33±0.742	0.68±0.182
9kg≦体重< 16kg	1.2	14	1回目	1.98±0.284	1152±176	4.31±0.693	0.73±0.079
			9回目	2.18±0.300	1269±204	3.92±0.658	0.73±0.079
			13回目	2.19±0.409	1277±248	3.93±0.744	0.73±0.079
16kg≦体重≦ 23kg	1.1	14	1回目	2.27±0.277	1171±177	3.89±0.524	0.76±0.066
			9回目	2.46±0.385	1273±234	3.61±0.597	0.76±0.066
			13回目	2.51±0.426	1301±272	3.56±0.627	0.76±0.066
23kg< 体重≦ 34kg	0.95	6	1回目	2.27±0.246	1110±64	3.42±0.108	0.67±0.069
			9回目	2.52±0.291	1230±97	3.09±0.170	0.67±0.069
			13回目	2.61±0.234	1281±104	2.97±0.201	0.67±0.069
体重> 34kg	0.8	13	1回目	2.67±0.401	1213±178	2.73±0.398	0.62±0.053
			9回目	2.93±0.513	1323±177	2.49±0.298	0.62±0.053
			13回目	2.95±0.508	1338±215	2.49±0.377	0.62±0.053

母集団薬物動態解析で得られた推定値を示した。
*1　ABWは実体重を示す。
*2　母集団薬物動態解析時に時期間変動を考慮していないため、いずれの投与回においても同一の値を示した。

2. 代謝(外国人によるデータ)
ブスルファンは、グルタチオンS-トランスフェラーゼ(GST)によるグルタチオン抱合を第一段階とする代謝あるいは内因性物質との非特異的アルキル化による共有結合生成によって不活化される[15,16]。

※※〔臨床成績〕[12~14]

※●国内及び海外臨床試験(成人)の同種造血幹細胞移植に関する試験成績

本剤の有効性と安全性は、同種及び自家造血幹細胞移植を対象にシクロホスファミドを併用した前治療の国内1試験及び海外2試験において検討された。このうち同種移植に関する試験成績は以下のとおりである。

国内における8例が非血縁ドナーからの移植であったほかは、国内外とも血縁ドナーからの移植であった。HLA適合度は、血清型では全例一致していたが、国内の1例が遺伝子型一座不一致非血縁ドナーからの移植であった。

本剤の有効成分であるブスルファン0.8mg/kgを点滴静注により6時間毎に計16回、移植施行日(day0)のday-7からday-4に4日間連日投与し、その後シクロホスファミド60mg/kgを1日1回、day-3からday-2に2日間連日投与した後(BU/CY2レジメン)、day0に造血幹細胞が輸注された。国内の27例中10例、海外の61例中34例が末梢血幹細胞移植であり、その他の症例は骨髄移植であった。

同種移植における患者背景、主要な有効性に関する臨床試験成績を下表に示す(安全性については「4. 副作用」の項参照のこと)。

1. 患者背景

国内及び海外臨床試験の原疾患

原疾患	国内臨床試験	海外臨床試験
合計(%)	27(100)	61(100)
急性白血病	16(59.3)	26(42.6)
慢性骨髄性白血病	5(18.5)	17(27.9)
悪性リンパ腫	3(11.1)	9(14.8)
骨髄異形成症候群	3(11.1)	9(14.8)

2. 有効性

国内及び海外臨床試験成績

	国内臨床試験	海外臨床試験
骨髄抑制率	100%(27/27例)	100%(61/61例)
生着率	96.3%(26/27例)	98.4%(60/61例)
生着日数*1	14日(9~20日)	13日(9~29日)
100日生存率*2	96.0%	81.5%

*1 造血幹細胞移植後生着までに要した日数の中央値(範囲)
*2 Kaplan-Meier推定

●海外臨床試験(小児)の同種造血幹細胞移植、並びにユーイング肉腫ファミリー腫瘍及び神経芽細胞腫における自家造血幹細胞移植に関する試験成績

本剤の有効性と安全性は、海外で実施した同種及び自家造血幹細胞移植を対象(年齢0~18歳未満)に、本剤の目標AUC値を900~1350μmol・min/Lと設定し、シクロホスファミド又はメルファランを併用した前治療の試験において検討された。

同種移植は、5例が非血縁ドナーからの移植であったほかは、血縁ドナーからの移植であった。HLA適合度は、26例で一致していたが、1例が二座不一致血縁ドナーであり、残る1例は一座不一致非血縁ドナーからの移植であった。

同種移植では、本剤の有効成分であるブスルファン0.8~1.2mg/kg(承認用法・用量と同一の体重別投与量設定)を点滴静注により6時間毎に計16回、移植施行日(day0)のday-9からday-6に4日間連日投与し、その後シクロホスファミド50mg/kgを1日1回、day-5からday-2に4日間連日投与した後(BU/CY4レジメン)、day0に造血幹細胞が輸注された。自家移植では、ブスルファン0.8~1.2mg/kg(承認用法・用量と同一の体重別投与量設定)を点滴静注により6時間毎に計16回、移植施行日(day0)のday-6からday-3に4日間連日投与し、その後メルファラン140mg/m²を1回、day-1に投与した後(BU/L-PAMレジメン)、day0に造血幹細胞が輸注された。同種移植では28例中27例が骨髄移植であり、残る1例は末梢血幹細胞移植であった。自家移植では全例が末梢血幹細胞移植であった。

本試験の患者背景、主要な有効性に関する臨床試験成績を下表に示す(安全性については「4. 副作用」の項参照のこと)。

なお、自家移植27例の観察期間中央値は16.9ヶ月(範囲:5.4~26.5ヶ月)であり、神経芽細胞腫24例での2年再発率*及び無事象生存率*は、それぞれ31%及び50%、ユーイング肉腫ファミリー腫瘍3例での1年再発率*及び無事象生存率*は、0%及び67%であった。

* Kaplan-Meier推定

1. 患者背景

海外臨床試験の原疾患(小児)

原疾患	同種	自家
合計(%)	28(100)	27(100)
急性骨髄性白血病	14(50.0)	−
急性リンパ性白血病	1(3.6)	−
慢性骨髄性白血病	3(10.7)	−
骨髄異形成症候群	1(3.6)	−
鎌状赤血球症	5(17.9)	−
サラセミア	1(3.6)	−
Wiskott-Aldrich症候群	2(7.1)	−
白血球接着不全症	1(3.6)	−
神経芽細胞腫	−	24(88.9)
ユーイング肉腫	−	3(11.1)

2. 有効性

海外臨床試験成績(小児)

	同種移植	自家移植
骨髄抑制率	100%(28/28例)	100%(27/27例)
生着率	100%(28/28例)	100%(27/27例)
生着日数*1	21日(12~47日)	11日(10~15日)
100日生存率*2	100%	100%

*1 造血幹細胞移植後生着までに要した日数の中央値(範囲)
*2 Kaplan-Meier推定

●国内臨床試験(小児)の同種造血幹細胞移植に関する試験成績

本剤の小児に対する有効性と安全性は、国内で実施した成人及び小児に対する同種及び自家造血幹細胞移植を対象に、シクロホスファミドを併用した前治療の試験において検討された。

本試験での本剤の投与量は、成人及び小児ともに0.8mg/kg/回での臨床試験成績ではあるが、18歳未満の小児については3例が検討されている。これらの小児3例の試験成績は以下のとおりであった。

国内臨床試験成績(小児)

原疾患	体重	移植種	骨髄抑制	生着日数*2	生存日数*4
急性骨髄性白血病	43.2kg	同種移植	−3日	13日	50日+
急性骨髄性白血病	17.8kg*1	同種移植	0日	15日	100日+
慢性骨髄性白血病	46.7kg	同種移植	2日	−*3	28日+

*1 当該症例における本剤の投与量は、小児に対する実体重別の承認用法・用量とは異なる。
*2 造血幹細胞移植後生着までに要した日数
*3 移植後28日時点で生着不全と判断された。
*4 最終観察日を記載した。

※※〔薬効薬理〕

1. 作用・効果

(1)骨髄抑制作用

マウスにおいて好中球、リンパ球を含む血球数[16]及び骨髄中造血細胞数[17, 18]の減少を認め、イヌにおいても血球数の減少を認めた。

(2)抗腫瘍作用

*in vitro*において、種々のヒト腫瘍細胞株に対して増殖抑制を認めた[19~22]。

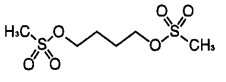
*in vivo*において、急性リンパ性白血病細胞移植マウスに10及び20mg/kgを3日間腹腔内投与したところ腫瘍増殖を抑制し、対照群と比較してそれぞれ25%、及び36%の平均生存期間を延長させた[23]。

2. 作用機序

細胞内に取り込まれた後にDNA鎖間又はDNA鎖内架橋形成などを介して細胞増殖を抑制し、骨髄抑制作用や抗腫瘍作用を示す。

※〔有効成分に関する理化学的知見〕

一般名:ブスルファン〔Busulfan(JAN)〕
化学名:Tetramethylenedimethanesulfonate
構造式:



分子式:$C_6H_{14}O_6S_2$
分子量:246.30
融　点:115~118℃
性　状:白色の結晶性の粉末である。ジエチルエーテルに溶けにくく、エタノール(95)に極めて溶けにくく、水にほとんど溶けない。

〔取扱い上の注意〕

1. 本剤は調製後、できるだけ速やかに使用すること。
2. 本剤は細胞毒性を有するため、調製時には手袋、マスク、防護メガネ等を着用し、十分に注意すること。皮膚、粘膜、眼等に本溶液が付着した場合には、直ちに多量の流水でよく洗うこと。

〔承認条件〕

国内での治験症例が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

〔包　装〕

ブスルフェクス点滴静注用60mg：1バイアル

※※〔主要文献及び文献請求先〕

主要文献

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文献請求先

主要文献に記載の社内資料につきましても下記にご請求ください。

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シオノギ製薬

【警告】

1. 本剤とペントスタチンを併用しないこと。[外国においてシクロホスファミドとペントスタチンとの併用により，心毒性が発現し死亡した症例が報告されている[1)]。]
2. 本剤を含むがん化学療法は，緊急時に十分対応できる医療施設において，がん化学療法に十分な知識・経験を持つ医師のもとで，本療法が適切と判断される症例についてのみ実施すること。適応患者の選択にあたっては，各併用薬剤の添付文書を参照して十分注意すること。また，治療開始に先立ち，患者又はその家族に有効性及び危険性を十分説明し，同意を得てから投与すること。
3. 造血幹細胞移植の前治療に本剤を投与する場合には，下記の点に注意すること。
(1) 造血幹細胞移植に十分な知識と経験を有する医師のもとで行うこと。
(2) 強い骨髄抑制により致命的な感染症等が発現するおそれがあるので，下記につき十分注意すること。
 1) 重症感染症を合併している患者には投与しないこと。
 2) 本剤投与後，患者の観察を十分に行い，感染症予防のための処置（抗感染症薬の投与等）を行うこと。
(3) 「禁忌」，「慎重投与」，「重要な基本的注意」の項を参照し，慎重に投与すること。
4. 治療抵抗性のリウマチ性疾患に本剤を投与する場合には，緊急時に十分対応できる医療施設において，本剤についての十分な知識と治療抵抗性のリウマチ性疾患治療の経験を持つ医師のもとで行うこと。

【禁忌（次の患者には投与しないこと）】

1. ペントスタチンを投与中の患者[1)]　[「相互作用」の項参照]
2. 本剤の成分に対し重篤な過敏症の既往歴のある患者
3. 重症感染症を合併している患者[特に造血幹細胞移植の前治療に本剤を投与する場合は，感染症が増悪し致命的となることがある。]

【組成・性状】

1. 組成

販売名	注射用エンドキサン100mg	注射用エンドキサン500mg
成分・含量（1瓶中）	シクロホスファミド水和物106.9mg（無水物として100mgに相当）	シクロホスファミド水和物534.5mg（無水物として500mgに相当）

2. 性状

販売名	注射用エンドキサン100mg	注射用エンドキサン500mg
性状・剤形	白色の結晶又は結晶性の粉末である。水にやや溶けやすい。（注射剤）	白色の結晶又は結晶性の粉末である。水にやや溶けやすい。（注射剤）
pH	4.0～6.0 20mg（無水物換算）/mL生理食塩液	4.0～6.0 20mg（無水物換算）/mL生理食塩液
浸透圧比〔生理食塩液に対する比〕	1.1～1.4 20mg（無水物換算）/mL生理食塩液	1.1～1.4 20mg（無水物換算）/mL生理食塩液

注1) 注意－医師等の処方箋により使用すること

【効能・効果】＊＊【用法・用量】＊＊

効能・効果	用法・用量
1. 下記疾患の自覚的並びに他覚的症状の緩解 多発性骨髄腫，悪性リンパ腫，肺癌，乳癌，急性白血病，真性多血症，子宮頸癌，子宮体癌，卵巣癌，神経腫瘍（神経芽腫，網膜芽腫），骨腫瘍 ただし，下記の疾患については，他の抗悪性腫瘍剤と併用することが必要である。 慢性リンパ性白血病，慢性骨髄性白血病，咽頭癌，胃癌，膵癌，肝癌，結腸癌，睾丸腫瘍，絨毛性疾患（絨毛癌，破壊胞状奇胎，胞状奇胎），横紋筋肉腫，悪性黒色腫	(1) 単独で使用する場合 通常，成人にはシクロホスファミド（無水物換算）として1日1回100mgを連日静脈内に注射し，患者が耐えられる場合は1日量を200mgに増量する。 総量3000～8000mgを投与するが，効果が認められたときは，できる限り長期間持続する。白血球数が減少してきた場合は，2～3日おきに投与し，正常の1/2以下に減少したときは，一時休薬し，回復を待って再び継続投与する。 間欠的には，通常成人300～500mgを週1～2回静脈内に注射する。 必要に応じて筋肉内，胸腔内，腹腔内又は腫瘍内に注射又は注入する。 また，病巣部を灌流する主幹動脈内に1日量200～1000mgを急速に，あるいは，持続的に点滴注入するか，体外循環を利用して1回1000～2000mgを局所灌流により投与してもよい。 なお，年齢，症状により適宜増減する。
	(2) 他の抗悪性腫瘍剤と併用する場合 単独で使用する場合に準じ，適宜減量する。 悪性リンパ腫に用いる場合，通常，成人にはシクロホスファミド（無水物換算）として1日1回750mg/m²（体表面積）を間欠的に静脈内投与する。 なお，年齢，症状により適宜増減する。

注射用エンドキサン（2）

効能・効果	用法・用量
2. 以下の悪性腫瘍に対する他の抗悪性腫瘍剤との併用療法 乳癌（手術可能例における術前，あるいは術後化学療法）	(1) ドキソルビシン塩酸塩との併用において，標準的なシクロホスファミドの投与量及び投与方法は，シクロホスファミド（無水物換算）として1日1回600mg/m²（体表面積）を静脈内投与後，20日間休薬する。これを1クールとし，4クール繰り返す。 なお，年齢，症状により適宜減量する。
	(2) エピルビシン塩酸塩との併用において，標準的なシクロホスファミドの投与量及び投与方法は，シクロホスファミド（無水物換算）として1日1回600mg/m²（体表面積）を静脈内投与後，20日間休薬する。これを1クールとし，4～6クール繰り返す。 なお，年齢，症状により適宜減量する。
	(3) エピルビシン塩酸塩，フルオロウラシルとの併用において，標準的なシクロホスファミドの投与量及び投与方法は，シクロホスファミド（無水物換算）として1日1回500mg/m²（体表面積）を静脈内投与後，20日間休薬する。これを1クールとし，4～6クール繰り返す。 なお，年齢，症状により適宜減量する。
3. 褐色細胞腫	ビンクリスチン硫酸塩，ダカルバジンとの併用において，通常，成人にはシクロホスファミド（無水物換算）として1日1回750mg/m²（体表面積）を静脈内投与後，少なくとも20日間休薬する。これを1クールとし，投与を繰り返す。 なお，患者の状態により適宜減量する。
4. 下記疾患における造血幹細胞移植の前治療 急性白血病，慢性骨髄性白血病，骨髄異形成症候群，重症再生不良性貧血，悪性リンパ腫，遺伝性疾患（免疫不全，先天性代謝障害及び先天性血液疾患：Fanconi貧血，Wiskott-Aldrich症候群，Hunter病等）	(1) 急性白血病，慢性骨髄性白血病，骨髄異形成症候群の場合 通常，成人にはシクロホスファミド（無水物換算）として，1日1回60mg/kgを2～3時間かけて点滴静注し，連日2日間投与する。
	(2) 重症再生不良性貧血の場合 通常，成人にはシクロホスファミド（無水物換算）として，1日1回50mg/kgを2～3時間かけて点滴静注し，連日4日間投与する。
	(3) 悪性リンパ腫の場合 通常，成人にはシクロホスファミド（無水物換算）として，1日1回50mg/kgを2～3時間かけて点滴静注し，連日4日間投与する。 患者の状態，併用する薬剤により適宜減量すること。
	(4) 遺伝性疾患（免疫不全，先天性代謝障害及び先天性血液疾患：Wiskott-Aldrich症候群，Hunter病等）の場合 通常，シクロホスファミド（無水物換算）として，1日1回50mg/kgを2～3時間かけて点滴静注し，連日4日間又は1日1回60mg/kgを2～3時間かけて点滴静注し，連日2日間投与するが，疾患及び患者の状態により適宜減量する。 Fanconi貧血に投与する場合には，細胞の脆弱性により，移植関連毒性の程度が高くなるとの報告があるので，総投与量40mg/kg（5～10mg/kgを4日間）を超えないこと。
5. 治療抵抗性の下記リウマチ性疾患 全身性エリテマトーデス，全身性血管炎（顕微鏡的多発血管炎，ヴェゲナ肉芽腫症，結節性多発動脈炎，Churg-Strauss症候群，大動脈炎症候群等），多発性筋炎/皮膚筋炎，強皮症，混合性結合組織病，及び血管炎を伴う難治性リウマチ性疾患	(1) 成人 通常，シクロホスファミド（無水物換算）として1日1回500～1000mg/m²（体表面積）を静脈内に注射する。原則として投与間隔を4週間とする。 なお，年齢，症状により適宜増減する。
	(2) 小児 通常，シクロホスファミド（無水物換算）として1日1回500mg/m²（体表面積）を静脈内に注射する。原則として投与間隔を4週間とする。 なお，年齢，症状により適宜増減する。

＜効能・効果に関連する使用上の注意＞

遺伝性疾患に対する造血幹細胞移植の前治療に用いる場合には，それぞれの疾患に対する治療の現状と造血幹細胞移植を実施するリスク・ベネフィットを考慮した上で本剤を適応すること。

＜用法・用量に関連する使用上の注意＞**

1. 造血幹細胞移植の前治療に本剤を投与する場合には，下記の点に注意すること。
(1) 肥満患者には，投与量が過多にならないように，標準体重から換算した投与量を考慮すること。
(2) 投与終了後24時間は150mL/時間以上の尿量を保つように，1日3L以上の輸液を投与するとともにメスナを併用すること。患者の年齢及び状態を考慮し，輸液の量を調節すること。
2. 褐色細胞腫患者において，本剤を含む化学療法施行後に高血圧クリーゼを含む血圧変動が報告されていることから，本剤を含む化学療法開始前にα遮断薬等を投与すること。
3. 悪性リンパ腫に用いる場合，本剤の投与量，投与スケジュー

ル等については，関連学会のガイドライン等，最新の情報を参考に投与すること。

4. **注射液の調製法**

シクロホスファミド（無水物換算）100mg あたり 5mL の生理食塩液，注射用水等を加えて溶解する。

静脈内等へのワンショット投与の場合には，溶液が低張となるため注射用水を使用しないこと。

点滴静注の場合には，溶解後適当な補液で希釈すること。

【使用上の注意】*

1. **慎重投与（次の患者には慎重に投与すること）**

(1) 肝障害のある患者［肝障害が増悪するおそれがある。］

(2) 腎障害のある患者［腎障害が増悪するおそれがある。］

(3) 骨髄抑制のある患者［骨髄抑制が増強するおそれがある。］

(4) 感染症を合併している患者［骨髄抑制作用により，感染症が増悪するおそれがある。］

(5) 水痘患者［致命的な全身障害があらわれることがある。］

(6) 高齢者［「高齢者への投与」の項参照］

(7) 造血幹細胞移植の前治療に本剤を投与する場合は，次の患者にも慎重に投与すること。

1) 膀胱に障害のある患者［膀胱の障害が悪化するおそれがある。］

2) Fanconi 貧血の患者［細胞の脆弱性が報告されており，副作用が強く発現するおそれがある。］

2. **重要な基本的注意**

(1) **骨髄抑制，出血性膀胱炎等**の重篤な副作用が起こることがあるので，頻回に臨床検査（血液検査，尿検査，肝機能・腎機能検査等）を行うなど，患者の状態を十分に観察すること。異常が認められた場合には，減量，休薬等の適切な処置を行うこと。出血性膀胱炎の防止のため尿量の増加を図ること。また，使用が長期間にわたると副作用が強くあらわれ，遷延性に推移することがあるので，投与は慎重に行うこと。

本剤を造血幹細胞移植の前治療に投与する場合には，出血性膀胱炎等の泌尿器系障害の発現頻度が高くなるとの報告[2]があるため，頻回に臨床検査（尿検査等）を行うこと。また，泌尿器系障害の発現抑制のため，投与終了後 24 時間は 150mL/時間以上の尿量を保つように，1 日 3L 以上の輸液を投与するとともにメスナを併用すること。

(2) **感染症，出血傾向**の発現又は増悪に十分注意すること。

(3) 本剤を造血幹細胞移植の前治療に使用する場合には，**肝中心静脈閉塞症**（hepatic veno-occlusive disease：VOD）の発現に注意すること。初期の症状として体重増加，肝腫及び肝の圧痛を有するとの報告があるので，体重，肝腫等に注意すること。（VOD の適切な治療法は確立されていない）

(4) 小児等に投与する場合には，副作用の発現に特に注意し，慎重に投与すること。

(5) 小児及び生殖可能な年齢の患者に投与する必要がある場合には，**性腺に対する影響**を考慮すること。なお，シクロホスファミドの総投与量の増加により，男女とも性腺障害のリスクが増加するとの報告がある[3]。

(6) 二次性悪性腫瘍（急性白血病，骨髄異形成症候群，悪性リンパ腫，膀胱腫瘍，腎盂・尿管腫瘍等）が発生したとの報告があるため，本剤の投与終了後も長期間経過を観察するなど十分注意すること。なお，シクロホスファミドの総投与量の増加により，発癌のリスクが増加するとの報告がある[3]。

(7) 褐色細胞腫に本剤を使用する際には，関連文献（「医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書：シクロホスファミド水和物（褐色細胞腫（傍神経節細胞腫を含む））」等）を熟読すること。

3. **相互作用**

本剤は，主に肝代謝酵素 CYP2B6 で代謝され，活性化される。また，CYP2C8，2C9，3A4，2A6 も本剤の代謝に関与していることが報告されている。

(1) **併用禁忌（併用しないこと）**

薬剤名等	臨床症状・措置方法	機序・危険因子
ベントスタチンコホリン	造血幹細胞移植の患者で，本剤投与中にベントスタチンを単回投与したところ，錯乱，呼吸困難，低血圧，肺水腫等が認められ，心毒性により死亡したとの報告がある。また，動物試験（マウス）においてベントスタチン（臨床用量の 10 倍相当量）とシクロホスファミド（LD_{50} 前後）又はその類縁薬であるイホスファミド（LD_{50} 前後）を同時期に単回投与したとき，それぞれを単独投与したときに比べて死亡率の増加が認められた[1]。	明らかな機序は不明である。本剤は用量依存性の心毒性があり，ベントスタチンは心筋細胞に影響を及ぼす ATP の代謝を阻害する。両剤の併用により心毒性が増強すると考えられている[1]。

(2) **併用注意（併用に注意すること）**

薬剤名等	臨床症状・措置方法	機序・危険因子
他の抗悪性腫瘍剤 アロプリノール 放射線照射	骨髄抑制等の副作用が増強することがあるので，異常が認められた場合には，減量，休薬等の適切な処置を行うこと。	共に骨髄抑制作用を有する。
フェノバルビタール	本剤の作用が増強することがある。	フェノバルビタールの酵素誘導により本剤の活性型への変換が促進される。
副腎皮質ホルモン クロラムフェニコール	本剤の作用が減弱することがある。	副腎皮質ホルモン，クロラムフェニコールは肝における本剤の代謝を競合的に阻害し，活性化を抑制する。
インスリン	血糖降下作用が増強されることがある。	本剤がインスリン抗体の生成を阻害するため，遊離のインスリン量が多くなり，血糖降下作用が増強される。
オキシトシン	オキシトシンの作用が増強されることがある。	機序は不明
バソプレシン	バソプレシンの作用が減弱されることがある。	本剤がバソプレシンの排泄を増加させる。
チオテパ	本剤の作用が減弱されるおそれがある。	本剤の活性化を抑制するとの報告がある。
アントラサイクリン系薬剤 ドキソルビシン塩酸塩，エピルビシン塩酸塩等	心筋障害が増強されるおそれがある。また，これらの薬剤との併用療法終了後に遅発性心毒性が発現したとの報告があるため，治療終了後も長期間経過を観察するなど十分注意すること。	明らかな機序は不明であるが，共に心筋障害を有する。
脱分極性筋弛緩剤 スキサメトニウム等	脱分極性筋弛緩剤の作用が増強され，遷延性無呼吸を起こすおそれがある。	本剤がコリンエステラーゼによる脱分極性筋弛緩剤の分解を阻害すると考えられている。

4. **副作用**

再評価結果時の安全性評価対象例 5021 例（経口投与を含む）中，主なものは，白血球減少 1903 例（37.90%），悪心・嘔吐 1041 例（20.73%），脱毛 1221 例（24.32%）等であった。

また，急性白血病等の造血幹細胞移植の前治療における本剤の第 2 相臨床試験の安全性評価対象例 67 例中，主なものは悪心・嘔吐 61 例（91%），下痢，口内炎各 42 例（各 63%），脱毛 38 例（57%）であった。

(1) **重大な副作用**

（副作用の発現頻度は再評価結果の成績による）

造血幹細胞移植の前治療に本剤を投与する場合には，副作用の発現頻度が高くなり，重篤性が強くなるおそれがあるので注意すること。

1) **ショック，アナフィラキシー（頻度不明）**：ショック，アナフィラキシーがあらわれることがあるので，観察を十分に行い，

注射用エンドキサン (4)

血圧低下，呼吸困難，喘鳴，蕁麻疹，不快感等があらわれた場合には投与を中止し，適切な処置を行うこと。

2) **骨髄抑制（頻度不明）**：汎血球減少，貧血，白血球減少，血小板減少，出血があらわれることがあるので，本剤投与期間中には末梢血液の観察を十分に行い，異常が認められた場合には，投与間隔の延長，減量，休薬等の適切な処置を行うこと。

3) **出血性膀胱炎，排尿障害（頻度不明※）**：出血性膀胱炎，排尿障害があらわれることがあるので，観察を十分に行い，異常が認められた場合には，減量，休薬等の適切な処置を行うこと。
本剤を造血幹細胞移植の前治療に投与する場合には，出血性膀胱炎等の泌尿器系障害の発現頻度が高くなるとの報告があるため，頻回に臨床検査（尿検査等）を行うこと。また，泌尿器系障害の発現抑制のため，投与終了後24時間は150mL/時間以上の尿量を保つように，1日3L以上の輸液を投与するとともにメスナを併用すること。
〔※：造血幹細胞移植の前治療に，メスナ未使用で本剤を投与した場合，出血性膀胱炎の発現頻度が35%（肉眼的血尿）であったとの報告がある[2]。〕[「重要な基本的注意」の項参照]

4) **イレウス，胃腸出血（5%未満）**：イレウス，胃腸出血があらわれることがあるので，観察を十分に行い，異常が認められた場合には，投与を中止するなど適切な処置を行うこと。

5) **間質性肺炎，肺線維症（頻度不明）**：間質性肺炎，肺線維症があらわれることがあるので，観察を十分に行い，異常が認められた場合には，投与を中止するなど適切な処置を行うこと。

6) **心筋障害，心不全（5%未満），心タンポナーデ，心膜炎（頻度不明）**：心筋障害，心不全，心タンポナーデ，心膜炎，心嚢液貯留があらわれることがあるので，観察を十分に行い，異常が認められた場合には，投与を中止するなど適切な処置を行うこと。特に本剤を高用量で投与する場合（造血幹細胞移植の前治療等）は，十分に注意すること。

7) **抗利尿ホルモン不適合分泌症候群（SIADH）（頻度不明）**：低ナトリウム血症，低浸透圧血症，尿中ナトリウム排泄量の増加，高張尿，痙攣，意識障害等を伴う抗利尿ホルモン不適合分泌症候群（SIADH）があらわれることがあるので，このような場合には投与を中止し，水分摂取の制限等適切な処置を行うこと。

8) **中毒性表皮壊死融解症（Toxic Epidermal Necrolysis：TEN），皮膚粘膜眼症候群（Stevens-Johnson症候群）（頻度不明）**：中毒性表皮壊死融解症，皮膚粘膜眼症候群があらわれることがあるので，観察を十分に行い，異常が認められた場合には投与を中止し，適切な処置を行うこと。

9) **肝機能障害，黄疸（頻度不明）**：肝機能障害，黄疸があらわれることがあるので，肝機能検査を行うなど観察を十分に行い，異常が認められた場合には，投与を中止するなど適切な処置を行うこと。

10) **急性腎不全（頻度不明）**：急性腎不全等の重篤な腎障害があらわれることがあるので，腎機能検査を行うなど観察を十分に行い，異常が認められた場合には，投与を中止するなど適切な処置を行うこと。

11) **横紋筋融解症（頻度不明）**：筋肉痛，脱力感，CK（CPK）上昇，血中及び尿中ミオグロビン上昇を特徴とする横紋筋融解症があらわれることがあるので，観察を十分に行い，異常が認められた場合には，投与を中止し，適切な処置を行うこと。

(2) その他の副作用

1) 再評価結果及び自発報告によるその他の副作用

種類＼頻度	5%以上	5%未満	頻度不明
肝臓		肝機能異常，黄疸	コリンエステラーゼ低下
腎臓		蛋白尿，浮腫	
消化器	悪心・嘔吐	口渇，潰瘍性口内炎，腹痛，便秘，下痢	食欲不振，味覚異常，胸やけ，おくび，腹部膨満感
過敏症		発疹	
皮膚	脱毛	皮膚炎，色素沈着，爪の変形・変色	
精神神経系		頭痛，眩暈，不眠，運動失調	倦怠感
呼吸器			肺水腫，鼻道刺激感
循環器		心電図異常，心悸亢進，低血圧	血圧上昇
内分泌系		副腎皮質機能不全	甲状腺機能亢進
性腺		無月経	無精子症，卵巣機能不全
その他		発熱，注射時熱感，局所痛，CK（CPK）上昇	創傷の治癒遅延，高血糖，低ナトリウム血症

2) 造血幹細胞移植の前治療に対する第2相臨床試験における安全性評価対象例の集計

種類＼頻度	5%以上	5%未満
血液		血清FDP増加，AT-3減少，播種性血管内凝固症候群
肝臓	AST（GOT）上昇，ALT（GPT）上昇，ビリルビン値上昇，Al-P上昇，LDH上昇	
腎臓		クレアチニン上昇，BUN上昇
消化器	悪心・嘔吐，下痢，口内炎，便秘	胃痛
皮膚	脱毛	そう痒，色素沈着
精神神経系		頭痛
循環器		心電図異常，不整脈
その他	発熱，感染，血清ナトリウム低下	咽頭炎，咽頭痛，疼痛，ウイルス性脳炎，血清カリウム上昇，血清クロール低下，血清総蛋白減少，血清マグネシウム低下

5. 高齢者への投与

高齢者では，生理機能が低下していることが多く，副作用があらわれやすいので，用量並びに投与間隔に留意すること。

6. 妊婦，産婦，授乳婦等への投与

(1) 妊婦又は妊娠している可能性のある婦人には投与しないことが望ましい。また，妊娠する可能性のある婦人及びパートナーが妊娠する可能性のある男性には，適切な避妊をするよう指導すること。妊娠中に本剤を使用するか，本剤を使用中に妊娠した場合は，胎児に異常が生じる可能性があることを患者に説明すること。[催奇形性を疑う症例報告があり，動物試験では，本剤2.5mg/kgを投与した雌ラットで胚・胎児の死亡及び催奇形作用が報告されている[4]。本剤5.1mg/kgを投与した雄ラットを，本剤を投与しない雌ラットと交配させたところ，胎児の死亡増加及び奇形を認めたとの報告がある[5]。]

(2) 授乳婦に投与する場合には，授乳を中止させること。[乳汁中に分泌されることが報告されている。]

7. 小児等への投与

(1) 自覚的並びに他覚的症状の緩解，乳癌及び褐色細胞腫に対する他の抗悪性腫瘍剤との併用療法，造血幹細胞移植の前治療の場合：低出生体重児，新生児，乳児，幼児又は小児に対する安全性は確立していない。[「重要な基本的注意」の項参照]

(2) 治療抵抗性のリウマチ性疾患の場合：低出生体重児，新生児，乳児又は幼児に対する安全性は確立していない。[低出生体重児，新生児に対しては使用経験がない。乳児，幼児に対しては使用経験が少ない。(「重要な基本的注意」の項参照)]

8. 適用上の注意

(1) **調製方法**：本剤は溶解後速やかに使用すること。

(2) **筋肉内注射時**：筋肉内注射にあたっては，下記の点に注意すること。

1) 筋肉内投与はやむを得ない場合にのみ必要最小限に行うこと。同一部位への反復注射は行わないこと。特に低出生体重児，新生児，乳児，幼児又は小児には注意すること。

2) 神経走行部位を避けること。

3) 注射針を刺入したとき，激痛を訴えたり血液の逆流をみた場合は直ちに針を抜き，部位をかえて注射すること。
4) 注射部位に疼痛，硬結をみることがある。

【薬物動態】

1. 血漿中濃度

各種の悪性腫瘍患者8例に注射用シクロホスファミドを静脈内投与したときの血漿中の活性代謝物（4-ヒドロキシシクロホスファミド＋アルドホスファミド）の薬物動態パラメータを表1に示す[6]。（外国人によるデータ）

表1 活性代謝物の薬物動態パラメータ

投与量[注1] (mg/kg)	n	Cmax (μg/mL)	AUC_{0-12} (μg・hr/mL)
20	8	1.31±0.73	4.66±1.20

注1：活性代謝物測定のために承認外の高用量を投与している。
（測定法：蛍光法）（mean±S.D.）

本剤を造血幹細胞移植の前治療に使用した際のシクロホスファミドの薬物動態パラメータを表2に示す。（外国人によるデータ）

表2 造血幹細胞移植の前治療時におけるシクロホスファミドの薬物動態パラメータ

半減期（hr）		P値	文献
Day1	Day2		
7.1	5.5	p<0.0005	7)
4.7±1.3	2.8±0.4	p<0.02	8)
8.7±4.6	3.6±0.9	p=0.00000	9)
6.77±1.27	4.51±0.99	p=0.00001	10)

（mean±S.D.）

2. 分布

(1) 分布容積：0.763±0.161 L/kg（mean±S.D.）[11]（外国人によるデータ）

(2) （参考）

マウスに ^{14}C-標識シクロホスファミド500mg/kgを腹腔内投与又は皮下投与した際の組織内濃度は，血液，肝では投与後1時間で最高濃度を示し，腸を除く他の組織では，2時間まで増加し，その後減少した。腸では4時間で最高濃度を示した[12]。

3. 代謝

(1) 本剤は，主に肝代謝酵素CYP2B6で代謝され，活性化される。また，CYP2C8，2C9，3A4，2A6も本剤の代謝に関与していることが報告されている。（*in vitro*）[13]

(2) 代謝物[14]：4-ヒドロキシシクロホスファミド※，アルドホスファミド※，ホスファミドマスタード※，アクロレイン，4-ケトシクロホスファミド，カルボキシホスファミド
（※：活性代謝物）

4. 排泄

（外国人によるデータ）

(1) 各種の悪性腫瘍患者26例に，^{14}C-標識シクロホスファミド6.8～80mg/kg※を静脈内投与した場合，尿中には投与量の約62％が2日以内に，約68％が4日以内に排泄された。また，糞便中には投与量の約1.8％が4日以内に排泄され，呼気中には投与量の約0.9～1.4％が4日以内に排泄された[15]。（※：一部承認外の高用量を含む。）

(2) 大部分は不活性代謝物として尿中に排泄され[14]，活性代謝物の尿中排泄率は12時間で投与量の約1％[6]，未変化体の尿中排泄率は24時間で投与量の約10％であった[16]。

5. その他

血漿蛋白結合率：シクロホスファミド12～24％[14]（外国人によるデータ）

【臨床成績】

1. 自覚的並びに他覚的症状の緩解

再評価結果における自覚的並びに他覚的症状の緩解による有効性評価対象例（本剤の単独投与例）4976例の疾患別有効率は，次のとおりであった。

表3 臨床成績

疾患名	有効例数/有効性評価対象例数	有効率（%）	疾患名	有効例数/有効性評価対象例数	有効率（%）
多発性骨髄腫	159/362	43.9	慢性白血病	92/191	48.2
悪性リンパ腫	616/1060	58.1	咽頭癌	17/28	60.7
肺癌	152/537	28.3	胃癌	57/270	21.1
乳癌	364/1005	36.2	膵癌	5/21	23.8
急性白血病	134/382	35.1	肝癌	13/33	39.4
真性多血症	2/3	－	結腸癌	31/132	23.5
子宮癌	63/304	20.7	睾丸腫瘍	17/27	63.0
卵巣癌	166/358	46.4	絨毛性疾患	25/39	64.1
神経腫瘍	42/84	50.0	横紋筋肉腫	22/34	64.7
骨腫瘍	28/61	45.9	悪性黒色腫	11/45	24.4

2. 造血幹細胞移植の前治療

(1) 急性白血病，慢性骨髄性白血病，骨髄異形成症候群，再生不良性貧血の有効性評価対象66例の患者に対して，他の前治療の併用下で，本剤1日50～60mg/kgを2～4日点滴静注し，その後造血幹細胞移植を実施し，前治療薬剤の評価を実施した。

(2) 本剤の骨髄抑制効果ありは98.5％（65例/66例），移植骨髄生着あり97.0％（64例/66例），前治療の総合効果は95.5％（63例/66例）で，すぐれた有効性を示した。

(3) 本剤は白血球数を速やかに減少（300/mm^3未満，平均7.5日）させ，その後白血球数1000/mm^3以上に比較的早く回復（移植後平均16.5日）させることから，造血幹細胞移植時の前治療の条件に合致するものと考えられた。

【薬効薬理】

1. 薬理作用

抗腫瘍効果

(1) 動物移植性腫瘍に対する効果（*in vivo*）

マウスのEhrlich癌，Bashford癌，ラットの吉田肉腫，Walker癌，Jensen肉腫等に対して明らかな腫瘍増殖抑制効果を示し，マウスL1210白血病，ラット腹水肝癌AH13等のほか多くの動物移植性腫瘍に対して延命効果を認めている[17～20]。

(2) 細胞学的効果（*in vitro*）

ラット吉田肉腫の試験において，短時間内に分裂像の減少，異常分裂像がみられ，細胞の膨化，核の崩壊，細胞質の融解を認めた[21]。

2. 作用機序

シクロホスファミドは生体内で活性化された後，腫瘍細胞のDNA合成を阻害し，抗腫瘍作用をあらわすことが認められている。

(1) マウスEhrlich癌（腹水型）に75mg/kgを腹腔内投与し，腫瘍細胞の核酸合成に及ぼす影響をみたところ，DNA及びRNAの合成を共に抑制したがDNAの方をより著明に抑制した[22]。

(2) マウスEhrlich癌（腹水型）に30，60，120mg/kgを腹腔内に投与した場合，いずれの投与量においても，腫瘍細胞分裂周期のG_2期（分裂前期）に作用し，M期（分裂期）への移行を遅らせ，その結果として細胞の増殖を抑制した。
なお，120mg/kg投与群においてはS期（DNA合成期）にも作用した[23]。

【有効成分に関する理化学的知見】

一般的名称：シクロホスファミド水和物（JAN）［日局］
Cyclophosphamide Hydrate

化学名：*N*,*N*-Bis(2-chloroethyl)-3,4,5,6-tetrahydro-2*H*-1,3,2-

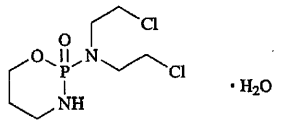
注射用エンドキサン（6）

oxazaphosphorin-2-amine 2-oxide monohydrate

分子式：$C_7H_{15}Cl_2N_2O_2P \cdot H_2O$

分子量：279.10

化学構造式：



性状：白色の結晶又は結晶性の粉末で，においはない。
酢酸（100）に極めて溶けやすく，エタノール（95），無水酢酸又はクロロホルムに溶けやすく，水又はジエチルエーテルにやや溶けやすい。

融点：45～53℃

分配係数：4.27［1-オクタノール/水］

【包装】

注射用エンドキサン 100mg：10瓶

注射用エンドキサン 500mg：1瓶

【主要文献】*

〔文献請求番号〕

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【文献請求先】

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アルケラン®静注用50mg
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注射用メルファラン

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日本標準商品分類番号
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薬価収載	2001年6月
販売開始	2001年6月
国際誕生	1963年9月

【警　　告】
(1) 本剤の投与は、緊急時に十分措置できる医療施設及び造血幹細胞移植に十分な知識と経験をもつ医師のもとで、本剤の投与が適切と判断される症例についてのみ行うこと。
(2) 本剤の使用にあたっては、患者又はそれに代わる適切な者に有効性及び危険性を十分に説明し、同意を得てから投与を開始すること。
(3) 本剤は強い骨髄抑制作用を有する薬剤であり、本剤を前処置剤として用いた造血幹細胞移植の施行後、骨髄抑制作用の結果、感染症を発現し死亡した例が認められている。
本剤投与後は重度の骨髄抑制状態となり、その結果致命的な感染症及び出血等を引き起こすことがあるので、下記につき十分注意すること。
1) 重症感染症を合併している患者には投与しないこと。
2) 本剤の投与後は患者の状態を十分に観察し、致命的な感染症の発現を抑制するため、感染症予防のための処置(抗感染症薬の投与等)を行い、必要に応じ無菌管理を行うこと。
3) 本剤の投与後は輸血及び血液造血因子の投与等適切な支持療法を行うこと。
(4) 本剤を前処置剤として用いた造血幹細胞移植の施行にあたっては、**「禁忌」**、**「慎重投与」**、**「重要な基本的注意」**の項を参照し、慎重に患者を選択すること。
本剤の使用にあたっては製品添付文書を熟読のこと。

【禁　　忌】(次の患者には投与しないこと)
(1) 重症感染症を合併している患者[感染症が増悪し致命的となることがある。]
(2) 本剤の成分に対し過敏症の既往歴のある患者

【組成・性状】

		1バイアル中の含量等
成分	日局メルファラン	50mg
添加物	ポビドンK12	20mg
	塩酸(pH調節剤)	
専用溶解液 添加物	プロピレングリコール	6 mL
	エタノール	0.52mL
	クエン酸ナトリウム水和物	
性状	白色～微黄白色の凍結乾燥した塊状になった粉末の注射剤	
pH(専用溶解液10mLに溶解した時)	6.0～7.0	
溶状(専用溶解液10mLに溶解した時)	無色～微黄色澄明	

【効能・効果】
下記疾患における造血幹細胞移植時の前処置
白血病、悪性リンパ腫、多発性骨髄腫、小児固形腫瘍

【用法・用量】
造血幹細胞移植時の前処置として下記のとおり静脈内投与する。
ただし、移植は本剤の投与終了から24時間以上あけて行うこととする。

成人(白血病、悪性リンパ腫、多発性骨髄腫)：
メルファランとして1日1回60mg/m²を3日間投与(メルファラン3日間総量180mg/m²)する。
多発性骨髄腫に対してはメルファランとして1日1回100mg/m²を2日間投与(メルファラン2日間総量200mg/m²)も可とする。
小児(白血病、小児固形腫瘍)：
メルファランとして1日1回70mg/m²を3日間投与(メルファラン3日間総量210mg/m²)する。

なお、メルファラン総量及び1日投与量は、患者の状態、併用する薬剤、全身放射線照射併用により適宜減量する。

用法・用量に関連する使用上の注意
(1) 肥満患者では投与量が過多にならないように、標準体重に基づいた体表面積から換算した投与量を考慮すること。
(2) 腎障害のある患者では本剤のクリアランスが低下するおそれがあり、本剤による副作用が増強するおそれがあるので、投与量が過多にならないよう考慮すること。なお、減量の目安は確立されていない(**「薬物動態」**の項参照)。
(3) 本剤の投与前日から投与終了後24時間は、水分補給及び利尿剤の投与を行い十分な尿量を確保すること。なお、補液量は2,000mL/日以上、確保すべき尿量は100mL/h以上を目安とし、患者の年齢及び状態を勘案し調整すること。

<注射液の調製法及び投与法>
メルファラン50mg(1バイアル)に専用溶解液10mLを加え激しく振盪して完全に溶解し、希釈する場合には100mL以上の日局生理食塩液を用いること。なお、本剤は室温(約25℃)で用時調製し、溶解後又は希釈後に混濁又は結晶が認められる場合には使用しないこと。
溶解後は、安定性が低下するので速やかに使用し、室温においては少なくとも調製から1.5時間以内に投与を終了すること。投与に際し、他の注射剤との配合又は混注は行わないこと。(**「適用上の注意」**及び**「取扱い上の注意」**の項参照)

【使用上の注意】
1．**慎重投与**(次の患者には慎重に投与すること)
(1) 腎機能障害のある患者(**「用法・用量に関連する使用上の注意」**及び**「薬物動態」**の項参照)
(2) 肝機能障害のある患者[肝機能障害が増悪するおそれがある。]
(3) 心機能障害のある患者(特にアントラサイクリン系薬剤等、心毒性を有する薬剤による前治療歴のある患者)[致命的な心機能障害を発現するおそれがある。]
(4) 感染症を合併している患者[感染症が増悪し致命的となることがある。]
(5) 高齢者(**「高齢者への投与」**の項参照)
2．**重要な基本的注意**
(1) 本剤を前処置剤として用いた造血幹細胞移植は、各医療施設において定められている造血幹細胞移植の手法に従って実施すること。
(2) 本剤を前処置剤として用いた造血幹細胞移植にあたっては、患者の状態及び臓器機能(心、肺、肝、腎等)を十分検討し、造血幹細胞移植を実施可能と判断される患者にのみ投与し、以下の事項について特に注意すること。
1) 本剤の投与中は心電図、血圧及び尿量等のモニターを行うこと。また、投与後は定期的に臨床検査(血液検査、肝機能検査、腎機能検査等)及び尿量のモニター等を行うこと。
2) 本剤の投与後は患者の状態を十分に観察し、致命的な感染症の発現を抑制するため、感染症予防のための処置(抗感染症薬の投与等)を行い、必要に応じ無菌管理を行うこと。
3) 本剤の投与後は輸血及び血液造血因子の投与等適切な支持療法を行うこと。
(3) 感染症が増悪し致命的となることがあるので、重症感染症を合併している患者においては投与しないこと。
(4) 本剤の投与に際しては、患者の状態を十分に観察し、水分補給や利尿剤の投与により十分な尿量を確保すること(**「用法・用量に関連する使用上の注意」**の項参照)。
(5) 本剤の用量規制因子は下痢及び口内炎等の粘膜障害である。本剤を前処置剤として用いた造血幹細胞移植の施行に先立ち、口腔内病巣の治療、口腔内及び腸内の殺菌等の適切な処置を行うこと。
(6) 本剤を前処置剤として用いた造血幹細胞移植は、下記のことを踏まえ、患者に対する有益性及び危険性を考慮し十分説明した上で行うこと。
1) 閉経前の女性においては、卵巣機能抑制の結果、一時的又は永久的な無月経及び不妊症に陥る可能性が高いとの報告がある。

2) 動物試験(ラット及びイヌ)において精子形成抑制作用が認められたとの報告があるので、男性患者においては、一時的又は永久的な不妊症を起こす可能性がある。
3) 造血幹細胞移植を施行した小児においては、成長障害等が起こる可能性がある。
4) 本剤は動物試験(ラット及びマウス)において遺伝毒性が認められている。また、本剤を投与した患者において染色体異常が認められている。

3．相互作用

併用注意(併用に注意すること)

薬剤名等	臨床症状・措置方法	機序・危険因子
シクロスポリン、タクロリムス	本剤投与後に移植片対宿主病(GVHD)予防のためシクロスポリン又はタクロリムスを投与した骨髄移植患者において腎不全等の腎障害が発現したとの報告がある。	機序は不明である。
ナリジクス酸	ナリジクス酸服用中の小児患者に本剤(140mg/m²)の投与を開始したところ、その1～2日後に下痢(血便)を発現し死亡(剖検で出血性腸炎を認めた)したとの報告がある。	本剤との関連性は言及されていないが、ナリジクス酸による出血性腸炎を増強するおそれがある。

※4．副作用

国内臨床試験において、安全性評価対象症例41例中、副作用は全例に合計164件報告され、主な副作用は下痢38例(92.7%)、口内炎・粘膜炎33例(80.5%)、悪心・嘔吐26例(63.4%)、AST(GOT)・ALT(GPT)上昇21例(51.2%)であった。また、成人及び小児における特徴的な副作用は認められなかった。

成人・小児両試験で共通して発現した有害事象は、消化器、肝臓、循環器、泌尿器の障害及び代謝異常であった。Grade3以上の副作用は、下痢4件(9.8%)、口内炎・粘膜炎15件(36.6%)、悪心・嘔吐8件(19.5%)、直腸潰瘍1件(2.4%)、AST(GOT)・ALT(GPT)上昇8件(19.5%)、心筋症1件(2.4%)、不整脈1件(2.4%)及び咽頭炎1件(2.4%)であった。感染症(感染症の疑いを含む)は35例(85.4%)にみられた。試験期間中(移植後3ヵ月以内)、重篤な有害事象が2例(MRSA感染による肺炎及び心筋症(増悪)各1例)にみられ、そのうち1例は死亡した(死因：MRSA腸炎からの肺炎)。また、追跡調査時(観察期間の範囲：69～1462日)に、14例の死亡が確認された。その死因は、原病悪化が10例、ジギタリス中毒による心室細動からの脳の低酸素症及び肺水腫が各1例、他の抗癌剤を前処置剤とした末梢血幹細胞移植の敗血症・播種性血管内凝固症候群による死亡が1例ならびに胆管細胞癌による死亡が1例であった。死因は胆管細胞癌の1例を除き、いずれも本剤との因果関係は「なし」と判定された。また、造血幹細胞移植後に臨床上問題となる合併症として、感染症による出血性膀胱炎が1件(成人・感染症)、溶血性尿毒症症候群が2件(いずれも小児・追跡調査時に判明)確認された。(承認時)

使用成績調査において、安全性評価対象症例2603例中、臨床検査値異常を含む副作用は1643例(63.1%)報告された。その主なものは、下痢611例(23.5%)、AST(GOT)・ALT(GPT)の上昇等を伴う肝機能障害545例(20.9%)、口内炎・粘膜炎等の粘膜障害475例(18.2%)、悪心465例(17.9%)、感染症336例(12.9%)、嘔吐264例(10.1%)であった(再審査終了時)。

(1) **重大な副作用**

1) **感染症及び出血等**：本剤投与後は重度の骨髄抑制状態となり、その結果**感染症**(12.8%)**及び出血**(1.6%)**等**を引き起こし、**致命的**となることがある。本剤の投与後は患者の状態を十分に把握し、致命的な感染症の発現を抑制するため、感染症予防のための処置(抗感染症薬の投与等)を行い、必要に応じ無菌管理を行うこと。また、輸血及び血液造血因子の投与等適切な支持療法を行うこと。
2) **ショック、アナフィラキシー**：**ショック、アナフィラキシー**(0.2%)があらわれることがあり、そのような症状に伴ってまれに**心停止**(頻度不明)が起こることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。
3) **胃腸障害**：**悪心**(18.4%)、**嘔吐**(10.7%)及び**下痢**(24.5%)、**口内炎・粘膜炎**等の粘膜障害(19.3%)が高頻度にあらわれ、**直腸潰瘍**(0.04%)等の症状が起こることがあるので、観察を十分に行い、異常が認められた場合には適切な処置を行うこと。
4) **重篤な肝機能障害、黄疸**：**AST(GOT)・ALT(GPT)の上昇、ビリルビン値上昇、AI-P上昇、LDHの上昇等を伴う肝機能障害**(21.5%)や**黄疸**(0.7%)、また、黄疸、急激な体重増加、有痛性の肝腫大等を伴う**肝中心静脈閉塞(症)**(1.1%)があらわれることがあるので、観察を十分に行い、異常が認められた場合には適切な処置を行うこと。
5) **心筋症、不整脈**：**心筋症**(0.1%)、**不整脈**(0.8%)があらわれることがあるので、観察を十分に行い、異常が認められた場合には適切な処置を行うこと。投与中の場合は投与を中止すること。
6) **間質性肺炎、肺線維症**：**間質性肺炎**(0.7%)、**肺線維症**(頻度不明)があらわれることがあるので、観察を十分に行い、異常が認められた場合には適切な処置を行うこと。投与中の場合は投与を中止すること。
7) **溶血性貧血**：**溶血性貧血**(頻度不明)があらわれることがあるので、観察を十分に行い、異常が認められた場合には適切な処置を行うこと。投与中の場合は投与を中止すること。

(2) **その他の副作用**

次のような症状が投与中又は投与後もあらわれることがあるので、観察を十分に行い、異常が認められた場合には、適切な処置を行うこと。

	1～5%未満	1%未満	頻度不明[注]
腎臓	腎機能障害(BUN上昇、クレアチニン上昇等)	乏尿	
消化器	食欲不振		
過敏症	皮疹(斑状丘疹性皮疹、蕁麻疹)	瘙痒、浮腫	
皮膚		脱毛	
全身症状			温熱感、刺痛感
その他		月経異常、痙攣	卵巣機能不全

注) 自発報告または海外のみで認められている副作用については頻度不明とした。

5．高齢者への投与

成人26例を対象とした国内臨床試験において、65歳以上の高齢者は1例であり、報告された副作用は悪心・嘔吐、下痢、口内炎・粘膜炎であった(「**臨床成績**」の項参照)。一般に、高齢者では生理機能が低下していることが多いため、本剤投与前に患者の状態及び臓器機能を十分検討し確認すること。投与開始後は、患者の状態を慎重に観察すること。

なお、高齢者に本剤を前処置剤として用いた造血幹細胞移植を施行するにあたっては、患者の全身状態を考慮し、慎重に患者を選択すること。

※6．妊婦、産婦、授乳婦等への投与

(1) 妊婦(特に妊娠3ヵ月以内)又は妊娠している可能性のある婦人には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。また、妊娠する可能性のある婦人及びパートナーが妊娠する可能性のある男性には、適切な避妊をするよう指導すること。妊娠中に本剤を使用する場合、又は本剤を使用中に妊娠した場合は、胎児に異常が生じる可能性があることを患者に説明すること。[動物試験で大量(1.0mg/kg以上)を雌ラットに投与した場合、胚・胎児の死亡及び催奇形性が報告されており、また他のアルキル化剤(シクロホスファミド)で催奇形性を疑う症例報告がある。5 mg/kg以上を雄マウスに投与した実験で生殖細胞に対する遺伝毒性が報告されている[1),2)]。]
(2) 授乳中の婦人に投与する場合には、授乳を中止させること。

7．小児等への投与

小児15例(1～14歳)を対象とした国内臨床試験において、小児に特徴的な副作用と考えられる症状等は認められなかった(「**臨床成績**」の項参照)。本剤を前処置剤として用いた造血幹細胞移植を小児に施行するにあたっては、成長障害等の可能性を十分に考慮した上で行うこと。なお、低出生体重児、新生児又は乳児に対する安全性は確立していない(使用経験がない)。

8．過量投与

本剤の用法・用量は、患者の成熟リンパ球や骨髄細胞を除去し移植する造血幹細胞を生着させること、及び腫瘍性疾患において体内に残存する腫瘍細胞の除去を目指している。したがって、本剤投与後は重度の骨髄抑制状態となることから、致命的な感染症及び出血等を引き起こすことがあるので、用法・用量に定められている投与量を超えて投与しないこと。

徴候、症状：本剤の投与後は重度の骨髄抑制状態となる。本剤を急速に静脈内投与すると、嘔気及び嘔吐、下痢、口内炎等の発現が認められる。なお、海外において、卵巣癌[注1)]に対する本剤290mg/m²の単回静脈内投与後、嘔吐、下痢、振戦、呼吸困難、QT延長、低ナトリウム血症、高アミラーゼ血症、尿路感染症、重度の骨髄抑制等を発現し、投与6日後に突然死亡(死因：不整脈と推察された)した症例が報告されている[3)]。

処置：本剤は特有の解毒剤を有しておらず、本剤は血液透析により除去されないとの報告がある[4)]。本剤の過量投与が疑われた場合は、輸血、血液造血因子、抗感染症薬の投与等の支持療法を行うこと。また、必要に応じ無菌管理を考慮し、血液学的検査を頻回に行い、患者の状態を十分観察すること。

注1) アルケラン静注用50mgの効能・効果は白血病、悪性リンパ腫、多発性骨髄腫、小児固形腫瘍における造血幹細胞移植時の前処置である。

9．適用上の注意
(1) 投与経路：本剤は静脈内にのみ投与すること。
(2) 調製：
1) 本剤の調製は、本剤の性状及び取扱いについて十分な知識のある医師及び薬剤師が直接又は医師の監督下のもと行うこと。
2) 本剤は室温(約25℃)で用時調製すること。
3) 糖類を含む輸液と配合すると分解しやすいので、希釈するときは日局生理食塩液を使用すること。
4) 溶解後又は希釈後に混濁又は結晶が認められる場合は使用しないこと。
5) 調製後の溶液は、沈殿することがあるので冷蔵しないこと。また、使用後の残液は廃棄すること。
6) 溶解後、室温では経時的に安定性が低下するので速やかに投与を開始し、投与量と投与速度を勘案し遅くとも調製から1.5時間以内に投与を終了すること。
(3) 投与時：
1) 本剤はアルキル化剤であり反応性が高いことから、他の注射剤との配合又は混注は行わないこと。
2) 直接末梢静脈に投与すると薬液の漏出による局所の組織障害を起こすおそれがあるので、中心静脈よりゆっくりと投与することが望ましい。
3) 投与方法は次のいずれか適当な方法で中心静脈内に投与すること。
①生理食塩液の管の側管からゆっくりと注入する。なお、溶液が粘稠のため薬液の注入前後に生理食塩液で管を洗い流すこと。
②点滴静注する。

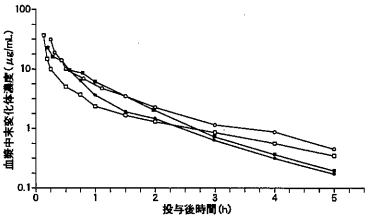
10. その他の注意
(1) アルキル化剤(メルファランを含む)の投与患者に急性白血病が発生したとの報告がある。
(2) マウス(1回0.75及び1.5mg/kgを週3回、6ヵ月間、腹腔内投与)及びラット(1回0.9及び1.8mg/kgを週3回、6ヵ月間、腹腔内投与)におけるがん原性試験で、マウスでは肺腫瘍及びリンパ肉腫の発生、ラットでは腹膜肉腫の発生が報告されている。

【薬物動態】[注]

1．血漿中濃度
メルファランを多発性骨髄腫又はその他の悪性腫瘍患者に高用量(140～220mg/m²)静脈内投与したときの薬物動態を検討した報告では、いずれの報告においても薬物動態パラメータはほぼ同様の値が認められ、未変化体は血漿中から$t_{1/2}\alpha$ 6.5～16分、$t_{1/2}\beta$ 41～83分で速やかに二相性に消失した[9)～6)]。投与24時間後には血漿中未変化体濃度は定量限界(20ng/mL)以下になった[6)]。
悪性腫瘍患者にメルファラン200mg/m²もしくは140mg/m²を2～20分間で静脈内投与したときの薬物動態パラメータは以下のとおりである。

投与量(mg/m²)	例数	Cmax(μg/mL)	$t_{1/2}\alpha$(min)	$t_{1/2}\beta$(min)	Vc(L)	Vdss(L)	AUC(μg·min/mL)	CL(mL/min)
140	11	13.5± 5.4	8.7±3.9	81.1±63.5	16.4± 6.2	39.8±20.7	505±128	522±145
200	16	21.1±14.7	9.1±8.2	68.0±32.1	19.9±14.6	41.6±17.2	615±167	641±184
全平均	27	———	8.9±6.7	73.3±46.8	18.5±11.9	40.9±18.4	———	592±177

造血悪性腫瘍患者4例にメルファラン220mg/m²を単回静脈内投与したときの血漿中未変化体濃度推移を以下に示す[5)]。



15歳未満の小児悪性腫瘍患者15例及び15歳以上の成人悪性腫瘍患者11例にメルファラン140mg/m²を静脈内投与したとき、小児と成人の間で薬物動態パラメータに有意な違いは認められなかった[9)]。

対象	$t_{1/2}\beta$(min)	AUC(μg・min/mL)	CL(L/min/m²)	Vdss(L/m²)
小児患者	36.8±17.2	346±122	0.447±0.170	16.0±5.5
成人患者	47.6±13.8	414±151	0.372±0.146	18.4±6.7
全平均	41.4±16.5	375±137	0.415±0.162	17.0±6.1

2．代謝
メルファランは、モノヒドロキシ体及びジヒドロキシ体に加水分解される。メルファランの加水分解に代謝酵素の関与は認められていない。ヒト血漿中及び尿中にメルファランを添加したとき、未変化体はそれぞれ半減期1.3～2.5時間(平均1.9±0.4時間)及び1.5～31.5時間(平均8.9±11.3時間)で消失した[10)]。

3．排泄
悪性腫瘍患者にメルファラン220mg/m²を静脈内投与したとき、尿中未変化体排泄率は3.8～41.8％(平均21.3±17.1％)であり、総クリアランスは137～295mL/min/m²(平均205±66mL/min/m²)であった[9)]。

4．血漿蛋白結合率
in vitroでのヒト血漿蛋白への結合率は0.1～9.0μMの濃度範囲で約55～76％であった[11)]。アルブミン及びα1-酸性糖蛋白との結合が認められた[11),12)]。γ-グロブリンとの結合は認められなかった[11)]。

5．腎機能低下患者における薬物動態
28例の悪性腫瘍患者にメルファランを70～200mg/m²静脈内投与したとき、患者のEDTAクリアランス(CL_{EDTA})と総クリアランス(CL)の間に相関性(CL=217.7+3.68×CL_{EDTA}、r=0.5326、p=0.0035)が認められた。また、造血幹細胞移植患者[8)]、卵巣癌患者[13)]、多発性骨髄腫患者等[14)]において、腎機能(クレアチニンクリアランス(CL_{CR})もしくはCL_{EDTA})と薬物動態パラメータの間に相関性が認められている。なお、CL_{CR}とCL及び腎クリアランスの相関を認めなかったとの報告[13)]や、CL_{EDTA}とAUC及びMRTの相関は認めたものの、消失半減期との相関は認めなかったとの報告[15)]もある。また、多発性骨髄腫に関しては、腎障害を有する患者に対して1日1回100mg/m²を2日間投与後に自家末梢血幹細胞移植を実施した結果、移植関連死亡は認められず、移植した幹細胞の生着、生存期間の延長、腎障害の改善等の良好な成績が得られた例も報告されている[16),17)]。これらの報告では水分補給や利尿薬投与等による尿量確保の管理に関しては不明確であるが、腎障害を有する患者では十分な尿量確保の管理が特に重要である。
注) いずれも外国人による成績である。本剤承認用量(1回)は60～100mg/m²である(「用法・用量」の項参照)。

【臨床成績】

造血器腫瘍(以下、成人)及び小児がん(以下、小児)を対象に、のべ15施設41症例について実施した国内第Ⅱ相試験成績は次の通り。

1．患者背景

成人の患者背景

項目		症例数(%)
合計		26(100)
性別	男	18(69.2)
	女	8(30.8)
年齢	Median[Min-Max]	44.0[20-65]
診断名	多発性骨髄腫	11(42.3)
	白血病	5(19.2)
	急性リンパ性白血病	3(11.5)
	急性骨髄性白血病	1(3.8)
	骨髄異形成症候群	1(3.8)
	悪性リンパ腫	10(38.5)
	非ホジキンリンパ腫	9(34.6)
	ホジキンリンパ腫	1(3.8)
移植時病態＊	完全寛解期	9(34.6)
	部分寛解期	14(53.8)
	再発	3(11.5)
移植の種類	同種骨髄移植	4(15.4)
	自家骨髄移植	2(7.7)
	自家末梢血幹細胞移植	19(73.1)
	自家骨髄／末梢血幹細胞移植	1(3.8)
Regimen	Regimen1	16(61.5)
	Regimen2	10(38.5)
G-CSF 投与期間(日)	Median[Min-Max]	12.0[0-40]
	投与例数	25(96.2)
血小板輸血量(単位)及び期間(日)	輸血量：Median[Min-Max]	87.5[20-1305]
	輸血期間：Median[Min-Max]	16.0[1-87]
	輸血例数	26(100)
赤血球輸血量(mL)及び期間(日)	輸血量：Median[Min-Max]	600.0[0-13600]
	輸血期間：Median[Min-Max]	1.0[0-77]
	輸血例数	18(69.2)
抗生物質の投与期間(日)	Median[Min-Max]	20.0[0-132]
	投与例数	22(84.6)
無菌室退室日(日)	Median[Min-Max]	13.5[8-42]

Regimen1：本剤180mg/m²＋全身放射線照射、Regimen2：本剤200mg/m²
＊：移植時病態とは、造血幹細胞移植の前処置開始前の病態をいう。

小児の患者背景

項目		症例数(%)
合計		15(100.0)
性別	男子	10(66.7)
	女子	5(33.3)
年齢	Median[Min-Max]	7.0[1-14]
診断名	白血病	4(26.7)
	急性リンパ性白血病	2(13.3)
	急性骨髄性白血病	2(13.3)
	固形腫瘍	11(73.3)
	神経芽腫	5(33.3)
	ウィルムス腫瘍	2(13.3)
	悪性リンパ腫	1(6.7)
	横紋筋肉腫	1(6.7)
	膵芽腫	1(6.7)
	骨肉腫	1(6.7)
移植時病態＊	完全寛解期	6(40.0)
	部分寛解期	4(26.7)
	寛解不能	4(26.7)
	再発	1(6.7)
移植の種類＃	同種骨髄移植	7(50.0)
	自家骨髄移植	2(14.3)
	自家末梢血幹細胞移植	5(35.7)
Regimen＃	Regimen1	8(57.1)
	Regimen2	6(42.9)
G-CSF 投与期間(日)＃	Median[Min-Max]	18.0[0-25]
	投与例数	10(71.4)
血小板輸血量(単位)及び期間(日)＃	輸血量：Median[Min-Max]	100.0[60-180]
	輸血期間：Median[Min-Max]	31.5[11-85]
	輸血例数	14(100)
赤血球輸血量(mL)及び期間(日)＃	輸血量：Median[Min-Max]	663.5[0-2400]
	輸血期間：Median[Min-Max]	38.0[0-82]
	輸血例数	11(78.6)

項目		症例数(%)
抗生物質の投与期間(日)#	Median [Min-Max]	17.5 [0-43]
	投与例数	13 (92.9)
無菌室退室日(日)#	Median [Min-Max]	19.5 [11-54]

Regimen1：本剤210mg/m²＋全身放射線照射、Regimen2：本剤210mg/m²
＊：移植時病態とは、造血幹細胞移植の前処置開始前の病態をいう。
#：投薬完了せず移植前に中止した1例を除く

2．骨髄(幹細胞)生着日

移植後、白血球数1000/mm³以上かつ好中球数500/mm³以上となった日を骨髄(幹細胞)生着日とした。

成人における骨髄(幹細胞)生着日及び血球指標の回復日数(造血幹細胞移植の種類別)

項目	評価対象例数	自家移植			同種骨髄移植(4例)
		自家骨髄移植(3例)	末梢血幹細胞移植(19例)	合計(22例)	
骨髄(幹細胞)生着日	26	16.0(15-22)	10.0(8-13)	10.0(8-22)	12.5(11-15)
白血球数＞1000/mm³	26	14.0(13-22)	10.0(8-13)	10.0(8-22)	12.5(11-15)
好中球数＞500/mm³	26	16.0(15-22)	10.0(8-13)	10.0(8-22)	12.5(11-15)
血小板数＞3×10⁴/mm³	26	42.0(38-62)	18.0(9-90)	20.0(9-90)	22.0(18-24)
血小板数＞5×10⁴/mm³	26	62.0(38-86)	18.0(9-90)	23.0(9-90)	23.0(18-27)
網状赤血球＞10‰	22	35.0(28-36)	15.0(11-26)	15.0(11-36)	14.5(13-15)

＊自家骨髄移植：自家骨髄移植と末梢血幹細胞移植を併用した1例を含む。
＊血小板数：観察期間(3ヵ月)に血小板数が未回復であった4例(いずれも末梢血幹細胞移植)は90日で打ち切りとした。
＊網状赤血球：評価不能4例(いずれも末梢血幹細胞移植)を除外した。

小児における骨髄(幹細胞)生着日及び血球指標の回復日数(造血幹細胞移植の種類別)

項目	評価対象例数	自家移植			同種骨髄移植(7例)
		自家骨髄移植(2例)	末梢血幹細胞移植(5例)	合計(7例)	
骨髄(幹細胞)生着日	14	19,67	11.0(11-15)	13.0(11-67)	18.0(12-24)
白血球数＞1000/mm³	14	15,38	11.0(10-15)	11.0(10-38)	18.0(12-24)
好中球数＞500/mm³	14	19,67	11.0(11-15)	13.0(11-67)	17.0(12-24)
血小板数＞2×10⁴/mm³	14	69,73	42.0(15-47)	43.0(15-73)	28.0(23-45)
血小板数＞5×10⁴/mm³	11	69,90	15,27 (2例)	48.0(15-90) (4例)	28.0(23-45)
網状赤血球＞10‰	13	41,53	15.0(14-18) (4例)	16.5(14-53) (6例)	24.0(14-30)

＊血小板数(＞5×10⁴/mm³)：観察期間(3ヵ月)に未到達の1例(自家骨髄移植)は90日で打ち切りとし、評価不能3例(いずれも末梢血幹細胞移植)を除外した。
＊網状赤血球：評価不能1例(末梢血幹細胞移植)を除外した。

3．その他の有効性

項目	3年生存率 (n：評価対象例数) 生存期間中央値(範囲)	3年無病生存率 (n：評価対象例数) 無病生存期間中央値(範囲)	奏効率(PR以上) (評価可能のみ)
全体	64.9% (n=37) 1089日(69-1462)	54.1% (n=37) 1038日(69-1462)	50.0% (9/18)
成人	60.9% (n=23) 1062日(69-1358)	52.2% (n=23) 1012日(69-1246)	46.2% (6/13)
多発性骨髄腫	37.5% (n=8) 450日(69-1358)	12.5% (n=8) 320.5日(69-1154)	50.0% (4/8)
悪性リンパ腫	80.0% (n=10) 1167.5日(148-1246)	80.0% (n=10) 1167.5日(98-1246)	40.0% (2/5)
白血病	60.0% (n=5) 1038日(497-1233)	60.0% (n=5) 1038日(169-1233)	−
小児	71.4% (n=14) 1135日(170-1462)	57.1% (n=14) 1098.5日(92-1462)	60.0% (3/5)
小児固形腫瘍	60.0% (n=10) 1098.5日(170-1462)	50.0% (n=10) 699.5日(92-1462)	60.0% (3/5)
白血病	100% (n=4) 1202.5日(1018-1265)	75.0% (n=4) 1202.5日(278-1265)	−

移植実施前に投与を中止した小児の1例を除く
−：評価対象例なし

4．安全性

有害事象及び副作用の発現頻度

項目		成人				小児				合計			
安全性評価対象		26例				15例				41例			
有害事象発現例数・件数		26例・123件				15例・62件				41例・185件			
副作用発現例数・件数		26例・107件				15例・57件				41例・164件			
有害事象・副作用の種類		有害事象		副作用		有害事象		副作用		有害事象		副作用	
消化器	下痢	25	96.2%	25	96.2%	13	86.7%	13	86.7%	38	92.7%	38	92.7%
	口内炎・粘膜炎	21	80.8%	21	80.8%	12	80.0%	12	80.0%	33	80.5%	33	80.5%
	悪心・嘔吐	19	73.1%	18	69.2%	8	53.3%	8	53.3%	27	65.9%	26	63.4%
	腹痛	2	7.7%	2	7.7%	−	−	−	−	2	4.9%	2	4.9%
	食欲不振	1	3.8%	1	3.8%	−	−	−	−	1	2.4%	1	2.4%
	直腸潰瘍	1	3.8%	1	3.8%	−	−	−	−	1	2.4%	1	2.4%
肝臓	AST(GOT)・ALT(GPT)上昇	14	53.8%	11	42.3%	12	80.0%	10	66.7%	26	63.4%	21	51.2%
	ビリルビン値上昇	1	3.8%	1	3.8%	2	13.3%	2	13.3%	3	7.3%	3	7.3%
	LDH上昇	3	11.5%	1	3.8%	3	20.0%	1	6.7%	6	14.6%	2	4.9%
	Al-P上昇	2	7.7%	1	3.8%	1	6.7%	1	6.7%	3	7.3%	2	4.9%
	ウロビリノーゲン陽性	−	−	−	−	1	6.7%	1	6.7%	1	2.4%	1	2.4%
循環器	頻脈	1	3.8%	1	3.8%	1	6.7%	1	6.7%	2	4.9%	2	4.9%
	心筋症	1	3.8%	1	3.8%	−	−	−	−	1	2.4%	1	2.4%
	心房細動	1	3.8%	1	3.8%	−	−	−	−	1	2.4%	1	2.4%
	不整脈	1	3.8%	1	3.8%	−	−	−	−	1	2.4%	1	2.4%
	心不全	1	3.8%	0	0%	−	−	−	−	1	2.4%	0	0%
中枢・末梢	振戦	1	3.8%	0	0%	−	−	−	−	1	2.4%	0	0%
泌尿器	蛋白尿	3	11.5%	3	11.5%	1	6.7%	1	6.7%	4	9.8%	4	9.8%
	血尿	3	11.5%	2	7.7%	1	6.7%	1	6.7%	4	9.8%	3	7.3%
	腎障害	1	3.8%	1	3.8%	−	−	−	−	1	2.4%	1	2.4%
	急性腎不全	1	3.8%	0	0%	−	−	−	−	1	2.4%	0	0%
皮膚	発疹	3	11.5%	3	11.5%	−	−	−	−	3	7.3%	3	7.3%
	色素沈着	1	3.8%	1	3.8%	−	−	−	−	1	2.4%	1	2.4%
	発赤	−	−	−	−	1	6.7%	1	6.7%	1	2.4%	1	2.4%
呼吸器	咽頭炎	7	26.9%	7	26.9%	−	−	−	−	7	17.1%	7	17.1%
	間質性肺炎	−	−	−	−	1	6.7%	1	6.7%	1	2.4%	1	2.4%
	気管支炎	1	3.8%	0	0%	−	−	−	−	1	2.4%	0	0%
代謝異常	尿糖	1	3.8%	1	3.8%	1	6.7%	1	6.7%	2	4.9%	2	4.9%
	高カリウム血症	1	3.8%	1	3.8%	−	−	−	−	1	2.4%	1	2.4%
感覚器	味覚異常	−	−	−	−	1	6.7%	1	6.7%	1	2.4%	1	2.4%
その他	倦怠感	1	3.8%	1	3.8%	1	6.7%	1	6.7%	2	4.9%	2	4.9%
	下腿疼痛	−	−	−	−	1	6.7%	1	6.7%	1	2.4%	1	2.4%
	浮腫	1	3.8%	0	0%	−	−	−	−	1	2.4%	0	0%
	発熱	2	7.7%	0	0%	−	−	−	−	2	4.9%	0	0%
	顔面浮腫	1	3.8%	0	0%	−	−	−	−	1	2.4%	0	0%
	鼻出血	−	−	−	−	1	6.7%	0	0%	1	2.4%	0	0%
	頭痛	1	3.8%	1	3.8%	−	−	−	−	1	2.4%	1	2.4%
感染症(感染症の疑いを含む) 38℃以上の発熱期間中央値		22例 6.5日		84.6% (0〜44日)		13例 8.0日		86.7% (0〜39日)		35例 7.5日		85.4% (0〜44日)	
急性GVHD＊		4例		100%		3例		42.9%		7例		63.6%	
慢性GVHD＊		4例		100%		0例		0%		4例		36.4%	

＊：GVHDの評価対象は、成人4例及び小児7例(同種骨髄移植実施例)

【薬効薬理】

1．骨髄抑制作用[18),19)]

メルファランには骨髄細胞のコロニー形成抑制作用及び骨髄抑制作用(in vivo マウス)が認められた。

2．抗腫瘍効果[20)〜27)]

メルファランは用量依存性の抗腫瘍効果を示し、広い抗腫瘍スペクトルを有する。

(1) マウスのSarcoma180腹水腫瘍、Ehrlich腹水癌、L1210白血病、P388白血病、B16黒色腫、Lewis肺癌、Colon-26結腸癌、Colon-38結腸癌、CD8F1乳癌及びラットのWalker癌肉腫256、吉田肉腫、Jensen肉腫に対して腫瘍増殖抑制作用を示した。

(2) ヌードマウス可移植性ヒト腫瘍系であるMX-1乳癌、LX-1肺癌、CX-1結腸癌に対する抗腫瘍作用が認められた。

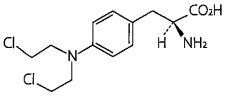
(3) ヌードマウス移植ヒト神経芽腫、骨肉腫、免疫抑制マウス移植横紋筋肉腫及びヌードラット移植神経膠腫に対する抗腫瘍作用が認められた。

3．作用機序[28)]

メルファランは、細胞内に取りこまれた後にDNA鎖間又はDNA鎖内架橋形成あるいはDNA-蛋白架橋形成を通して抗腫瘍作用や骨髄抑制作用を示すものと考えられる。

【有効成分に関する理化学的知見】

一般名：メルファラン(Melphalan)
化学名：4-Bis(2-chloroethyl)amino-L-phenylalanine
分子式：$C_{13}H_{18}Cl_2N_2O_2$
分子量：305.20
構造式：



性　状：白色〜淡黄白色の結晶性の粉末である。水、メタノール又はエタノール(95)に溶けにくく、ジエチルエーテルにほとんど溶けない。希塩酸又は希水酸化ナトリウム試液に溶ける。光によって徐々に着色する。
旋光度[α]$_D^{20}$：約−32°(乾燥物に換算したもの0.5g、メタノール、100mL、100mm)

【取扱い上の注意】

本剤の溶液に触れると皮膚反応が起こることがあるので、取扱い時には手袋、マスク、防護メガネ等を着用し、十分に注意すること。皮膚に本溶液が付着した場合には、直ちに石鹸で洗い、水で完全に洗い落とすこと。

【包　装】

1バイアル(専用溶解液10mL　1バイアル添付)

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