Product Monograph

Including Patient Medication Information

Pr **TEPADINA®**

Thiotepa for Injection, BP

Lyophilised powder for infusion upon reconstitution and dilution, 15 mg or 100 mg,

For intravenous use

Lyophilised powder, 200 mg or 400 mg thiotepa/bag with solvent for reconstitution,

For intravenous use

Antineoplastic Agent

ATC Code: L01AC01

Manufacturer:
ADIENNE SA
Via Zurigo 46 - 6900
Lugano - Switzerland

Date of Authorization:
2026-03-27

Distributor / Importer:
Andone Pharmaceutical Inc.
2010 Winston Park Drive, Suite 200
Oakville, ON L6H 5R7
Canada

Control Number: 299984

Recent Major Label Changes

1. Indications	2026-02
4. Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	2026-02
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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

TEPADINA (Thiotepa for Injection) is indicated for:

- *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*

TEPADINA 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 TEPADINA as part of a HDCT regimen in geriatric patients (>65 years of age) with CNS lymphoma. Caution is needed in these patients.

2. Contraindications

TEPADINA is contraindicated in:

- Patients who are hypersensitive to this drug or component of the container. For a complete listing, please see the Dosage Forms, Strengths, Composition, and Packaging section of the product monograph.
- Female patients who are pregnant or breastfeeding (please see Warnings and Precautions).
- Concomitant use with live virus or bacterial vaccines including yellow fever vaccine (please see Warnings and Precautions).

3. Serious Warnings and Precautions Box

Serious Warnings and Precautions

TEPADINA 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 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 Warnings and Precautions, **Cardiovascular**).
- Hepatotoxicity: Liver function must be monitored regularly and caution is advised in patients with hepatic impairment (see Warnings and Precautions, **Hepatic/biliary/pancreatic** and 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 Warnings and Precautions, **Hepatic/biliary/pancreatic**, Hepatic Impairment, 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 Warnings and Precautions, **Respiratory** and Drug Interactions).

- Neurotoxicity may be greater in patients with prior brain or craniospinal irradiation (see Warnings and Precautions, **Neurologic and Psychiatric**).

- Renal toxicity (see Warnings and Precautions, **Renal**).

- TEPADINA could cause fetal harm when administered to a pregnant female (see Warnings and Precautions, **Special Populations,** Pregnancy)**.**

- Serious drug interactions (see Drug Interactions).

4. Dosage and Administration

4.1. Dosing Considerations

TEPADINA 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 TEPADINA 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 - TEPADINA high-dose chemotherapy regimens used in CNS lymphoma patients

Reference	Days of TEPADINA administration[a]	HDCT regimen	TEPADINA 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

Reference	Days of TEPADINA administration[a]	HDCT regimen	TEPADINA Dose	
			Total Daily Dose	Cumulative Dose
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
ADN013 Study[c]	----	----	----	520mg/m^2

[a]Infusion of autologous blood stem cells on Day 0; [b]Three patients additionally received rituximab; [c]ADN013 Study post-market data; TT: Tepadina; Bu: Busulfan; Cy: Cyclophosphamide: BCNU: Carmustine; VP-16: Etoposide; R: Rituximab; Mel: Melphalan.

The recommended doses of TEPADINA are intended only as part of a HDCT regimen followed by SCT.
Special populations:

- **Pediatrics (<18 years of age):** Health Canada has not authorized an indication for pediatric use.
- **Geriatrics (>65 years of age):** There is limited clinical data on the use of high-dose TEPADINA as part of a HDCT regimen in geriatric patients with CNS lymphoma. Caution is needed in these patients.
- **Hepatic impairment:** The safety and efficacy of high-dose TEPADINA has not been established in patients with hepatic impairment. TEPADINA 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.
- **Renal impairment:** The safety and efficacy of high-dose TEPADINA 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.
- **Obesity**: Consideration might be given to using adjusted body weight for calculating BSA (see Pharmacokinetics, **Special Populations and Conditions**).

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

TEPADINA 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 TEPADINA 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.

Reconstitution in Multichamber Flexible bag
The bag must only be removed from the aluminum wrapper immediately before the use.

TEPADINA 200 mg and 400 mg must be reconstituted with 200 mL and 400 mL sodium chloride 9 mg/mL (0.9%) solution for injection respectively. The final reconstituted solution is obtained after breaking the peelable seal of the dual chamber bag and mixing the contents (powder and solvent) until complete dissolution of the powder.

After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.
Only colourless solutions, without any particulate matter, must be used.

Dose Adjustments of Multichamber Flexible bag Calculated According to the Posology
If necessary, dose adjustment of TEPADINA must be operated as per specific application (*Recommended Dose and Dosage Adjustment*).
In order to ensure the dose to be administered, an adjustment may be needed by withdrawal or addition of the solution, as follows:

- withdrawal (*if the required dose is less than 200 mg or 400 mg*)

withdraw an appropriate volume of the reconstituted solution (1 mg/mL), as needed, with a graduated syringe using the luer port (Step 5 of the Instruction for Use) or set an infusion pump with the amount of medicinal product to be administered in mL;

- addition (*if the required dose is greater than 200 mg or 400 mg*)
  the appropriate volume of the reconstituted solution from TEPADINA 15 mg or 100 mg vials (10 mg/mL) should be transferred into the Multichamber Flexible bag through the dedicated luer port (Step 5 of the Instruction for Use as mentioned in the below instructions).

Preparation of the Multichamber Flexible bag for Administration

Before administering the product in Multichamber Flexible bag to the patient, refer to the instruction for use in the panels below:

Figure A

1 - Overpouch Notch

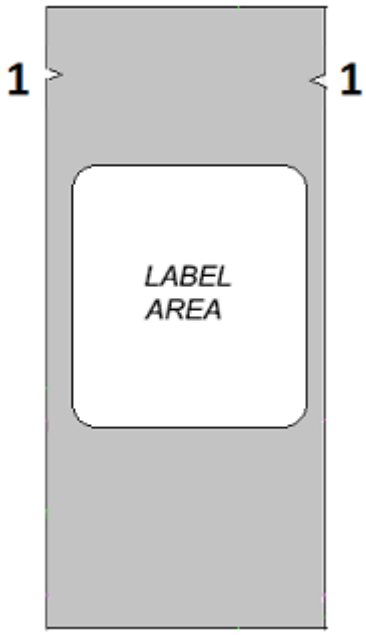
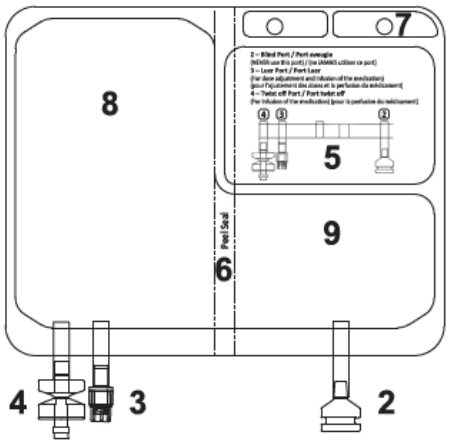


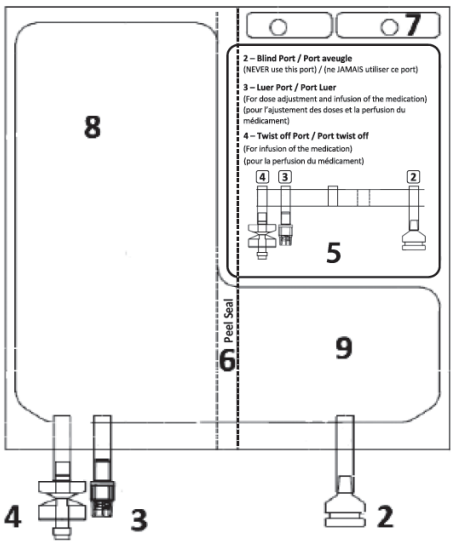
Figure B

2 – Blind Port (NEVER use this port)
3 – Luer Port
4 – Twist off Port
5 – Label Area
6 – Peel Seal (Must break to activate)
7 – Hole (For hanging the bag)
8 – Solvent chamber
9 – Powder chamber

TEPADINA 200 mg



TEPADINA 400 mg



<table>
<tr><th colspan="2">1 – REMOVE OVERPOUCH</th></tr>
<tr><td>a) Place bag on a clean, stable surface before opening.
b) Tear from Overpouch Notch located close to the ports (Figure A – point 1).
c) Tear short sides open to access the inner bag as per Figure C.

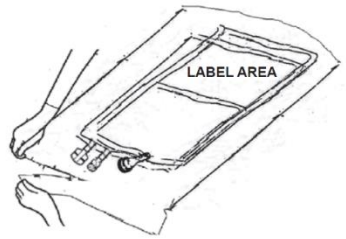
Figure C
 
</td><td>d) Remove the dual chamber flexible bag from the aluminum secondary packaging and unfold the bag Figure D.

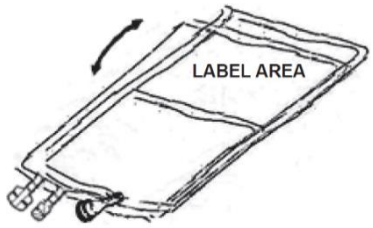
Figure D
 
</td></tr>
<tr><th>2 – INSPECT BAG PRIOR TO ACTIVATION</th><th>3 – ACTIVATE THE BAG</th></tr>
<tr><td>Place bag on a clean, stable surface with text side up and ports pointing away from you, as per Figure E.
Check that there are no liquid or product leakages from the connection ports 2, 3, 4 and from the chamber 8, 9.
Check the integrity of peel seal 6, verifying the absence of liquid in the chamber 9.

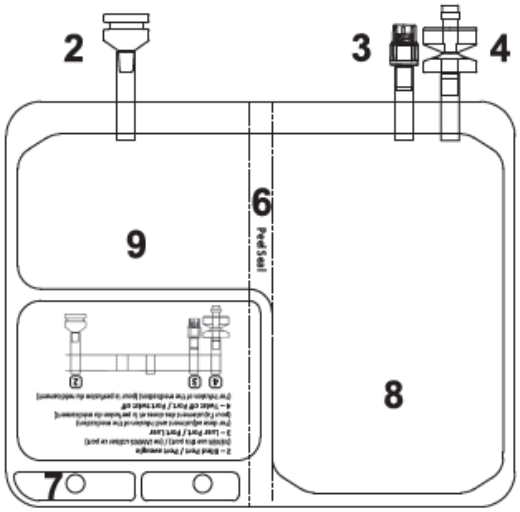
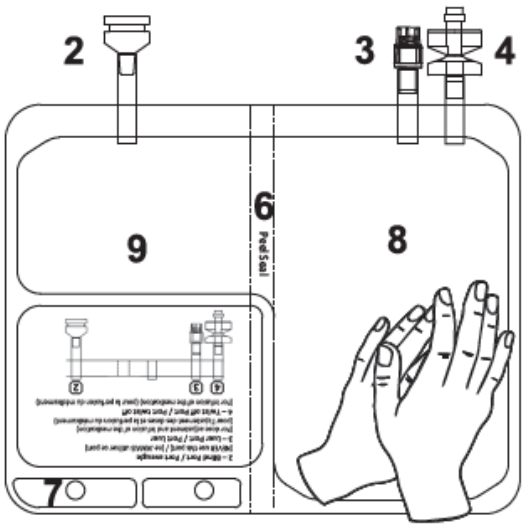
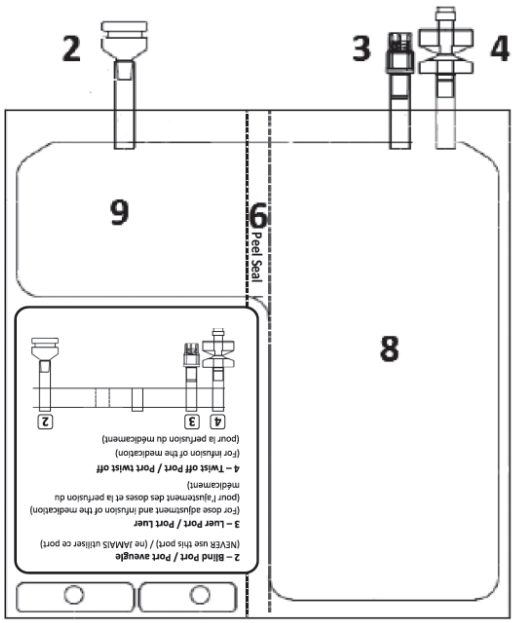
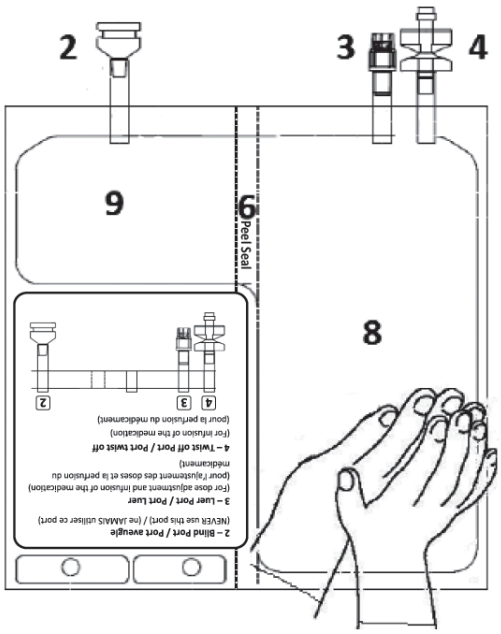
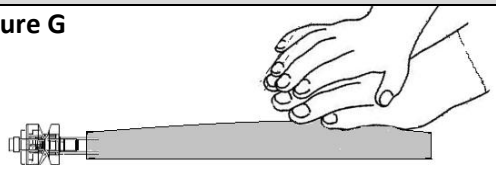
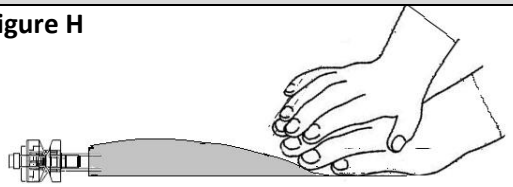
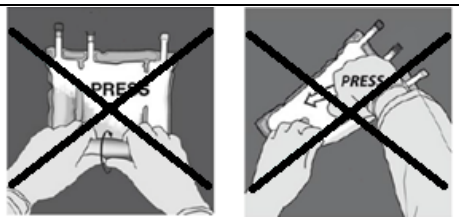
Figure E
TEPADINA 200 mg
 
</td><td>Overlap your hands, on the lower portion of chamber 8 (as per Figure F).
Press firmly in order to apply uniform pressure until peel seal 6 is completely activated (it may take up to 5 seconds of continued pressure to break the peel seal 6).

Figure F
TEPADINA 200 mg
 
</td></tr>
</table>

TEPADINA 400 mg	TEPADINA 400 mg
	
BAG BEFORE ACTIVATION	**BAG AFTER ACTIVATION**
Figure G 	**Figure H** 
Do NOT squeeze or press strongly.	**Figure I** 

<table>
<tr><th colspan="3">4 – INSPECT BAG TO CONFIRM ACTIVATION</th></tr>
<tr><td colspan="1">Check the peel seal 6 is now completely activated.
Chamber 8 and 9 are merged.

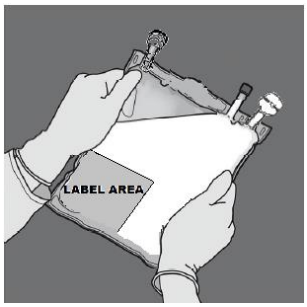
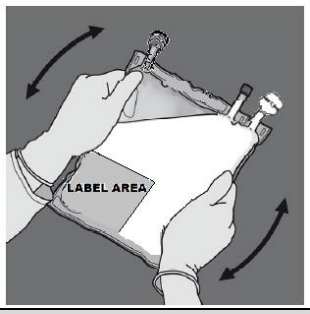
Figure J
 
</td><td colspan="2">Mix gently until complete dissolution of product.

Figure K
 
</td></tr>
<tr><th colspan="3">5 – DOSE ADJUSTMENT - Please refer to the sections “Recommended Dose and Dosage Adjustment” and “Dose Adjustments of Multichamber Flexible bag Calculated According to the Posology”</th></tr>
<tr><td>Identify the Luer Port 3 if correcting dose is needed.
Remove the plastic cap from Luer Port.

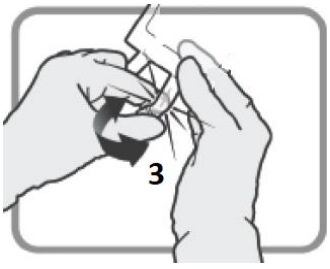
 

Figure L</td><td>Screw the luer lock device as per Figure M.
Do not use unproper non luer lock devices on port 3.

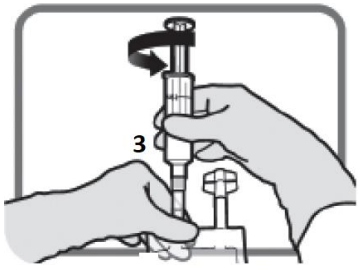
 

Figure M

Ensure that the connection is fully seated and tighten.</td><td>Operate dose adjustment as per sections 4.2 and 4.3

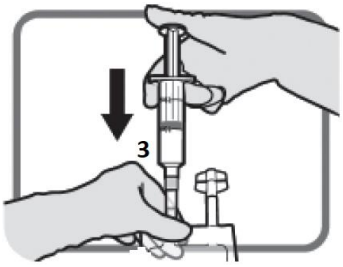
 

Figure N

Unscrew the device once finished.

Put the plastic cap on Luer Port 3 before proceeding with infusion</td></tr>
</table>

6 – CONNECTION - The infusion set may be connected to the bag through either of the spike connector or the luer connector

OPTION A – SPIKE CONNECTION

Identify Twist off Port **4** in case of spike infusion set.
Twist off the plastic cap before inserting the spike.

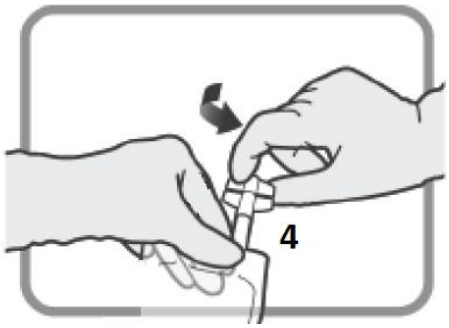


Figure O

Insert the spike connector.

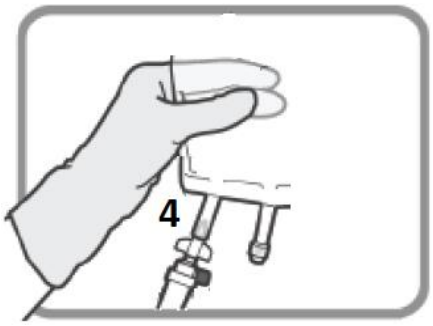


Figure P

OPTION B – LUER CONNECTION

Select luer cap port **3** in case of luer connector infusion set.
Remove the plastic cap from Luer Port **3** before connect the luer connector.

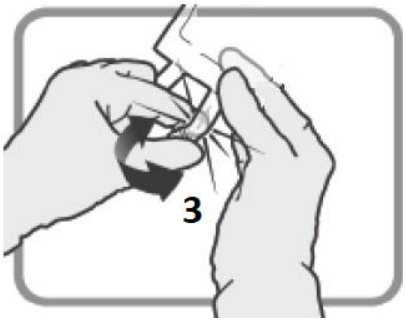


Figure Q

Insert the luer connector.

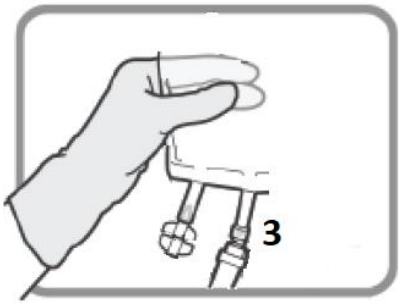


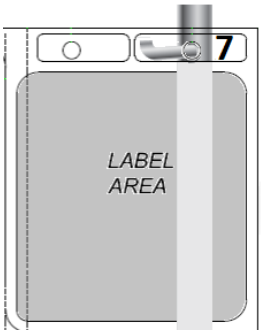
Figure R

Ensure that the connection is fully seated and tighten.

7 – HANG THE BAG

Hang the bag by the hole **7**.

Figure S



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.

TEPADINA 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.

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

5. Overdose

The principal toxic effect of TEPADINA is profound myelosupression and pancytopenia but skin, gastrointestinal, hepatic, renal, cardiac, pulmonary and CNS toxicity can occur (see Warnings and Precautions). There is no known specific antidote for TEPADINA 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 the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 3 - Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous, after reconstitution and dilution	Lyophilised powder for infusion upon reconstitution and dilution 15 mg, 100 mg	TEPADINA does not contain any excipients.
Intravenous, after reconstitution	Lyophilised powder and solvent for solution for infusion 200 mg, 400 mg Dual chamber bag containing 200 mg or 400 mg of powder in one chamber and 200 mL or 400 mL sodium chloride 9 mg/mL (0.9%) solution for injection in the other chamber.	Powder: none Solvent: sodium chloride and water for injections

Description

TEPADINA 15 mg and 100 mg
Type I clear glass vial with a stopper, containing either 15 mg or 100 mg Thiotepa for Injection. The stopper does not contain natural latex rubber. Pack size of 1 vial.

TEPADINA 200 mg and 400 mg
TEPADINA is supplied as a dual chamber bag containing 200 mg or 400 mg of powder in one chamber and 200 mL or 400 mL sodium chloride 9 mg/mL (0.9%) solution for injection in the other chamber.

The bag is made of a multilayer polyolefin/styrene – block copolymer and it is assembled with three tubes made of the same polyolefin/styrene material, fitted with different closure systems:

- twist off port (polypropylene);
- nip-cap connector composed of luer lock closure (silicone/polycarbonate) and cap connector (polypropylene);
- blind port which is only used during manufacturing (lyophilization) is made of polypropylene equipped with chlorobutyl lyo stopper and sealed with aluminum flip-off seals.

Each bag is packed in an aluminum wrapper. Pack size of 1 bag.

Non-medicinal ingredients in the solvent are sodium chloride and water for injections.
The powder does not contain any excipients.

7. Warnings and Precautions

Please see 3 Serious Warnings and Precautions Box.

General

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) should be considered for the prevention and management of infections during the neutropenic period.

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

Concomitant use with phenytoin and fosphenytoin should be avoided (see Drug Interactions).

Thiotepa must not be concurrently administered with cyclophosphamide when both medicinal products are present in the same high-dose chemotherapy (HDCT) regimen. TEPADINA must be delivered after the completion of any cyclophosphamide infusion (see Drug Interactions).

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

The safety assessment of high-dose TEPADINA 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 TEPADINA 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 TEPADINA.

Carcinogenesis and Genotoxicity

TEPADINA 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 TEPADINA (see 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 TEPADINA (see Monitoring and laboratory tests).

Dependence, Tolerance and/or Abuse Liability

TEPADINA has not been studied for its potential to cause dependence, tolerance and/or abuse; however, there may be a theoretical risk of the occurrence of one or more of these risks. Healthcare professionals should consider the patient's history of drug use and monitor appropriately.

Driving and Operating Machinery

Convulsion, hallucination, delirium, dizziness, headache and blurred vision have been reported in patients treated with TEPADINA. 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 TEPADINA-containing HDCT regimens.

Endocrine and Metabolism

Anorexia, weight loss and dehydration have been reported in CNS lymphoma patients treated with TEPADINA-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 TEPADINA-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 TEPADINA-containing HDCT. Management of mucositis often requires total parenteral nutrition (see Adverse Reactions, Special Populations/Pediatrics).

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 TEPADINA 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 TEPADINA and after transplant for at least 30 days (see **Monitoring and Laboratory Test**).

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

TEPADINA is hepatotoxic. Increased transaminases, alkaline phosphatase, gamma-glutamyltransferase and bilirubin as well as elevated amylase have been reported in TEPADINA 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 Serious Warnings and Precautions Box).

Immune

Depressed immunity caused by the profound myelosuppressive effects of high-dose TEPADINA occurs

in patients treated with TEPADINA-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 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 TEPADINA-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 TEPADINA 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 TEPADINA.

Musculoskeletal

Back pain, myalgia and arthralgia have been reported.

Neurologic and Psychiatric

TEPADINA 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 TEPADINA 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 TEPADINA 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 TEPADINA-containing HDCT regimens.

Renal

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

Reproductive Health

- **Fertility**

Pre-clinical toxicity studies show that TEPADINA impairs spermatogenesis and ovarian function in mice (see Contraindications, Non-Clinical Toxicology, Pregnancy).
Azoospermia and amenorrhea occur with TEPADINA use and TEPADINA commonly causes infertility in male and female patients. Fertility preservation strategies should be discussed with male patients and female patients of child bearing potential.

- **Function**

Vaginal haemorrhage and menopausal symptoms have been reported.

Respiratory

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

Skin

TEPADINA is excreted through the skin. Skin toxicity reported with TEPADINA 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. Pregnancy

TEPADINA must not be used during pregnancy (see Contraindications, Special Handling Instructions). There are no studies providing data from the use of TEPADINA in pregnancy. Based on its mechanism of action, TEPADINA has the potential to cause fetal harm; including teratogenicity and fetal death (see Non-Clinical 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 child bearing potential should be advised to avoid becoming pregnant while receiving treatment with TEPADINA. Effective methods of contraception should be used during therapy if either the patient or the partner is of child bearing potential.
If the patient becomes pregnant while receiving TEPADINA, the patient should be informed of the potential hazard to the fetus.

7.1.2. Breastfeeding

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

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 TEPADINA as part of a HDCT regimen have not been established in pediatric CNS lymphoma patients.

Cases of leukoencephalopathy have been observed following treatment with TEPADINA 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 TEPADINA 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 TEPADINA.

Cases of mucosal inflammation were observed in the ADN013 study with a markedly higher frequency in the pediatric 68% (15/22) than in the adult 17% (17/101) populations.

7.1.4. Geriatrics

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

7.1.5. 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.

7.1.6. Renal Impairment

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

8. Adverse Reactions

8.1. Adverse Reaction Overview

The most commonly reported adverse events in the clinical studies of CNS lymphoma patients treated with TEPADINA-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

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Treatment emergent adverse events reported with the use of high-dose TEPADINA 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 TEPADINA-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)	Diarrhea (1)	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)
		Mucositis (1) Diarrhea (2) Infections (4)		

a: Number of enrolled patients that were treated with a TEPADINA-containing HDCT regimen.
N.R.: not reported

Table 5 - Treatment emergent adverse events reported in refractory or relapsed PCNSL patients administered with a TEPADINA-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.
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 TEPADINA-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 TEPADINA-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)	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)
			Stomatitis (7) Nausea (2) Vomiting (2) Diarrhea (3)	

a: Number of enrolled patients that were treated with a TEPADINA-containing HDCT regimen.
N.R.: not reported

Table 7 - Treatment emergent adverse events reported in newly diagnosed or relapsed PCNSL patients administered with a TEPADINA-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)
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 TEPADINA-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 TEPADINA-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)	Bacterial infection (1) Cerebrovascular accident (1)

Reference	N[a]	Adverse Events Grade 1-2 or moderate (n)	Adverse Events Grade 3-4 or serious (n)	Adverse Events Grade 5 (n)
			Delirium (7) Ataxia (1) Dysphagia (1) Weakness (1)	

a: Number of patients treated with a TEPADINA-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

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

Health Canada has not authorized an indication for pediatric use.

8.5. Post-Market Adverse Reactions

Adverse drug reactions collected during the post-marketing period have regarded a population of uncertain size and it has been not possible to reliably estimate their frequency or establish a causal relationship to the drug. Additional data were collected from the post approval sponsored study ADN013 -"A Multi-Centre, Prospective, Observational Post-Authorization Long-term Study of the Use of TEPADINA® as Part of a High-Dose Chemotherapy Regimen Followed by Hematopoietic Stem Cell Transplantation (HCT) in Canadian and American Patients" which enrolled 123 patients including 22 pediatric.

Treatment emergent adverse events (TEAEs) occurring following high-dose therapy with TEPADINA are listed in the table below:

	All patients No. (%)	Pediatric patients No. (%)	Adult patients No. (%)
No. of Patients	**123**	**22**	**101**
Myelosuppression	113 (92%)	18 (82%)	95 (94%)
Infections	63 (51%)	15 (68%)	48 (48%)
Mucosal inflammation	32 (26%)	15 (68%)	17 (17%)
Skin toxicity	31 (25%)	5 (23%)	26 (26%)
Delirium/Confusion	-	-	18 (18%)
Nervous system disorders	9 (7%)	1 (5%)	8 (8%)

9. Drug Interactions

9.1. 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.

9.3. Drug-Behaviour Interactions

The interaction of TEPADINA with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

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

Non-proprietary name(s) of the drug product(s)	Source of evidence	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.

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
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.
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. TEPADINA 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.

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
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.
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: 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 TEPADINA 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

- **Pregnancy and breastfeeding:** TEPADINA must not be used during pregnancy (see Contraindications). There are no studies providing data from the use of TEPADINA in pregnancy.
  It is not known whether TEPADINA is excreted in human milk.

- **Pediatrics:** TEPADINA 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 Impairment:** 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 Impairment:** 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 TEPADINA 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

TEPADINA 15 mg and 100 mg

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

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. TEPADINA 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.

TEPADINA 200 mg and 400 mg

Inactivated bag
Store and transport refrigerated (2 °C to 8 °C). Do not freeze.
Keep the bag in the aluminum wrapper in order to protect from activation.

After activation of the bag and reconstitution

Chemical and physical in-use stability of the reconstituted product in the activated bag has been demonstrated for up to 168 hours when stored refrigerated at 2°C to 8°C or up to 56 hours when stored at room temperature below 25°C.
From a microbiological point of view, the product should be used immediately after activation and reconstitution. 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 reconstitution 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.

TEPADINA is cytotoxic, carcinogenic, mutagenic and teratogenic. Pregnant staff and breastfeeding mothers should be excluded from the reconstitution and administration of TEPADINA. 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 TEPADINA 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 2: Scientific Information

13. Pharmaceutical Information

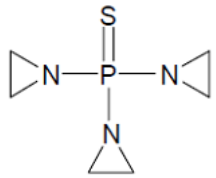
Drug Substance

Non-proprietary name of the drug substance(s): Thiotepa

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

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

Pharmaceutical standard: In house

14. Clinical Trials

14.1. CNS Lymphoma

Clinical evidence in support of the use of TEPADINA 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 TEPADINA-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 TEPADINA-containing HDCT regimen

Publications	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	Chemosensitivity[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
Alimohamed 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
Montemurro 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 2001	20/22	53.0 (27.0-64.0)	n.s.	10 (50.0) 10 (50.0)	n.s.	17 (85.0) 3 (15.0)	10
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	15 (55.5) 12 (44.5)	14*

Publications	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	Chemosensitivity[a] Yes N (%) No N (%)	Prior cranio-spinal irradiation[a] N
					ECOG PS n.a.: 1		
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.	5 (62.5) 3 (37.5)	Median KPS: 90% (60% – 90%)*	8 (100.0) 0 (0.0)	1

[a] Number of patients treated with TEPADINA-containing HDCT

* data on all enrolled patients

n.s. = Not Specified; KPS: Karnofsky performance status; ECOG PS: Eastern Cooperative Oncology Group performance status

Response rate was the main efficacy endpoint to assess the benefit of TEPADINA-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

11, 12, 13, 14 and 15a when reported. Due to differences across studies in defining and reporting efficacy endpoints, study results were not pooled.

Table 11 - Efficacy results in newly diagnosed PCNSL patients administered with a TEPADINA-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 TEPADINA-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 TEPADINA-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 TEPADINA-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 TEPADINA-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 TEPADINA-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 TEPADINA-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 TEPADINA-containing HDCT regimen followed by ASCT.
CR: complete response; DFS: disease-free survival; PFS: progression-free survival; OS: overall survival.

Table 15a - Efficacy results in PCNSL and SCNSL patients administered with a TEPADINA-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 TEPADINA-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.

Further evidence in support of the use of TEPADINA 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 Study ADN013.

This is a multi-centre, prospective, observational registry-based study to collect long-term data on the safety and efficacy of TEPADINA®. The study included US and Canadian patients receiving TEPADINA® in a conditioning regimen prior to HCT, for primary or secondary CNS lymphoma. The total study accrual was 123 patients (101 adults and 22 pediatric patients), including 101 CNS lymphoma adult patients (Canadian and US) and 22 Canadian pediatric patients with any indication who received TEPADINA® in conditioning regimen (none with CNS lymphoma).
The mean cumulative dose administered was 14.02 mg/kg (equal to 518.74 mg/m^2) in adults over a median duration of 4 days (range from 1 day to 8 days) prior to transplant and 19.7 mg/kg (equal to 492.5 mg/m^2) in pediatric population over a median duration of 4 days (range from 2 days to 7 days) prior to transplant. The mean cumulative dose in the overall population was 15.04 mg/kg.

The efficacy outcomes were provided at 100 days, 6 months, 1 year, 2 years, 3 years, 4 years and 5 years post-transplant. (*Table 15b*)

Table 15b - Efficacy results in PCNSL and SCNSL patients administered with a TEPADINA-containing HDCT regimen in Study ADN013

Clinical setting	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
Newly diagnosed PCNSL patients administered with a TEPADINA-containing HDCT regimen	ADN013 Study	66	CR: 56 (83.3) PR: 9 (13.6) SD: 1 (1.5)	100 days	CR: 57 (86) PR: 2 (3) PD: 1 (2) SU: 4 (6) Death: 2 (3)	100-day PFS = 100.0%	100-day OS = 95.3%
				6 months	CR: 58 (88) PR: 1 (1.5) SD: 1 (1.5) PD: 1 (1.5) SU: 2 (3) Death: 3 (4.5)	6-month PFS = 100.0%	6-month OS = 87.5%
				12 months	CR: 60 (91) PR: 1 (1.5) SD: 1 (1.5) Death: 4 (6)	1-year PFS = 85.7%	1-year OS = 82.8%
				24 months	CR: 53 (80) PR: 1 (1.5) SU: 1 (1.5) Death: 11 (17)	2-year PFS = 85.7%	2-year OS = 78.1%
				36 months	CR: 48 (73) PR: 1 (1.5) SU: 5 (7.5) Death: 12 (18)	3-year PFS = 70.1%	3-year OS = 76.4%
				48 months	CR: 37 (56) SU: 16 (24) Death: 13 (20)	4-year PFS = 61.4%	4-year OS = 74.0%

Clinical setting	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
				60 months	CR: 17 (26) SU: 36 (54) Death: 13 (20)	5-year PFS = 61.4%	5-year OS = 74.0%
Relapsed/refractory PCNSL patients administered with a TEPADINA-containing HDCT regimen	ADN013 Study	15	CR: 9 (60) PR: 6 (40)	100 days	CR: 11 (73.3) PR: 2 (13.3) SU: 2 (13.3)	100-day PFS = 93.3%	100-day OS = 100.0%
				6 months	CR: 15 (100)	6-month PFS = 86.7%	6-month OS = 100.0%
				12 months	CR: 12 (80) SU: 1 (7) Death: 2 (13)	1-year PFS = 72.2%	1-year OS = 85.7%
				24 months	CR: 12 (80) SU: 1 (7) Death: 2 (13)	2-year PFS = 72.2%	2-year OS = 85.7%
				36 months	CR: 8 (53) SU: 3 (20) Death: 4 (27)	3-year PFS = 56.2%	3-year OS = 70.1%
				48 months	CR: 6 (40) SU: 4 (27) Death: 5 (33)	4-year PFS = 46.8%	4-year OS = 61.4%
				60 months	CR: 5 (33.3) SU: 5 (33.3) Death: 5 (33.3)	5-year PFS = 46.8%	5-year OS = 61.4%
SCNSL patients administered with a TEPADINA-containing HDCT regimen	ADN013 Study	20	CR: 14 (70) PR: 6 (30)	100 days	CR: 14 (70) PR: 2 (10) SD: 1 (5) PD: 1 (5) Death: 2 (10)	100-day PFS = 84.2%	100-day OS = 90.0%
				6 months	CR: 14 (70) PR: 2 (10) SD: 1 (5) PD: 1 (5) Death: 2 (10)	6-month PFS = 73.7%	6-month OS = 90.0%
				12 months	CR: 13 (65) PR: 1 (5) SD: 1 (5) PD: 1 (5) SU: 1 (5) Death: 3 (15)	1-year PFS = 57.9%	1-year OS = 85%
				24 months	CR: 10 (50) SD: 1 (5) SU: 3 (15) Death: 6 (30)	2-year PFS = 52.1%	2-year OS = 74.4%
				36 months	CR: 8 (40) SD: 1 (5) SU: 3 (15) Death: 8 (40)	3-year PFS = 46.3%	3-year OS = 63.8%

Clinical setting	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
				48 months	CR: 3 (15) SD: 1 (5) SU: 8 (40) Death: 8 (40)	4-year PFS = 46.3%	4-year OS = 63.8%
				60 months	CR: 1 (5) SU: 11 (55) Death: 8 (40)	5-year PFS = N.R.	5-year OS = N.R.

[a]Number of patients treated with a TEPADINA-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.

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.

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

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

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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTEPADINA®

Thiotepa for injection, BP

This patient medication information is written for the person who will be taking **TEPADINA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **TEPADINA**, talk to a healthcare professional.

Serious warnings and precautions box

TEPADINA administration must be supervised by a doctor experienced in the use of anticancer medicines.

TEPADINA 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 TEPADINA. 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 TEPADINA 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. TEPADINA should NOT be used during pregnancy because it can harm your baby.
- Serious interactions with other medicines. See section **The following may also interact with TEPADINA**, below, for information about these medicines.

What TEPADINA is used for:

- TEPADINA is used to treat adult patients with central nervous system (CNS) lymphoma. It is used in combination with other anticancer medicines and is followed by stem cell transplantation.

How TEPADINA works:

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

The ingredients in TEPADINA are:

TEPADINA 15 mg and 100 mg (vial)

Medicinal ingredients: thiotepa.
Non-medicinal ingredients: TEPADINA does not contain any other ingredients.

TEPADINA 200 mg and 400 mg (dual chamber bag)

Medicinal ingredients: thiotepa.
Non-medicinal ingredients: sodium chloride, water for injections.

TEPADINA comes in the following dosage forms:

Powder for solution for infusion (vial):

- 15 mg
- 100 mg

Powder and solvent for solution for infusion (dual chamber bag):

- 200 mg thiotepa with 200 mL sodium chloride 9 mg/mL (0.9% solution for injection)
- 400 mg thiotepa with 400 mL sodium chloride 9 mg/mL (0.9% solution for injection)

  Note: Thiotepa powder and solvent (sodium chloride) are in separate chambers in a dual chamber bag.

Do not use TEPADINA if:

- you are allergic to thiotepa or other ingredients in TEPADINA;
- 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 TEPADINA. 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 TEPADINA 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:

- TEPADINA 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 TEPADINA.
- Your healthcare professional may recommend you to drink more fluids to stay hydrated during treatment with TEPADINA.
- **Infections**
  - TEPADINA weakens your immune system and can increase your risk of infections. To prevent and manage infections, your healthcare professional may prescribe you anti-infective medicines.
- **Cancer**
  - TEPADINA may cause another type of cancer in the future. Your healthcare professional will discuss this risk with you.
- **Female patients**

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

  Breastfeeding
  - Do NOT breastfeed while receiving TEPADINA. 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 TEPADINA.
- **Male patients**
  - Do NOT father a child during treatment with TEPADINA.
  - Use effective birth control method while receiving TEPADINA. Talk to your healthcare professional for advice on effective methods of birth control.

- **Fertility in Males and Females**
  - TEPADINA may reduce your ability to have children in both male and female patients.
  - If you plan to have children, talk to your healthcare professional before you start treatment with TEPADINA. Your healthcare professional will discuss fertility preservation options with you.
- **Check-ups and testing**
  - You will have visits with your healthcare professional to monitor your health. They will:
    - do regular blood tests before and during treatment to check your blood cell counts.
    - monitor the functioning of your heart and your kidneys during treatment with TEPADINA.
    - monitor the functioning of your liver by checking your liver enzyme levels during treatment with TEPADINA.
- **Driving and using machines**
  - TEPADINA 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 TEPADINA.

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

Serious drug interactions:

Serious drug interactions with TEPADINA include:
- 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 TEPADINA:

- 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 TEPADINA:

TEPADINA 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 healthcare professional will decide how much TEPADINA you should receive based on your height and your weight.

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

Overdose:

In the event you were accidentally given a higher dose of TEPADINA than prescribed, your healthcare professional will decide whether to perform blood tests and to undertake supportive care, if necessary.

If you think you, or a person you are caring for, have been given too much TEPADINA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Possible side effects from using TEPADINA:

These are not all the possible side effects you may have when taking TEPADINA. If you experience any side effects not listed here, tell your healthcare professional.

- Anorexia, decreased appetite, weight loss
- Joint pain
- Muscle pain
- Changes in muscle tone: back pain, joint pain
- Pain or inflammation at the injection site
- Cough
- 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
- Having no menstrual periods
- Loss of fertility in men and women

TEPADINA may cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		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):		X	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
bleeding, bruising, chills, fatigue, fever, infections, weakness.			
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	
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,		X	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
shortness of breath (can be sudden), blood clot in lungs.			
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	
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	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
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	
Hypersensitivity (allergic 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, tell 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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

TEPADINA will be managed and stored by healthcare professionals.

If you want more information about TEPADINA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.adienne.com or by calling 1-800-217-7405.

This leaflet was prepared by ADIENNE SA.

Andone Pharmaceutical Inc.

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