PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] Thiotepa for Injection USP

Lyophilised powder for solution upon reconstitution and dilution,

15 mg / vial and 100 mg / vial, intravenous

USP

Antineoplastic Agent
ATC code: L01AC01

"Thiotepa for Injection USP is indicated:

- in combination with other chemotherapeutic products as part of a high-dose chemotherapy (HDCT) consolidation regimen followed by autologous stem cell transplantation (ASCT) for adult patients with central nervous system (CNS) lymphoma

and has been issued marketing authorization with conditions. Patients should be advised of the nature of the authorization. For further information for Thiotepa for Injection USP please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html. Note that trials to verify the clinical benefit of the medicinal ingredient in Thiotepa for Injection USP are being carried out by the manufacturer of the Canadian Reference Product."

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Submission Control Number: 272936

Date of Initial Authorization:
May 18, 2022

Date of Revision:
October 4, 2023

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product subject to conditions. Note that the manufacturer of the Canadian Reference Product will carry out additional clinical trials to verify the anticipated benefit of the medicinal ingredient in this product (thiotepa) within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

Not Applicable	

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Thiotepa for Injection USP (thiotepa for injection) is indicated:

- *in combination with other chemotherapeutic products as part of a high-dose chemotherapy (HDCT) consolidation regimen followed by autologous stem cell transplantation (ASCT) for adult patients with central nervous system (CNS) lymphoma*

and has been issued marketing authorization with conditions. Patients should be advised of the nature of the authorization. For further information for Thiotepa for Injection USP please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html. Note that trials to verify the clinical benefit of the medicinal ingredient in Thiotepa for Injection USP are being carried out by the manufacturer of the Canadian Reference Product.

Thiotepa for Injection USP should be administered under the supervision of a physician who is experienced in the use of HDCT followed by SCT.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

There is limited clinical data on the use of high-dose thiotepa for injection as part of a HDCT regimen in geriatric patients (>65 years of age) with CNS lymphoma. Caution is needed in these patients.

2 CONTRAINDICATIONS

Thiotepa for Injection USP is contraindicated in:

- Patients who are hypersensitive to this drug or component of the container. For a complete listing, see the 6 DOSAGE FORMS, STRENGHTS, COMPOSITION AND PACKAGING section of the product monograph.
- Female patients who are pregnant or breastfeeding (see 7 WARNINGS AND PRECAUTIONS).
- Concomitant use with live virus or bacterial vaccines including yellow fever vaccine (see 7 WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Thiotepa for Injection USP should only be administered under the supervision of a physician who is experienced in the use of high-dose chemotherapy (HDCT) and stem cell transplantation (SCT).

- Profound myelosuppression (anemia, neutropenia and thrombocytopenia) including refractory and fatal cases (see 7 WARNINGS AND PRECAUTIONS, **Hematologic**).
- Cardiotoxicity may occur. Cardiac function must be monitored regularly and caution is advised in patients with history of cardiac disease (see 7 WARNINGS AND PRECAUTIONS, **Cardiovascular**).
- Hepatotoxicity: Liver function must be monitored regularly and caution is advised in patients with hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, **Hepatic/Biliary/Pancreatic** and **Patients with Hepatic Impairment**).
- Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or prior SCT may be at an increased risk of hepatic veno-occlusive disease (see 7 WARNINGS AND PRECAUTIONS, **Hepatic/Biliary/Pancreatic**, **Patients with Hepatic Impairment**, **Patients with Renal Impairment** and **Special Populations**).
- Pulmonary toxicity, including fatal cases, may occur and there may be additive effects produced by other cytotoxic agents (busulfan, fludarabine and cyclophosphamide) (see 7 WARNINGS AND PRECAUTIONS, **Respiratory** and 9 DRUG INTERACTIONS).
- Neurotoxicity may be greater in patients with prior brain or craniospinal irradiation (see 7 WARNINGS AND PRECAUTIONS, **Neurologic**).
- Renal toxicity (see 7 WARNINGS AND PRECAUTIONS, **Renal**).
- Thiotepa for Injection USP could cause fetal harm when administered to a pregnant female (see 7 WARNINGS AND PRECAUTIONS, **Special Populations**, **Pregnant Women**).
- Serious drug interactions (see 9 DRUG INTERACTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Thiotepa for Injection USP should be administered under the supervision of a physician who is experienced in the use of high-dose chemotherapy (HDCT) regimens followed by stem cell transplantation (SCT).

Dosing of obese patients based on total body weight may result in higher than expected thioTEPA/TEPA exposure. Consideration might be given to using adjusted body weight for calculating body surface area. Obese patients should be closely monitored for signs of toxicity.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose for Thiotepa for Injection USP as part of HDCT regimens ranges from 185 mg/m^2/day to 370 mg/m^2/day, administered intravenously as one or two daily infusions over 2 to 3 consecutive days prior to ASCT. Do not exceed a total maximum cumulative dose of 750 mg/m^2 during the administration of the HDCT regimen.

Table 1 - Thiotepa for injection high-dose chemotherapy regimens used in CNS lymphoma patients

Reference	Days of thiotepa for injection administration[a]	HDCT regimen	Thiotepa for injection Dose	
			Total Daily Dose	Cumulative Dose
Cheng 2003	Days -8 to -7	TT/Bu/Cy	300 mg/m^2	600 mg/m^2
Sierra del Rio 2011	Days -9 to -7	TT/Bu/Cy	250 mg/m^2	750 mg/m^2
Illerhaus 2008	Days -5 to -4	TT/BCNU	185 mg/m^2	370 mg/m^2
Alimohamed 2012	Days -8 and -7	TT/Bu/Cy	300 mg/m^2	600 mg/m^2
Illerhaus 2006	Days -5 to -4	TT/BCNU	185 mg/m^2	370 mg/m^2
Montemurro 2007	Days -4 to-3	TT/Bu	185 mg/m^2	370 mg/m^2
Omuro 2015	Days -9 to -7	TT/Bu/Cy	250 mg/m^2	750 mg/m^2
Bojic 2015	Days -5 to -4	TT/BCNU/R[b]	185 mg/m^2	370 mg/m^2
Soussain 1996	Days -9 to -7	TT/Bu/Cy	250 mg/m^2	750 mg/m^2
Soussain 2001	Days -9 to -7	TT/Bu/Cy	250 mg/m^2	750 mg/m^2
Soussain 2008	Days -9 to -7	TT/Bu/Cy	250 mg/m^2	750 mg/m^2
Soussain 2012	Days -9 to -7	TT/Bu/Cy	250 mg/m^2	750 mg/m^2
Cote 2012	Days -9 to -7	TT/Bu/Cy	250 mg/m^2	750 mg/m^2
Chen 2015	Days -9 to -7	TT/Bu/Cy/R	250 mg/m^2	750 mg/m^2
Lee 2015	Days -4 to -3	TT/Bu	185 mg/m^2	370 mg/m^2
Oh 2016	Days -8 to -7	TT/Bu/Cy	300 mg/m^2	600 mg/m^2
	Days -6 to -5	TT/Bu/Mel/R	250 mg/m^2	500 mg/m^2
Korfel 2013	Days -4 to -3	TT/BCNU/VP16	370 mg/m^2	740 mg/m^2
Welch 2015	Days -9 to -7	TT/Bu/Cy	250mg/m^2	750 mg/m^2

[a]Infusion of autologous blood stem cells on Day 0; [b]Three patients additionally received rituximab; TT: thiotepa for injection; Bu: Busulfan; Cy: Cyclophosphamide: BCNU: Carmustine; VP-16: Etoposide; R: Rituximab; Mel: Melphalan

The recommended doses of Thiotepa for Injection USP are intended only as part of a HDCT regimen followed by SCT.

Special populations:

- **Renal impairment:** The safety and efficacy of high-dose thiotepa for injection has not been established in patients with renal impairment. Dedicated pharmacokinetic studies in patients with renal impairment have not been conducted. Patients with renal impairment should be treated with caution and monitored for signs of toxicity.

- **Hepatic impairment:** The safety and efficacy of high-dose thiotepa for injection has not been established in patients with hepatic impairment. Thiotepa for Injection is mainly metabolized by the liver and the risk of increased exposure in patients with hepatic impairment is unknown. Patients with hepatic impairment should be treated with caution and monitored for signs of toxicity.

- **Obesity**: Consideration might be given to using adjusted body weight for calculating BSA (see 10.3 Pharmacokinetics, **Special Populations and Conditions**).

- **Geriatrics (>65 years of age):** There is limited clinical data on the use of high-dose thiotepa for injection as part of a HDCT regimen in geriatric patients with CNS lymphoma. Caution is needed in these patients.

- **Pediatrics (<18 years of age):** Health Canada has not authorized an indication for pediatric use.

4.3 Reconstitution

Parenteral Products:

Reconstitution of vials

Reconstitute with Sterile Water for Injection as follows:

Table 2 - Reconstitution

Vial Size	Volume of Sterile Water to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
15 mg	1.5 mL	1.5 mL	10 mg/mL
100 mg	10 mL	10 mL	10 mg/mL

Thiotepa for Injection USP must be reconstituted with sterile water for injection. Using a syringe fitted with a needle, aseptically withdraw sterile water for injection (see chart above). 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 clear 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%) solution for injection in order to obtain a final Thiotepa for Injection USP concentration between 0.5 and 1 mg/mL.

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. Infusion solutions should be administered using an infusion set equipped with a 0.2 µm in-line filter (polyethersulfone-fluid filter membrane B. Braun).

This medicinal product must not be mixed with other medicinal products except those mentioned in Reconstitution.

4.4 Administration

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration.

Thiotepa for Injection USP must be administered by a qualified healthcare professional as a 2 to 4 hours intravenous infusion via a central venous catheter. Infusion solutions should be administered using an infusion set equipped with a 0.2 µm in-line filter.

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

5 OVERDOSAGE

The principal toxic effect of Thiotepa for Injection USP is profound myelosupression and pancytopenia but skin, gastrointestinal, hepatic, renal, cardiac, pulmonary and CNS toxicity can occur (see 7 WARNINGS AND PRECAUTIONS). There is no known specific antidote for Thiotepa for Injection USP overdose.

Management of overdosage would include appropriate treatment of any concurrent infection, myelosuppression or other toxicity, close monitoring of the hematologic status and institution of vigorous supportive measures as medically indicated to sustain the patient through any period of toxicity that might occur.

For management of a suspected drug overdose contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous, after reconstitution and dilution	Lyophilised powder for solution upon reconstitution and dilution 15 mg, 100 mg	Thiotepa for Injection USP does not contain any excipients.

Thiotepa for Injection USP

Type I clear glass vial with a stopper, containing either 15 mg or 100 mg Thiotepa for Injection USP. The stopper is not made with natural rubber latex. Pack size of 1 single use vial. Preservative free.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

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

Grade 3-4 mucositis occurs in the majority of patients treated with thiotepa for injection -containing HDCT. Management of mucositis often requires total parenteral nutrition.

Administration of live attenuated vaccines (including yellow fever vaccines) should be avoided until the immunosuppressive effects have been resolved (see 2 CONTRAINDICATIONS).

Concomitant use with phenytoin and fosphenytoin should be avoided (see 9 DRUG INTERACTIONS).

Thiotepa must not be concurrently administered with cyclophosphamide when both medicinal products are present in the same high-dose chemotherapy (HDCT) regimen. Thiotepa for Injection USP must be delivered after the completion of any cyclophosphamide infusion (see 9 DRUG INTERACTIONS).

During the concomitant use of thiotepa and inhibitors or inducers of CYP2B6 or CYP3A4, patients should be carefully monitored (see 9 DRUG INTERACTIONS).

The safety assessment of high-dose thiotepa for injection as part of a high-dose chemotherapy (HDCT) regimen is derived from published literature where patients, including those with CNS lymphoma, were treated. As such, the safety information is limited by the information selected for inclusion into published reports. As high-dose thiotepa for injection is administered in combination with other chemotherapeutic agents, it is not always possible to assign, nor to exclude, causality to particular adverse events. The following sections describe adverse events reported with the use of HDCT regimens that include thiotepa for injection.

Carcinogenesis and Mutagenesis

Thiotepa for injection has been shown in pre-clinical studies to be mutagenic and carcinogenic. Treatment-related secondary malignancies, including myelodysplastic syndrome and acute non-lymphocytic leukemia, have been reported with the use of thiotepa (see 16 NON-CLINICAL TOXICOLOGY).

Cardiovascular

Cardiac-related adverse events such as arrhythmia (including tachycardia and atrial fibrillation) congestive cardiac failure, cardiomyopathy and myocarditis have been reported. Vascular disorders observed include hypertension, lymphedema and embolism. Cerebral aneurysm has also been reported.

Patients with organ dysfunction were generally excluded from clinical trials. Caution is advised in patients with a history of cardiac disease. Severe cardiotoxicity, including cases with a fatal outcome, have been reported in patients with reduced ejection fraction prior to stem cell transplantation. Regular monitoring of cardiac function is recommended in patients treated with Thiotepa for Injection USP.

Driving and Operating Machinery

Convulsion, hallucination, delirium, dizziness, headache and blurred vision have been reported in patients treated with thiotepa for injection. Patients experiencing these symptoms should use caution when driving or operating machines.

Ear/Nose/Throat

Ototoxicity (including hearing impairment and tinnitus) has been reported in patients treated with thiotepa for injection-containing HDCT regimens.

Endocrine and Metabolism

Anorexia, weight loss and dehydration have been reported in CNS lymphoma patients treated with thiotepa-containing HDCT regimens. Hyponatremia associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been reported. Decreased appetite, hyperglycemia and hypopituitarism have been reported.

Gastrointestinal

Gastrointestinal toxicity occurs very commonly in patients receiving thiotepa for injection-containing HDCT regimens, including severe nausea, vomiting and diarrhea. Other gastrointestinal events reported include grade 3 stomatitis, colitis, pancreatitis, typhilitis, chronic enterocolitis (including Clostridium difficile colitis), as well as esophagitis, dyspepsia, abdominal pain, constipation, gastrointestinal perforation, and ileus.

Grade 3-4 mucositis occurs in the majority of patients treated with thiotepa for injection-containing HDCT. Management of mucositis often requires total parenteral nutrition.

Genitourinary

Hemorrhagic cystitis, dysuria, oliguria, cystitis and hematuria have been reported. Consideration should be given to administration of bladder protective agents. Patients must be adequately hydrated to reduce the risk of genitourinary toxicity.

Hematologic

High-dose thiotepa for injection causes profound myelosuppression in all patients. Reported median time for platelet recovery ranged from 8 to 18 days; median time for neutrophil recovery was between 7.5 to 11 days. Persistent grade 3-4 thrombocytopenia and severe febrile neutropenia have been reported. Refractory thrombocytopenia has been associated with fatal hemorrhage. Thrombotic micro-angiopathy involving the CNS has also been reported.

Frequent complete blood counts, including differential white blood cell counts, and platelet counts need to be performed during treatment and until recovery is achieved. Daily white blood cell counts and platelets are recommended during therapy with Thiotepa for Injection USP and after transplant for at least 30 days (see **Monitoring and Laboratory Test**).

Infections

Increased susceptibility to infection and sepsis have been reported very commonly. Serious infections, including sepsis, septic shock, fever and chills, may occur after ASCT. Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) is recommended for the prevention and management of infections during the neutropenic period.

Hemorrhage

Cases of epistaxis and cerebral hemorrhage (including fatalities) possibly secondary to thrombocytopenia have been reported.

Thrombosis

Pulmonary embolism, including fatal cases, has been reported.

Hepatic/Biliary/Pancreatic

Thiotepa for Injection USP is hepatotoxic. Increased transaminases, alkaline phosphatase, gamma-glutamyltransferase and bilirubin as well as elevated amylase have been reported in thiotepa for injection treated patients. Cases of veno-occlusive liver disease, hepatomegaly, jaundice and pancreatitis have also been reported. Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or prior SCT may be at an increased risk of hepatic veno-occlusive liver disease (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

Immune

Depressed immunity caused by the profound myelosuppressive effects of high-dose Thiotepa for Injection USP occurs in patients treated with thiotepa for injection-containing HDCT regimens. Live vaccines (including yellow fever vaccines) should not be administered to immunocompromised patients.

Severe immunosuppression has led to serious, sometimes fatal, infections (see 7 WARNINGS AND PRECAUTIONS, **Hematologic**). Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) should be considered for the prevention and management of infections during the neutropenic period. Latent infections can be reactivated. Reactivation of cytomegalovirus (CMV) has occurred with thiotepa for injection-containing HDCT regimens administration. Monitoring and pre-emptive treatment of patients with positive CMV serology are advised. Acute and chronic graft-versus-host diseases have been reported, including some with fatal outcome.
Hypersensitivity reactions have been observed. Engraftment syndrome occurs frequently.

Monitoring and Laboratory Tests

Hematologic

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 for Injection USP and after transplant for at least 30 days.

Clinical Chemistry

Monitor hepatic function (including ALT, AST, alkaline phosphatase, total bilirubin and GGT) and amylase regularly following ASCT. Patients with any degree of hepatic impairment require close monitoring of liver function.

Renal function (creatinine and eGFR), electrolytes (e.g. sodium, potassium, phosphate), magnesium, and calcium should be assessed periodically.

Urinalysis should be performed at regular intervals to assess for hematuria.

Cardiac monitoring

Cardiac function should be monitored regularly in patients treated with Thiotepa for Injection USP.

Muscoskeletal

Back pain, myalgia and arthralgia have been reported.

Neurologic and Psychiatric

Thiotepa for Injection USP is a lipophilic alkylating agent that crosses the blood-brain barrier and achieves cerebrospinal fluid concentrations equivalent to plasma concentrations. Severe neurotoxicity can occur in Thiotepa for Injection USP treated patients. Neurotoxicity may be greater in patients with prior brain or craniospinal irradiation. Cases of leukoencephalopathy, including fatal cases, have been observed. Other neuropsychiatric events associated with the use of thiotepa for injection include: cognitive disorder, memory deficits, confusional state, delirium or change in mental status, agitation, hallucination, anxiety, extrapyramidal disorder, convulsion, dizziness, headache, blurred vision, encephalopathy and paraesthesias.

Ophthalmologic

Conjunctivitis and cataracts have been observed in patients treated with thiotepa for injection-containing HDCT regimens.

Patients with Renal Impairment

Patients with renal impairment should be treated with caution and monitored for signs of toxicity.

Patients with Hepatic Impairment

Patients with hepatic impairment should be treated with caution and regular monitoring of serum transaminase, alkaline phosphatase and bilirubin is recommended for prompt detection of signs of toxicity.

Renal

Renal failure, increased creatinine levels and increased urea levels have been reported.

Reproductive Health: Female and Male Potential

- **Fertility**

Pre-clinical toxicity studies show that thiotepa for injection impairs spermatogenesis and ovarian function in mice (see 16 TOXICOLOGY). Azoospermia and amenorrhea occur with thiotepa for injection use and thiotepa for injection commonly causes infertility in male and female patients. Fertility preservation strategies should be discussed with male patients and

female patients of childbearing potential.

- **Teratogenic Risk**

Thiotepa for injection was shown pre-clinically to be teratogenic and to cause fetal death (see 16 TOXICOLOGY). Thiotepa for Injection USP must not be used during pregnancy (see 2 CONTRAINDICATIONS). Effective methods of contraception should be used during therapy if either the patient or the partner is of childbearing potential.

Vaginal haemorrhage and menopausal symptoms have been reported.

Respiratory

Pulmonary toxicity occurs in patients treated with thiotepa for injection-containing HDCT. Idiopathic pneumonia syndrome, pulmonary oedema, cough and pneumonitis have been reported. Fatal acute respiratory distress has also been reported.

Skin

Thiotepa for Injection USP is excreted through the skin. Skin toxicity reported with thiotepa for injection use includes rash (predominantly involving axillae, groin and elbows), pruritus, urticaria, erythrodermic psoriasis, alopecia, pigmentation disorders, Stevens-Johnson syndrome (including fatal cases) and toxic epidermal necrolysis.

7.1 Special Populations

7.1.1 Pregnant Women

Thiotepa for Injection USP is contraindicated in pregnancy. There are no studies in pregnant women using thiotepa for injection. Based on its mechanism of action, Thiotepa for Injection USP has the potential to cause fetal harm; including teratogenicity and fetal death (see 16 TOXICOLOGY). Women of childbearing potential should use effective contraception during treatment. A pregnancy test should be performed and confirmed negative before treatment is initiated. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Thiotepa for Injection USP. If the patient becomes pregnant while receiving Thiotepa for Injection USP, the patient should be informed of the potential hazard to the fetus.

7.1.2 Breast-feeding

It is not known whether thiotepa for injection is excreted in human milk. Due to its pharmacological properties and its potential toxicity for nursing infant, breastfeeding is contraindicated during treatment with Thiotepa for Injection USP.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): CNS lymphoma does not typically occur in pediatric patients. The safety and efficacy of high-dose thiotepa for injection as part of a HDCT regimen have not

been established in pediatric CNS lymphoma patients.

Cases of leukoencephalopathy have been observed following treatment with thiotepa for injection in adult and pediatric patients with multiple previous chemotherapies, including methotrexate and radiotherapy. Some cases have been fatal.

Cases of pulmonary arterial hypertension have been observed following treatment with thiotepa for injection in pediatric patients. All cases had a fatal outcome.

Cases of hypothyroidism, paresis, cardiac arrest, pulmonary hemorrhage, respiratory arrest and growth retardation have also been observed in pediatric patients administered with high-dose thiotepa for injection.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): There is limited clinical data on the use of high-dose thiotepa for injection as part of a HDCT regimen in geriatric patients with CNS lymphoma. Caution is needed in these patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most commonly reported adverse events in the clinical studies of CNS lymphoma patients treated with thiotepa for injection-containing high-dose chemotherapy (HDCT) were myelosupression, infections, diarrhea, nausea, vomiting, stomatitis, edema, mucositis, neurotoxicity, skin rash and alopecia.

Serious adverse events included thrombocytopenia, neutropenia, pancytopenia, febrile neutropenia, refractory thrombocytopenia, hemorrhage, pulmonary embolism, pneumonia, sepsis, leukoencephalopathy, micro-angiopathy, convulsion, extrapyramidal symptoms, delirium, mucositis, veno-occlusive disease, gastrointestinal graft-versus-host disease, typhilitis, pancreatitis, hemorrhagic cystitis, acute renal insufficiency and Stevens-Johnson syndrome.

8.2 Clinical Trial Adverse Reactions

Treatment emergent adverse events reported with the use of high-dose thiotepa for injection as part of a high-dose chemotherapy (HDCT) regimen followed by autologous stem cell transplantation (ASCT) are derived from published literature where CNS lymphoma patients were treated. As such, the safety information is limited by the information selected for inclusion into published reports. Adverse events in the tables below are not pooled nor listed by MedDRA organ classes as there are major reporting differences across publications.

Table 4 - Treatment emergent adverse events reported in newly diagnosed PCNSL patients administered with a thiotepa for injection-containing HDCT regimen

Reference	N[a]	Adverse Events Grade 1-2 or moderate (n)	Adverse Events Grade 3-4 or serious (n)	Adverse Events Grade 5 (n)
Alimohamed, 2012	21	Stomatitis (frequent) Nausea (frequent) Skin rash (frequent) Peripheral edema (frequent)	Typhilitis (1) Diarrhea/Auto GvHD (2) Delirium (1) Atrial fibrillation (1) Heart failure (1)	Pneumonia (3) Sepsis (3)
Illerhaus 2006	23	Mucositis (6)	Neutropenia (23) Thrombocytopenia (23) Neutropenic fever (12) Fungal pneumonia (1)	N.R.
Montemurro, 2007	16	N.R.	Colitis (1) Mucositis (3) Pneumonia (1) Convulsions (1) Extrapyramidal symptoms (1) Infections (2)	Sepsis (2) Pneumonia (3) Neurotoxicity (2)
Omuro, 2015	26	N.R.	Febrile neutropenia (11) Infections (6) Skin rash (2) Encephalopathy (1) Dehydration (1) Cardiac failure (1) Weight loss (1) Nausea (1) Diarrhea (1) Mucositis (1)	Stevens-Johnson syndrome (1) Septic shock (1) Chronic enterocolitis (1)
Bojic, 2015	5	Nausea (3) Vomiting (3) Mucositis (1) Diarrhea (2) Infections (4)	Diarrhea (1)	N.R.

[a]: Number of enrolled patients that were treated with a thiotepa for injection-containing HDCT regimen
N.R.: not reported

Table 5 - Treatment emergent adverse events reported in refractory or relapsed PCNSL patients administered with a thiotepa for injection -containing HDCT regimen

Reference	N[a]	Adverse Events Grade 1-2 or moderate (n)	Adverse Events Grade 3-4 or serious (n)	Adverse Events Grade 5 (n)
Soussain, 1996	5	Infection – CMV and hepatitis B virus (1)	Vomiting (1) Alopecia (4)	N.R.

Reference	N[a]	Adverse Events Grade 1-2 or moderate (n)	Adverse Events Grade 3-4 or serious (n)	Adverse Events Grade 5 (n)
Soussain, 2001	20	Infection (15)	Neutropenia (20) Thrombocytopenia (20) Infection (4) Veno-occlusive disease (1) Encephalopathy (2) Leukoencephalopathy (3)	Hemorrhage (1) Leukoencephalopathy (2)
Soussain, 2008	27	Leukoencephalopathy (2)	Leukoencephalopathy (3)	Neurotoxicity (1)
Soussain, 2012	32[b]		Pancreatitis (1) Acute renal insufficiency (1) Hemorrhagic cystitis (1)	Acute respiratory distress syndrome (1) Multi-organ failure (1) Pulmonary embolism (1) Sepsis (2) Neurotoxicity (4)

[a]: Number of enrolled patients that were treated with a thiotepa for injection -containing HDCT regimen.
[b]: Retrospective studies over 79 patients, of which 47 were from Soussain 2001 and Soussain 2008. Here presented data relate to the remaining 32 patients only.
N.R.: not reported

Table 6 - Treatment emergent adverse events reported in SCNSL patients administered with a thiotepa for injection-containing HDCT regimen

Reference	N[a]	Adverse Events Grade 1-2 or moderate (n)	Adverse Events Grade 3-4 or serious (n)	Adverse Events Grade 5 (n)
Lee, 2015	12		Veno-occlusive disease (1) Neutropenic fever (2)	
Oh, 2016	23	Mucositis (23) Nausea (23) Vomiting (23) Diarrhea (23) Rash (23)	Febrile neutropenia (5) Bacteremia (3) Septic shock (1) Refractory thrombocytopenia (2)	Septic shock (2)
Korfel, 2013	24	N.R.	Anemia (10) Leukopenia (24) Thrombocytopenia (24) Infection (11) Stomatitis (7) Nausea (2) Vomiting (2) Diarrhea (3)	N.R.

[a]: Number of enrolled patients that were treated with a thiotepa for injection-containing HDCT regimen
N.R.: not reported

Table 7 - Treatment emergent adverse events reported in newly diagnosed or relapsed PCNSL patients administered with a thiotepa for injection-containing HDCT regimen

Reference	N[a]	Adverse Events Grade 1-2 or moderate (n)	Adverse Events Grade 3-4 or serious (n)	Adverse Events Grade 5 (n)

Reference	N[a]	Adverse Events Grade 1-2 or moderate (n)	Adverse Events Grade 3-4 or serious (n)	Adverse Events Grade 5 (n)
Cheng, 2003	7*	Mucositis (7) Herpes zoster (1)	Febrile neutropenia (6) Hemorrhagic cystitis (1) Diarrhea (1) Cholestasis (1)	Septic shock (1)

[a]: Number of enrolled patients that were treated with a thiotepa for injection -containing HDCT regimen.
*: 1 relapsed PCNSL patient and 6 newly diagnosed PCNSL

Table 8 - Treatment emergent adverse events reported in PCNSL and SCNSL patients administered with a thiotepa for injection-containing HDCT regimen

Reference	N[a]	Adverse Events Grade 1-2 or moderate (n)	Adverse Events Grade 3-4 or serious (n)	Adverse Events Grade 5 (n)
Welch, 2015	15[b]	N.R.	Febrile neutropenia (5) Diarrhea (3) Mucositis (1) Pericarditis (1) Colitis (1) Anorexia (1) Fatigue (2)	N.R.
Chen, 2015	29[c]	Mucositis (common) Diarrhea (common)	Neutropenia (29) Thrombocytopenia (29) Bacterial infection (9) Fungal infection (1) CMV reactivation (1) Delirium (1) Aspiration (1) Thrombotic micro-angiopathy (1) Seizure (1) Engraftment syndrome (6)	Cognitive decline (1)
Côté, 2012	32[d]	Cystitis (3)	Bacterial infection (7) Fungal infection (2) Mucositis (23) Engraftment syndrome (1) Congestive heart failure (1) Delirium (7) Ataxia (1) Dysphagia (1) Weakness (1)	Bacterial infection (1) Cerebrovascular accident (1)

[a]: Number of patients treated with a thiotepa for injection-containing HDCT regimen.
[b]: 7 relapsed PCNSL patients and 8 relapsed SCNSL patients
[c]: 18 PCNSL patients and 11 SCNSL patients
[d]: 16 PCNSL patients and 16 SCNSL patients N.R.: Not reported

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Live attenuated virus or bacterial vaccines, including yellow fever vaccine (see **Drug-Drug Interactions**)
- Phenytoin (see **Drug-Drug Interactions**)
- Cyclophosphamide and other myelosuppressive or myelotoxic agents, for example (e.g.), melphalan, busulfan, fludarabine, treosulfan etc. (see **Drug-Drug Interactions**)

9.2 Drug Interactions Overview

Thiotepa appears to be metabolised to tepa via CYP3A4 and CYP2B6 *in vitro*.

Thiotepa is a major inhibitor for CYP2B6 *in vitro*, and may thereby potentially increase plasma concentrations of co-administered CYP2B6 substrates. CYP2B6 catalyzes the metabolic conversion of cyclophosphamide to its active form 4-hydroxycyclophosphamide (4-OHCP). The related findings and effects are discussed further below in Table 9.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 9 - Established or Potential Drug-Drug Interactions

Drug(s)	Ref	Effect	Clinical comment
Live attenuated vaccines (including yellow fever)	T	Risk of systemic, possibly fatal infection. This risk is increased in patients who are already immunosuppressed by their underlying disease.	Co-administration must be avoided. An inactivated virus or bacterial vaccine should be used instead.
Phenytoin	T	Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicinal product. Risk of increased toxicity or loss of efficacy of thiotepa, as phenytoin is a known inducer of CYP3A *in vitro*.	Concomitant use not recommended.
Cyclosporin, tacrolimus	T	Excessive immunosuppression. Risk of lymphoproliferation.	Caution should be exercised for co-administration; patients should be closely monitored.

Drug(s)	Ref	Effect	Clinical comment
Succinyl-choline	T	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.	Caution should be exercised during the use of depolarizing muscular relaxants soon after high-dose thiotepa. Observation for profound and prolonged respiratory depression and muscle weakness is recommended if these drugs must be used together.
Cyclophosphamide (and other myelosuppressive/myelotoxic agents, i.e. melphalan, busulfan, fludarabine, treosulfan)	T	The concomitant use of thiotepa and other myelosuppressive or myelotoxic agents may potentiate the risk of haematologic adverse reactions and pulmonary toxicity due to overlapping toxicity profiles of these medicinal products.	Thiotepa must not be concurrently administered with cyclophosphamide when both medicinal products are present in the same conditioning treatment. Thiotepa for Injection USP must be delivered after the completion of any cyclophosphamide infusion.
Oral Anticoagulants	T	Anticancer chemotherapy has the potential to affect the effectiveness and safety of concomitantly administered oral anticoagulants.	Caution should be exercised and patients should be closely monitored following the co-administration. The frequency of International Normalized Ratio monitoring (INR) monitoring should be increased.
CYP3A4 and CYP2B6 inducers	T	Co-administration of thiotepa with inducers of CYP3A4 and CYP2B6 may decrease thiotepa plasma concentrations and potentially increase the concentrations of the active metabolite TEPA.	When co-administration with CYP2B6 and CYP3A4 inducers is unavoidable, patients should be closely monitored.
CYP3A4 and CYP2B6 inhibitors	T	Co-administration of thiotepa with inhibitors of CYP3A4 and CYP2B6 may increase the plasma concentrations of thiotepa and potentially decrease the concentrations of the active metabolite TEPA.	When co-administration with CYP2B6 and CYP3A4 inhibitors is unavoidable, patients should be closely monitored.

Drug(s)	Ref	Effect	Clinical comment
CYP2B6 substrates	T	Co-administration of thiotepa with CYP2B6 substrates (cyclophosphamide) may lead to decreased concentrations of the active 4-OHCP.	In case of concomitant use with cyclophosphamide, please refer to the above clinical comment.

Legend: C = Case Study, CT = Clinical Trial, T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 Pharmacodynamics

The primary pharmacodynamic action of thiotepa for injection consists of damaging the DNA and cellular structure of malignant cells. When used in the conventional dose range, thiotepa's dose-limiting toxicity is bone marrow suppression. Autologous stem cell transplantation (ASCT) permits the use of thiotepa at doses higher than the conventional dose range and when combined with non-cross resistant cytotoxic agents, it is expected to provide improved cytoreduction and ideally disease eradication. Active metabolites of thiotepa have alkylating effects; however their clinical role is unclear.

10.3 Pharmacokinetics

Absorption:

Thiotepa is to be administered intravenously. 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. 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 of thiotepa at non-myeloablative doses in children with refractory malignancies, cerebrospinal fluid (CSF) medicinal product exposure is nearly equivalent to that achieved in plasma; the mean ratio of AUC in CSF to plasma for thiotepa is 0.92 and 0.99 for triethylenephosphoramide (tepa), a major metabolite of thiotepa. CSF and plasma concentrations of tepa exceed the concentrations of the parent compound.

Metabolism:

Thiotepa undergoes rapid and extensive hepatic metabolism and metabolites could be detected in urine within 1 hour after infusion. Thiotepa undergoes oxidative desulfuration via the cytochrome P450 CYP2B and CYP3A isoenzyme families to form the major metabolite tepa and also likely conjugation with glutathione to form thiotepa-mercapturate. 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.

Elimination:

The total clearance of thiotepa ranged from 11.4 to 23.2 L/h/m^2. The elimination half-life of thiotepa varied from 1.4 to 3.7 hours, the elimination half-life of tepa varied from 4.9 to 17.6 hours. The identified metabolites tepa, monochlorotepa and thiotepa-mercapturate are all excreted in the urine. 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. Thiotepa was also detected in skin and sweat of patients receiving high-dose regimens, although the percentage of skin excretion in the total dose of administration was unknown.

Special Populations and Conditions

- **Pediatrics:** Thiotepa for Injection USP is not indicated for pediatric patients, as CNS lymphoma is not typically seen in this population.

- **Geriatrics:** Thiotepa metabolism and elimination have not been assessed in elderly patients.

- **Hepatic Insufficiency:** No pharmacokinetic studies have been conducted in

patients with hepatic impairment. Since thiotepa is mainly metabolized through the liver, thiotepa exposure may be increased in patients with hepatic impairment.

- **Renal Insufficiency:** No pharmacokinetic studies have been conducted in patients with renal impairment. Urinary excretion is a major route of elimination of alkylating metabolites of thiotepa. Renal impairment may increase the exposure to these metabolites.

- **Obesity:** The pharmacokinetic profile of high-dose thiotepa for injection has not been established in obese patients. Increased thioTEPA/TEPA exposure has been reported in obese patients dosed on body surface area (BSA) calculated using total body weight. Consideration might be given to using adjusted body weight for calculating BSA.

11 STORAGE, STABILITY AND DISPOSAL

Unopened vial

Store and transport refrigerated (2 to 8 °C). Do not freeze. Keep out of reach and sight of children.

After reconstitution

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

After dilution

Chemical and physical in-use stability after dilution has been demonstrated for 24 hours when stored at 2 to 8 °C and for 4 hours when stored at 25°C. Thiotepa for Injection USP is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

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.

12 SPECIAL HANDLING INSTRUCTIONS

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.

Thiotepa for Injection USP is cytotoxic, carcinogenic, mutagenic and teratogenic. Pregnant staff and breastfeeding mothers should be excluded from the reconstitution and administration of Thiotepa

for Injection USP. Use caution during handling and preparation. Avoid ingestion, inhalation, or skin and eye contact. Skin reactions may occur with accidental exposure. Use of gloves and protective clothing to prevent accidental skin contact is recommended. If Thiotepa for Injection USP solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water, and seek medical attention.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

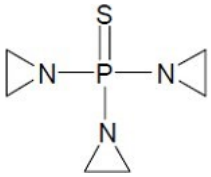
Drug Substance

Proper name: Thiotepa

Chemical name: N,N′,N′′-triethylenethiophosphoramide
Aziridine,1,1′,1′′-phosphinothioylidynetris
Tris(1-aziridinyl)phosphine sulfide

CAS Number: 52-24-4

Molecular formula and molecular mass: $C_6H_{12}N_3PS$, 189.23 g/mol



Structural formula:

Physicochemical properties: White crystalline powder.
Unstable in acid medium.
Solubility in water: 19g/100mL (25°C)
Solubility in other solvents: 1:2 in ethanol; 1:2 in chloroform; 1:~4 in ether

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Clinical evidence in support of the use of thiotepa for injection as part of a high-dose chemotherapy (HDCT) regimen followed by autologous stem cell transplantation (ASCT) for the consolidation treatment of adult patients with CNS lymphoma is derived from 18 published open-label clinical trials, 7 of which consisted of retrospective analyses. The majority of the studies were non-comparative; seven of them included a comparator group which consisted of patients considered ineligible to receive HDCT followed by ASCT. Patients received doses that ranged from 185 mg/m^2/day to 370 mg/m^2/day as one or two daily infusions administered intravenously over 2 to 3 consecutive days prior to ASCT, without exceeding the total maximum cumulative dose of 750 mg/m^2.

A total of 303 adult patients with CNS lymphoma received consolidation therapy consisting of thiotepa for injection-containing HDCT followed by ASCT. All patients were immunocompetent. CNS lymphomas were mostly primary B-cell types and their location included the brain parenchyma, the meninges, the spinal cord, and or the eye(s).

Table 10 - Summary of patient demographics for clinical trials in adult CNS lymphoma patients treated with a thiotepa for injection-containing HDCT regimen

Public-ations	Patients Exposed to Thiotepa[a]/all patients (N/N)	Median Age (years) (Range)	Elderly[a] (> 65 years old) N (%)	Gender[a] Male N (%) Female N (%)	Performance status[a] N	Chemosensit-ivity[a] Yes N (%) No N (%)	Prior cranio-spinal irradiation[a] N
Newly Diagnosed PCNSL							
Illerhaus 2008	11/13	53.0 (38.0-67.0)	3 (27.3)	5 (45.5) 6 (54.5)	KPS 30%: 1 KPS 70%: 2 KPS 80%: 1 KPS 90%: 6 KPS 100%: 1	8 (72.7) 3 (27.3)	0
Alimoha med 2012	21/21	56.0 (34.0-69.0)	3 (14.3)	12 (57.1) 9 (42.9)	ECOG PS 1: 4 ECOG PS 2: 8 ECOG PS 3: 6 ECOG PS 4: 3	18 (85.7) 3 (14.3)	0
Illerhaus 2006	23/30	54.0 (27.0-64.0)	n.s.	25* (83.3) 5* (16.7)	Median KPS: 70% (range 30% – 100%)*	23 (100) 0 (0.0)	0
Montem urro 2007	16/23	54.5 (18.0-69.0)	3 (18.8)	8 (50.0) 8 (50.0)	KPS 30%: 1 KPS 40%: 2 KPS 60%: 2 KPS 70%: 4 KPS 80%: 3 KPS 90%: 2 KPS 100%: 2	14 (87.5) 2 (12.5)	0
Omuro 2015	26/32	57.0 (23.0-67.0)	n.s.	17* (53.1) 15* (46.9)	Median KPS: 80 (40-100)	25 (96.2) 1(3.8)	0
Bojic 2015	5/5	42.0 (33.0-48.0)	n.s.	2 (40.0) 3 (60.0)	n.s.	5 (100.0) 0 (0.0)	0
Cote 2012	16/16	49.5 (26.0-67.0)	n.s.	5 (31.3) 11 (68.7)	ECOG PS <2: 16 ECOG PS ≥2: 0	15 (93.8) 1 (6.2)	2
Refractory PCNSL							
Soussain 1996	5/11	57.0 (45.0-88.0)	n.s.	1(20.0) 4 (80.0)	n.s.	0 (0.0) 5 (100.0)	2
Soussain	20/22	53.0	n.s.	10 (50.0)	n.s.	17 (85.0)	10

Public-ations	Patients Exposed to Thiotepa[a]/all patients (N/N)	Median Age (years) (Range)	Elderly[a] (> 65 years old) N (%)	Gender[a] Male N (%) Female N (%)	Performance status[a] N	Chemosensit-ivity[a] Yes N (%) No N (%)	Prior cranio-spinal irradiation[a] N
2001		(27.0-64.0)		10 (50.0)		3 (15.0)	
Soussain 2008	27/43	52.0 (23.0-65.0)	n.s.	22* (51.2) 21* (48.8)	ECOG PS < 2: 30 ECOG PS ≥2: 12 ECOG PS n.a.: 1	15 (55.5) 12 (44.5)	14*
Cheng 2003	1	41.0	n.s.	1 (100.0) 0 (0.0)	KPS 50% = 1	1 (100.0) 0 (0.0)	0
Sierra del Rio 2011	13/22	57.0 (22.0-65.0)	n.s.	9 (69.2) 4 (30.8)	ECOG PS 0: 3 ECOG PS 1: 8 ECOG PS 2: 2	11 (84.6) 2 (15.4)	0
Chen 2015	18/18	54.0 (24.0-69.0)	n.s.	7 (38.9) 11 (61.1)	n.s.	18 (100.0) 0 (0.0)	0
Welch 2015	7/8	53 (35.0-61.0)	n.s.	3 (42.9) 4 (57.1)	Median KPS 80% (80% – 100%)	7 (100.0) 0 (0.0)	3
SCNSL							
Cote 2012	16/16	45.0 (21.0-67.0)	n.s.	10 (62.5) 6 (37.5)	ECOG PS <2: 16 ECOG PS ≥2: 0	15 (93.8) 1 (6.3)	1
Lee 2015	12/31	54.5 (24.0-63.0)	n.s.	5 (41.7) 7 (58.3)	ECOG PS <2: 12 ECOG PS ≥2: 0	11 (91.7) 1 (8.3)	2
Oh 2016	23/23	62.0 (20.0-66.0)	n.s.	11 (47.8) 12 (52.2)	ECOG PS 2 – 4: 15	22 (95.7) 1 (4.3)	3
Chen 2015	11/12	63.0 (53.0-74.0)	n.s.	6 (50.0) 6 (50.0)	n.s.	11 (91.7) 0 (0.0)	2
Korfel 2013	24/30	58.0 (29.0-65.0)	n.s.	15* (50.0) 15* (50.0)	ECOG PS 0-1: 18 ECOG PS 2: 12	21 (87.5) 3 (12.5)	0
Welch 2015	8/9	47.5 (29.0-64.0)	n.s.	~~4~~ 5 (62.5) ~~4~~ 3 (37.5)	Median KPS: 90% (60% – 90%)*	8 (100.0) 0 (0.0)	1

[a] of patients treated with thiotepa for injection-containing HDCT
* data on all enrolled patients
n.s. = Not Specified; KPS: Karnosfsky performance status; ECOG PS: Eastern Cooperative Oncology Group performance status

14.2 Study Results

Response rate was the main efficacy endpoint to assess the benefit of thiotepa for injection-containing HDCT regimens in CNS lymphoma patients. Survival analyses were conducted for the majority of studies. Overall survival (OS), progression free-survival (PFS) or disease-free survival (DFS) are included in Tables 9 to 13 when reported. Due to differences across studies in defining andreporting efficacy endpoints, study results were not pooled.

Table 11 - Efficacy results in newly diagnosed PCNSL patients administered with a thiotepa for injection-containing HDCT regimen

Publications	Patients[a] N	Response status prior to HDCT-ASCT N (%)	Follow-up duration Median (range)	Efficacy Data		
				ORR to HDCT-ASCT N (%)	DFS/PFS	OS
Illerhaus 2006	23	CR: 10 (38.4)[b] PR: 14 (54)[b] SD: 1 (3.8)[b] PD: 1 (3.8)[b]	63 months (4-84)	CR 15 (65.2) PR 8 (34.8)	N.R.	Estimated 3- and 5-year OS= 87.0%
Montemurro 2007	16	CR: 3 (18.8) PR: 11 (68.8) SD: 1 (6.2) PD: 1 (6.2)	15 months (1-69)	CR: 11 (70.0) PR: 2 (13.0) SU: 2 (13.0) PD: 1 (6.5)	2-year DFS =48.0%	2-year OS= 61.0%
Illerhaus 2008	11	CR: 4 (36.4) PR: 4 (36.4) SD: 1 (9.0) PD: 2 (18.2)	25 months (2-50)	CR: 7 (64.0) PR: 4 (36.0)	3-year DFS= 77.0%	3-year OS = 77.0%
Alimohamed 2012	21	CR: 5 (23.8) PR: 13 (61.9) PD: 3 (14.3)	60 months (7-125)	N.R.	5-year PFS= 44.0%	5-year OS= 44.0%
Omuro 2015–	26	CR: 18 (69.2) PR: 7 (26.9) SD: 1 (3.9)	45 months (27-86)	CR: 21 (81) PR: 3 (11) SD: 1 (4) PD: 1 (4)	1-year PFS = 85.0% Estimated 2-, 3-, and 5 year PFS = 81.0%	1-year OS = 88.0% Estimated 2-, 3-, and 5 year OS = 81.0%
Bojic 2015	5	N.R.	8 months (3-51)	CR: 3 (60.0)	N.R.	N.R.

[a]Number of patients treated with a thiotepa for injection-containing HDCT regimen followed by ASCT;
[b]percentage calculated on the whole patients who received the mobilization therapy (N=26)
ORR: Objective Response rate; CR: complete response, PR: partial response, SD: stable disease; PD: progressive disease; SU: status unknown; DFS: disease-free survival; PFS: progression-free survival; OS: overall survival; N.R.: not reported in the publication.

Table 12 - Efficacy results in relapsed/refractory PCNSL patients administered with a thiotepa for injection-containing HDCT regimen

Publications	Patients[a] N	Response status prior to HDCT-ASCT N (%)	Follow-up duration Median (range)	Efficacy Data		
				ORR to HDCT-ASCT N (%)	DFS/PFS	OS
Soussain 1996	5	PD: 5 (100.0)	26.0 months (16.0-27.0)	CR: 5 (100.0)	N.R.	N.R.
Soussain 2001	20	CR: 8 (40.0) PR: 4 (20.0) SD: 1 (5.0) PD: 7 (35.0)	41.5 months (N.R.)	CR: 16 (80.0) PR: 2 (10.0) SD: 1 (5.0) PD: 1 (5.0)	3-year probability of DFS= 53%	3-year probability of OS=60%
Soussain 2008	27	CR: 12 (44.5) PR: 3 (11.1) SD: 1 (3.7) PD: 11 (40.7)	36.0 months (N.R.)	CR: 26 (96.0) PD: 1 (3.7)	Median PFS =41.1 months	Median OS = 58.6 months
Sierra del Rio 2011	13	CR: 5 (38.5) PR: 6 (46.1) PD: 2 (15.4)	22.0 months (3.0-35.0)	CR: 10 (76.9) PR: 2 (15.4) SU: 1 (7.7)	Median PFS =22.0 months	Median OS =22.0 months

[a]Number of patients treated with a thiotepa for injection-containing HDCT regimen followed by ASCT;
CR: complete response, PR: partial response, SD: stable disease; PD: progressive disease; SU: status unknown; DFS: disease-free survival; PFS: progression-free survival; OS: overall survival; N.R.: not reported in the publication.

Table 13 - Efficacy results in SCNSL patients administered with a thiotepa for injection-containing HDCT regimen

Publications	Patients[a] N	Response status prior to HDCT-ASCT N (%)	Follow-up duration Median (range)	Efficacy Data		
				ORR to HDCT-ASCT N (%)	DFS/PFS/TTF	OS
Lee 2015	12	CR: 10 (83.3) PD: 2 (16.7)	19.0 months (9.0-58.0)	CR: 6 (50.0) PR: 5 (41.7) PD: 1 (8.3)	N.R.	1.5 years OS = 50.0%
Oh 2016	23	CR: 9 (39.1) PR: 13 (56.5) PD: 1 (4.4)	27.8 months (4.2-113.6)	CR: 20 (87.0) PR: 3 (13.0)	2-year PFS = 76.1%	2-year OS= 76.1%
Korfel 2013	24	CR: 7 (25.9)[b] PR: 13 (48.1) SD: 2 (7.5) PD: 4 (14.8) SU: 1 (3.7)	21.0 months (10.0-32.0)	CR: 15 (63.0) PR: 2 (8.0) PD: 7 (29.0)	2-year TTF = 58.0%	2-year OS = 68.0%

[a]Number of patients treated with a thiotepa for injection-containing HDCT regimen followed by ASCT;
[b]percentage calculated on the whole patients who completed the induction therapy (N=27)
CR: complete response, PR: partial response, SD: stable disease; PD: progressive disease; SU: status unknown; DFS: disease-free survival; PFS: progression-free survival; OS: overall survival; N.R.: not reported in the publication.
TTF: time to treatment failure, measured from start of study therapy (for HD-ASCT from time of ASCT) to first progression, relapse or death due to lymphoma or to therapy-related toxicity.

Table 14 - Efficacy results in relapsed PCNSL patients administered with a thiotepa for injection-containing HDCT regimen

Publications	Patients[a] N	Response status prior to HDCT-ASCT N (%)	Follow-up duration Median (range)	Efficacy Data		
				ORR to HDCT-ASCT N (%)	*DFS/PFS*	*OS*
Cheng 2003	1	CR: 1 (100.0)	42 months	CR: 1 (100.0)	DFS 31 months	Survival: 42 months

[a] Number of patients treated with a thiotepa for injection-containing HDCT regimen followed by ASCT.
CR: complete response; DFS: disease-free survival; PFS: progression-free survival; OS: overall survival.

Table 15 - Efficacy results in PCNSL and SCNSL patients administered with a thiotepa for injection-containing HDCT regimen

Publications	Patients[a] N	Response status prior to HDCT-ASCT N (%)	Follow-up duration Median (range)	Efficacy Data		
				ORR to HDCT-ASCT N (%)	*DFS/PFS*	*OS*
Welch 2015	15[b]	CR: 15 (100.0)	34.0 months (7.0-86.0)	N.R.	mPFS not reached Estimated 3-year PFS: 93% Estimated 3 years ≈100% in PCNSL Estimated 3 years ≈87% in SCNSL	mOS not reached Estimated 3-year OS: 93% Estimated 3 years ≈100% in PCNSL Estimated 3 years ≈87% in SCNSL
Chen 2015	29[c]	CR: 27 (93.1) PR: 2 (6.9)	24.0 months (12-40)	CR: 29 (100.0)	Estimated 2-year PFS: 100% in PCNSL Estimated 2-year PFS: 51% in SCNSL	Estimated 2-year OS: 100% in PCNSL Estimated 2-year OS: 83% in SCNSL
Cote 2012	32[d]	CR: 18 (56.3) PR: 12 (37.5) SD: 1 (3.1) PD: 1 (3.1)	12.5 months (0.01-48.2)	N.R.	1-year PFS estimate = 90%	1-year OS estimate= 93%

[a] Number of patients treated with a thiotepa for injection-containing HDCT regimen followed by ASCT;
[b] 7 relapsed PCNSL patients and 8 relapsed SCNSL patients
[c] 18 PCNSL patients and 11 SCNSL patients
[d] 16 PCNSL patients and 16 SCNSL patients
CR: complete response, PR: partial response, SD: stable disease; PD: progressive disease; SU: status unknown; DFS: disease-free survival; PFS: progression-free survival; OS: overall survival; N.R.: not reported in the publication.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Non-conventional acute and repeat dose toxicity studies were performed. As to be expected with a nitrogen mustard-based alkylating agent, application of thioTEPA was shown to have relevant mutagenic, teratogenic and genotoxic unwanted effects. The major side effect of thioTEPA is bone marrow suppression in all animal models and in man. Bleeding, disturbance of coagulation, various organotoxic effects on CNS, liver, skin and most importantly the impairment of fertility have been recognised in preclinical models and observed in clinical settings, too.

Carcinogenicity: Thiotepa was shown to be carcinogenic in mice and rats.

Genotoxicity: Thiotepa was shown to be genotoxic *in vitro* and *in vivo*.

Reproductive and Developmental Toxicology: Thiotepa was shown to impair fertility by interfering with spermatogenesis in male mice and impairing ovarian function in female mice. It was teratogenic in mice and in rats, and fetolethal in rabbits. These effects were seen at doses lower than those used in humans.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrTEPADINA® (powder for solution, 15 mg / vial and 100 mg / vial), submission control #252188, Product Monograph, ADIENNE SA. (December 29, 2021).

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] Thiotepa for Injection USP

Read this carefully before you start taking **Thiotepa for Injection USP** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Thiotepa for Injection USP**.

Serious Warnings and Precautions

Thiotepa for Injection USP administration must be supervised by a doctor experienced in the use of anticancer medicines.

Thiotepa for Injection USP can cause severe side effects, which include:

- **Myelosuppression** (bone marrow suppression) which causes a large decrease in the production of blood cells and platelets by the bone marrow. This occurs in all patients receiving Thiotepa for Injection USP. It causes severe cases of any combination of the following conditions. These conditions may lead to death.
  - Neutropenia: a low amount of neutrophils, which are a type of white blood cell.
  - Thrombocytopenia: a low amount of platelets. Platelets help your blood clot.
  - Anemia: a low amount of red blood cells or hemoglobin.
- **Cardiac toxicity**: damage to the heart.
- **Liver toxicity**: damage to the liver.
- **Hepatic veno occlusive disease (VOD)**: a condition where liver veins are blocked. Patients who have received radiation therapy in the past, those who have received chemotherapy in the past or those who have received stem cell transplantation in the past have a greater risk of getting hepatic veno occlusive disease (VOD).
- **Pulmonary toxicity**: damage to the lungs. This effect may be increased when Thiotepa for Injection USP is used with other anticancer medicines like busulfan, fludarabine and cyclophosphamide.
- **Neurotoxicity**: damage to the nervous system. Patients who have received prior radiation therapy of the brain, skull or the spine can experience more severe damage to the nervous system.
- **Kidney toxicity**: damage to the kidneys.
- Harm to an unborn baby. Thiotepa for Injection USP should NOT be used during pregnancy because it can harm your baby.

- Serious interactions with other medicines. See section **The following may interact with Thiotepa for Injection USP**, below, for information about these medicines.

What is Thiotepa for Injection USP used for?

For the following indication Thiotepa for Injection USP has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada. For more information, talk to your healthcare professional.

- Thiotepa for Injection USP is used to treat adult patients with central nervous system (CNS) lymphoma. It is used in combination with other anticancer medicines and is followedby stem cell transplantation.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c to actively monitor the drug's performance after it has been sold, to report their findings to Health Canada, and in some circumstances, to complete more testing to make sure the drug works the way it should.

How does Thiotepa for Injection USP work?

Thiotepa for Injection USP belongs to a group of medicines known as cytotoxic agents. It is used in combination with other drugs to treat cancer. It treats cancer by stopping the cancer cells from growing which eventually kills them.

What are the ingredients in Thiotepa for Injection USP?

Medicinal ingredients: thiotepa.

Non-medicinal ingredients: Thiotepa for Injection USP does not contain any other ingredients.

Thiotepa for Injection USP comes in the following dosage forms:

15 mg or 100 mg: Powder in a glass vial.

Do not use Thiotepa for Injection USP if:

- you are allergic (hypersensitive) to thiotepa or other ingredients in Thiotepa for Injection USP;
- you are pregnant;
- you are breastfeeding;
- you are receiving a live virus or a live bacterial vaccine, including yellow fever vaccine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Thiotepa for Injection USP. Talk about any health conditions or problems you may have, including if you:

- have or have had liver problems;
- have or have had kidney problems;
- have or have had heart problems;
- have lung problems;
- have or have had problems with your bladder;
- have received radiation therapy in the past;
- have received chemotherapy in the past;
- have received stem cell transplantation in the past;
- have an active infection;
- have or have had in the past, an active infection with cytomegalovirus (CMV). This is because Thiotepa for Injection USP can cause your CMV to become active again;
- have seizures/fits (epilepsy) or have had them in the past (if treated with phenytoin or fosphenytoin);
- are planning to receive any vaccine;
- are obese;
- are older than 65 years of age.

Other warnings you should know about:

- Thiotepa for Injection USP can come through your skin when you sweat. You will be instructed by your healthcare professional to bathe often and to avoid touching others while receiving Thiotepa for Injection USP.
- Your healthcare professional may recommend you to drink more fluids to stay hydrated during treatment with Thiotepa for Injection USP.

Infections

Thiotepa for Injection USP weakens your immune system. Your doctor may prescribe you anti-infective medicines to prevent and manage infections.

Cancer

Thiotepa for Injection USP may cause another type of cancer in the future. Your doctor will discuss this risk with you.

Female patients

Pregnancy and birth control

- Thiotepa for Injection USP must NOT be used during pregnancy because it may cause harm to an unborn baby.
- You must tell your doctor if you are or think you may be pregnant before you receive Thiotepa for Injection USP. There are specific risks you should discuss with your healthcare professional.
- If you are able to become pregnant:
    - Your doctor will give you a pregnancy test before you receive Thiotepa for Injection USP. This is to make sure that you are not pregnant.
    - Avoid becoming pregnant while receiving Thiotepa for Injection USP.
    - You must use an effective birth control method while receiving Thiotepa for Injection USP. Talk to your doctor for advice on effective methods of birth control.
    - Tell your doctor right away if you become pregnant during treatment with Thiotepa for Injection USP.

Breastfeeding

- Do NOT breastfeed while receiving Thiotepa for Injection USP. It may pass into the breast milk and harm your baby.
- Talk to your healthcare professional about the best way to feed your baby during treatment with Thiotepa for Injection USP.

Male patients

- Do NOT father a child during treatment with Thiotepa for Injection USP.
- Use effective birth control method while receiving Thiotepa for Injection USP. Talk to your doctor for advice on effective methods of birth control.

Fertility in Males and Females

Thiotepa for Injection USP may decrease your ability to have children in both male and female patients. If you plan to have children, talk to your doctor before you start treatment with Thiotepa for Injection USP. Your doctor will discuss fertility preservation options with you.

Blood tests and monitoring

You will have to have regular blood tests before and during treatment to check your blood cell counts. Your doctor will also monitor the functioning of your heart and your kidneys during treatment with Thiotepa for Injection USP. They will also monitor the functioning of your liver by checking your liver enzyme levels during treatment with Thiotepa for Injection USP.

Driving and using machines

Thiotepa for Injection USP can cause spasms, confusion, dizziness, or vision problems.

Before you drive or do tasks that require special attention, wait until you know how you respond to Thiotepa for Injection USP.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

While taking Thiotepa for Injection USP, avoid:

- Live attenuated virus or bacterial vaccines, including yellow fever vaccine
- Phenytoin, a medicine used to treat seizures;
- Anticancer medicines that cause bone-marrow suppression (myelosuppression), including:
  - Cyclophosphamide
  - Melphalan, busulfan, fludarabine, treosulfan, etc.

The following may also interact with Thiotepa for Injection USP:

- Cyclosporin, a medicine that suppresses the immune system and is used to prevent organ rejection following transplantation. It is also used to treat rheumatoid arthritis and psoriasis;
- Tacrolimus, a medicine used to prevent organ rejection following transplantation;
- Succinylcholine is a medicine used as part of general anesthesia for surgery;
- Anticoagulants taken by mouth, which are medicines that prevent blood clotting.

How to take Thiotepa for Injection USP:

Thiotepa for Injection USP will be given to you by a healthcare professional. It will be infused directly into your vein. Each infusion will last 2 to 4 hours.

Usual dose:

Your doctor will decide how much Thiotepa for Injection USP you should receive based on your height and your weight.

You will receive a Thiotepa for Injection USP infusion once or twice a day. You will receive Thiotepa for Injection USP for 2 to 3 days in a row before you are given a stem cell transplant. Thiotepa for Injection USP will be given to you along with other anticancer medicines. Your doctor will decide how often and for how long you should receive Thiotepa for Injection USP.

Overdose:

In the event you should be accidentally administered a higher dose of Thiotepa for Injection USP than that prescribed, your doctor will decide whether to perform blood tests and to undertake supportive care, if necessary.

What are possible side effects from using Thiotepa for Injection USP?

These are not all the possible side effects you may feel when taking Thiotepa for Injection USP. If you experience any side effects not listed here, contact your healthcare professional.

- Anorexia, decreased appetite, weight loss
- Arthralgia (joint pain)
- Myalgia (muscle pain)
- Changes in muscle tone: back pain, joint pain
- Pain or inflammation at the injection site
- Cough
- Erythema (redness of the skin)
- Skin colour disorder (patches of skin become darker in color than the normal surrounding skin. Do not confuse with jaundice)
- Hair loss
- Weight gain
- Amenorrhea (having no menstrual periods)
- Loss of fertility in men and women

Thiotepa for Injection USP may cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Myelosuppression (a large decrease in the production of blood cell and platelets by the bone marrow): bleeding, bruising, chills, fatigue, fever, infections, weakness.		X	
Edema / water retention (excess fluid in body tissues): swelling of the body in the hands, feet or legs or elsewhere.		X	
Gastrointestinal problems (damage to the gastrointestinal system): abdominal pain, bloating, blood in stool, constipation, decreased appetite, diarrhea, nausea, vomiting, vomiting blood.		X	
Mucositis (inflammation and ulceration of the mucous membranes lining the digestive tract): painful ulcers, sores and blisters of the mouth, throat, stomach and intestines.		X	
Nervous system disorders (damage to the nervous system): agitation, blurred vision, confusion, convulsions, difficulty speaking, dizziness, hallucinations, headache, impaired thinking, loss of control of body movements, memory loss, mental status changes, nervousness, numbness and tingling, vision loss, muscle weakness, seizures.		X	
Sepsis and septic shock (life-threatening complication of an infection): chills, high or very low body temperature, little or no urine, low blood pressure, palpitations, rapid breathing, rapid heartbeat.		X	
COMMON			
Cardiac problems (damage to the heart): chest pain, fatigue, heart stops beating, palpitations, shortness of breath, swelling in the legs and ankles, weakness.		X	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Engraftment syndrome (an inflammatory condition occurring after the transplant): diarrhea, difficulty breathing that is worse when lying down, fever, skin rash, weight gain.		X	
Kidney problems: (damage to the kidneys): back and abdominal pain, change in the colour of urine (pale or dark) decrease in amount of urine produced, pain or discomfort when urinating, swelling of the legs and ankles.		X	
Liver problems (damage to the liver): abdominal pain, dark urine, fatigue, loss of appetite, nausea, vomiting, yellowing of the skin or eyes (jaundice).		X	
Lung problems (damage to the lungs) coughing up blood, difficulty breathing, sharp pain in the chest, shortness of breath (can be sudden), blood clot in lungs.		X	
UNCOMMON			
Dehydration		X	
Stevens-Johnson Syndrome and **Toxic Epidermal Necrolysis** (life-threatening skin conditions): blisters, rash, skin peeling, especially in mouth and eyes.		X	
UNKNOWN			
Stroke: disturbance of vision or speech, facial weakness, dizziness, fainting, numbness or weakness in an arm or leg, sudden severe headache, vomiting.		X	
Erythrodermic psoriasis (inflammation and scaling of the skin): severe redness, scaling and shedding of the skin over a large area of the body.		X	
Bladder infection: blood in urine, difficulty or increased need to urinate; pain or burning sensation when passing urine; urine that appears cloudy; pain in the pelvis; or mid-back pain.		X	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Graft versus host disease (a condition where the transplanted cells attack your body): Abdominal pain, diarrhea, itching, nausea, skin rash, redness and blistering, vomiting, yellowing of the skin and eyes (jaundice).		X	
Thromboembolism (blood clot): Pain, redness or swelling in the legs or feet that may be warm to the touch.		X	
High blood pressure: shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin.		X	
Hyperglycemia (high blood sugar): increased thirst, frequent urination.		X	
Cataract (a clouding of the lens in the eye which leads to a decrease in vision): vision disturbances.		X	
Hearing loss and ringing in the ears.		X	
Symptoms of menopause: hot flashes, irregular periods.		X	
Hypothyroidism (underactivity of the thyroid gland) in children: fatigue, weakness, weight gain.		X	
Hypopituitarism (underactivity of the pituitary gland): abdominal pain, fatigue, weakness, weight loss.		X	
Growth retardation (delaying in weight and height increase) in children.		X	
Hyponatremia (low level of sodium in the blood): coma, confusion, headaches, nausea, poor balance, seizure.		X	
Allergic (hypersensitivity) reaction: hives, rash, swelling of the face, lips or throat that may cause difficulty in breathing or swallowing.		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Thiotepa for Injection USP will be managed and stored by healthcare professionals. The information on how to store Thiotepa for Injection USP is meant for your healthcare professional.

Store powder refrigerated (2°C to 8°C). Do not freeze. Keep out of the reach and sight of children.

If you want more information about Thiotepa for Injection USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sterimaxinc.com, or by calling 1-800-881-3550.

This leaflet was prepared by SteriMax Inc.

Last Revised: October 4, 2023