New Zealand Datasheet

1 PRODUCT NAME
Thiotepa - Reach 15 mg Powder for Infusion
Thiotepa - Reach 100 mg Powder for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Thiotepa - Reach 15 mg: each vial contains 15 mg thiotepa powder.
Thiotepa – Reach 100 mg: each vial contains 100 mg thiotepa powder.
For the full list of excipients, see Section 6.1. List of Excipients.

3 PHARMACEUTICAL FORM
White crystalline powder for infusion

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Thiotepa – Reach 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. (refer to section 5.2 Clinical trials)

4.2 Dose and method of administration
Thiotepa - Reach administration must be supervised by a physician experienced in conditioning treatment prior to haematopoietic progenitor cell transplantation.

Consideration should be given to administering an antiemetic prior to commencing administration of Thiotepa – Reach (see Section 4.4 Special Warnings and Precautions for use).

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

Thiotepa - Reach 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/m2 (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.

Solid tumours
CNS TUMOURS
The recommended dose of thiotepa is 5mg/kg administered as two injections on one day, in combination with other chemotherapeutic medicinal products, prior to allogeneic HPCT.

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 Section 4.4 Special Warnings and Precautions for use).

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 Special Warnings and Precautions for use).

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

Thiotepa - Reach must be administered by a qualified healthcare professional as a 2-4 hours intravenous infusion via a central venous catheter.

Thiotepa - Reach 15 mg vial must be reconstituted with 1.5 mL of sterile water for injection. Thiotepa - Reach 100 mg 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 (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 Thiotepa - Reach concentration between 0.5 and 1 mg/mL. For instructions on reconstitution and further dilution prior to administration, see Reconstitution section below.

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 Special Precautions for disposal).

Preparation of Thiotepa - Reach

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 Thiotepa - Reach 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

Thiotepa - Reach 15 mg must be reconstituted with 1.5 mL of sterile water for injection.
Thiotepa - Reach 100 mg must be reconstituted with 10 mL of sterile water for injection.

Using a syringe fitted with a needle, aseptically withdraw the required amount of sterile water (1.5 mL for 15 mg vial and 10 mL for 100 mg vial). 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 mLsodium 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 Thiotepa - Reach concentration between 0.5 and 1 mg/mL.

Administration

Thiotepa - Reach 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 µmin-line filter. Filtering does not alter solution potency.

Disposal
Product is for single use in one patient only. Discard any residue

4.3 Contraindications
Hypersensitivity to the active substance.

Pregnancy and lactation (see Section 4.6 Fertility, pregnancy and lactation).

Concomitant use with yellow fever vaccine and with live virus and bacterial vaccines.

4.4 Special warnings and precautions for use
Myelosuppression
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.

Liver Function
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.

Prior treatment with radiation therapy
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 Adverse effects (undesirable effects)).

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

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

Pulmonary toxicity

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 Adverse effects (undesirable effects)).

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

Secondary malignancy
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 Interactions with other medicinal products and other forms of interaction).

Use with cyclophosphamide
Thiotepa must not be concurrently administered with cyclophosphamide when both medicinal products are present in the same conditioning treatment. Thiotepa-Reach must be delivered after the completion of any cyclophosphamide infusion (see Section 4.5 Interactions with other medicinal products and other forms of interaction).

Co-administration with inhibitors of CYP2B6 or CYP3A4
During the concomitant use of thiotepa and inhibitors of CYP2B6 or CYP3A4, patients should be carefully monitored clinically (see Section 4.5 Interactions with other medicinal products and other forms of interaction).

Impairment of fertility
As most alkylating agents, thiotepa might impair male or female fertility. Male patients should not father a child while treated and during the year after cessation of treatment. An evidence based guideline should be followed when discussing fertility preservation, including with paediatric patients and their carers. *(see Section 4.6 Fertility, pregnancy and lactation).*

Skin toxicity
Thiotepa - Reach is excreted through the skin and is a skin irritant. Patients should be advised to wash four times a day, with one wash using soap and the remaining three washes with water only. Showering is preferred. Four times a day washing should continue until 48 hours after the last dose.

4.5 Interaction with other medicines 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. Thiotepa-Reach 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

Effects on fertility

As most alkylating agents, thiotepa might impair male and female fertility.
Thiotepa impaired fertility in male mice at oral or intraperitoneal (IP) doses ≥ 0.7 mg/kg (2.24 mg/m^2), significantly less than the maximum recommended human dose (MRHD, 13 mg/kg, 481 mg/m^2 in adults) based on body surface area. Thiotepa interfered with spermatogenesis in mice and hamsters at doses less than the MRHD.

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.

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

Female patients should discuss fertility preservation with their physician before treatment

Use in pregnancy – Pregnancy Category D
Based on the mechanism of action and findings in animals, thiotepa can cause fetal harm when administered to a pregnant woman.

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. Thiotepa was teratogenic in mice and rats and lethal to rabbit fetuses at doses less than the MRHD.

Therefore, thiotepa is contraindicated during pregnancy.

Use in lactation.
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.

4.7 Effects on ability to drive and use machines
Thiotepa - Reach 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	Constipation Gastrointestinal perforation Ileus	Gastrointestinal ulcer	

	Vomiting Diarrhoea Dyspepsia Abdominal pain Enteritis Colitis			
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), notknown (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 suspected adverse effects
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose
There is no experience with overdoses of thiotepa. The most important adverse reactions expected incase 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.

Thiotepa is dialyzable.

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766).

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 nitrogenmustard. 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 Trials
The efficacy of thiotepa as a component of conditioning regimens prior to allogeneic and autologous HPCT for haematological conditions and solid tumours has been reported in published studies. The following paragraphs describe results from a selected group of published papers that generally provide low level evidence of efficacy.
The results of published clinical studies supporting the efficacy of thiotepa are summarised:

Adult population
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 therapeuticstrategies for treating patients with haematological diseases.

Relapse: In all conditioning treatments containing thiotepa, relapse rates at more than 1 year have beenreported 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 thesafety of the conditioning treatment including thiotepa for autologous HPCT in adult patients with haematological diseases.

LYMPHOMA
Thiotepa in combination with busulfan and melphalan showed engraftment at 92%, OS at 42-52%, EFS at 34-45% and 5-year relapse at 32-42%. Most patients were at high risk because of their very advanced disease or prior dose-limiting radiation therapy.

Thiotepa in combination with melphalan and carboplatin showed OS, EFS, relapse estimated at 2 years of 65%, 60% and 21%, respectively.

Thiotepa in combination with mitoxantrone and carboplatin resulted in a 5-year DFS of 43% in high risk patients

Thiotepa in combination with cyclophosphamide and etoposide regimen showed DFS at 66% and OS at 76%.

Thiotepa in combination with etoposide in high risk patients was accompanied at 3 years by an OS of 40% and an EFS of 32%.

Thiotepa in combination with carmustine resulted in a survival rate at 5 years of 87% and it was associated with a relapse mortality rate of 8.7%

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 effectivechoices for treating patients with solid tumours.

Relapse: In all conditioning treatments containing thiotepa, relapse rates at more than 1 year have beenreported 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 theconditioning treatment including thiotepa for autologous HPCT in adult patients with solid tumours.

BREAST CANCER
Thiotepa in combination with cyclophosphamide lead to a disease Free Survival (DFS) of 49% and Overall Survival (OS) of 58% at 6 year.

Thiotepa in combination with cyclophosphamide and carboplatin showed engraftment at 98%. OS was 66-81% and RFS was 59-65%. DFS with a median follow up of 51 months was 72%.

Thiotepa in combination with cyclophosphamide and carmustine showed an OS of 68 – 74.7% and RFS was 59.3-62%

Thiotepa in combination with cyclophosphamide and epirubicine showed a mean number of positive nodes at 17.6, and median follow-up was 48.6 months. In high dose group OS was 87%, 78% and 73% at 2, 3 and 4 years, respectively. EFS was 71%, 60% and 52% at 2, 3 and 4 years, respectively. 4 year event-free survival was 60% (95% CI 53-67) in the high-dose chemotherapy group and 44% in the control group (p=0.00069). The corresponding overall survival was 75% vs 70% (p=0.02).

Thiotepa in combination with cyclophosphamide and mitoxantrone OS and EFS at 4 years were 70% and 52%, respectively. There was a trend in favor of high-dose chemotherapy with respect to EFS.

OVARIAN CANCER
Thiotepa in combination with busulfan and melphalan showed actuarial survival, EFS and relapse probability at 18 months of 57%, 30% and 63%, respectively.

Allogeneic HPCT
Haematological diseases
Engraftment: Engraftment has been achieved (92%-100%) in all reported conditioning treatments andit 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 ofacute 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 upto 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 beenreported 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 HPCTin adult patients with haematological diseases.

LYMPHOMA

Thiotepa in combination with fludarabine and cyclophosphamide had engraftment of 100%, estimated OS at 3 year was 62 - 81% and relapse was 12 - 41% with estimated PFS at 3 year of 64%.

THALASSEMIA
Thiotepa in combination with cyclophosphamide and busulfan showed engraftment at 96%. Thalassemia-free survival and OS was 70%.

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 monthsranged 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 99.6months.

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 ofthe 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 asuccess 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 allhaematological diseases.

Overall Survival (OS): OS ranged from 50% to 100% with a follow-up ranging from 9.4 up to 121months.

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 ofthe conditioning treatment including thiotepa for allogeneic HPCT in paediatric patients with haematological diseases.

THALASSEMIA
Thiotepa in combination with busulfan and cyclophosphamide: In this cohort, rejection and mortality rates were 12.5% and 19%, respectively. 69% of the patients were alive with sustained engraftment of donor hematopoiesis, this leading to a projected thalassemia-free survival of 66%. Thiotepa added to BU/CY decreased rejection to 7% (2/28). The OS rate was 93% in class I-II pts and 69% in the cumulative population.

Thiotepa in combination with treosulfan and fludarabine: all patients engrafted. The overall cumulative incidence of graft failure was 11%. 17 patients were transfusion independent. 2 year estimated transfusion-free survival (TFS) was 85% and OS at 2 years was 95%.

5.2 Pharmacokinetic properties

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

Distribution
Thiotepa is a highly lipophilic compound. After intravenous administration, plasma concentrations ofthe 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 beenreported.
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 ofthe 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 ofother 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
Genotoxicity
Thiotepa was shown to be genotoxic. It induced gene mutation, DNA damage and chromosome aberration in multiple *in vitro* and *in vivo* assays.

Carcinogenicity
Thiotepa was carcinogenic in mice and rats. When thiotepa was administered intermittently for a year, it caused multiple tumours (including leukeamia) in mice and rats at doses significantly less than the MRHD. Thiotepa is expected to be carcinogenic in humans.

PHARMACEUTICAL PARTICULARS
6.1 List of excipients
None

6.2 Incompatibilities
Thiotepa - Reach is unstable in acid medium.
This medicinal product must not be mixed with other medicinal products except those mentioned in Section 4.2.

6.3 Shelf life
Unopened vial
15 mg vial: 17 months
100 mg vial: 24 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 below 25°C.

The prepared infusion solution should ideally be used immediately. If not used immediately, to prevent microbiological hazard, the infusion should not be stored for longer than 24 hours at 2°C – 8°C.

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 Shelf life.

6.5 Nature and contents of container

Type I clear glass vial with a rubber stopper (Bromo Butyl), containing 15 mg thiotepa.
Pack size of 1 vial.

Type I clear glass vial with a rubber stopper (Bromo Butyl), containing 100 mg thiotepa.
Pack size of 1 vial.

6.6 Special precautions for disposal

All materials used for dilution and administration should be disposed of according to local procedures applicable to the discarding of antineoplastic agents. Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

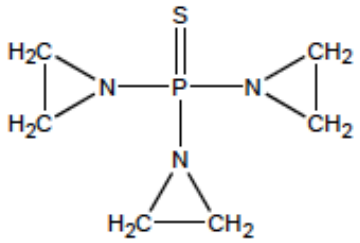
6.7 Physiochemical Properties

Thiotepa is a polyfunctional alkylating agent for use in the chemotherapy of certain neoplastic diseases.

Thiotepa is an ethylenimine-type compound, 1,1',1''-Phosphino-thioylidynetrisaziridine.

Thiotepa has also been known as TESPA and TSPA and is not the same as TEPA. The empirical formula is $C_6H_{12}N_3PS$ which corresponds to a molecular weight of 189.21.

Chemical structure



CAS number
52-24-4
Thiotepa is stable in alkaline medium and unstable in acid medium. It has a solubility of 19 g/100 mL in water and is soluble in ethanol, ether, benzene and chloroform. The pka is low (unspecified). When reconstituted with Sterile Water for Injection, the resulting solution has a pH of approximately 5.5-7.5.

7 MEDICINE SCHEDULE

Prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

10 DATE OF REVISION

21 September 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information