SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 15 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

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

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

Adults

AUTOLOGOUS HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 300 mg/m^2/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal

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

Solid tumours

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

ALLOGENEIC HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 185 mg/m^2/day (5 mg/kg/day) to 481 mg/m^2/day (13 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 3 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic

medicinal products, without exceeding the total maximum cumulative dose of 555 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.
LYMPHOMA
The recommended dose in lymphoma is 370 mg/m^2/day (10 mg/kg/day) divided in two daily infusions before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

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

Paediatric population

AUTOLOGOUS HPCT

Solid tumours

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

ALLOGENEIC HPCT

Haematological diseases

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

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

Special populations

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

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

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

Method of administration

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

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

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

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

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

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

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

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

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

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

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

4.5 Interactions with other medicinal products and other forms of interaction

Specific interactions with thiotepa

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

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

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

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

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

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

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

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Women of childbearing potential have to use effective contraception during treatment and a pregnancy test should be performed before treatment is started. Male patients should not father a child while treated and during the year after cessation of treatment (see section 5.3).

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

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

Fertility
As most alkylating agents, thiotepa might impair male and female fertility.
Male patients should seek for sperm cryopreservation before therapy is started (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

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

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

Tabulated list of adverse reactions

Adults

The adverse reactions considered at least possibly related to conditioning treatment including thiotepa, reported in adult patients as more than an isolated case, are listed below by system organ class and by frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

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

Gastrointestinal disorders	Nausea Stomatitis Oesophagitis Vomiting Diarrhoea Dyspepsia Abdominal pain Enteritis Colitis	Constipation Gastrointestinal perforation Ileus	Gastrointestinal ulcer	
Hepatobiliary disorders	Venoocclusive liver disease Hepatomegaly Jaundice			
Skin and subcutaneous tissue disorders	Rash Pruritus Alopecia	Erythema	Pigmentation disorder Erythrodermic psoriasis	Severe toxic skin reactions including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Back pain Myalgia Arthralgia			
Renal and urinary disorders	Cystitis haemorrhagic	Dysuria Oliguria Renal failure Cystitis Haematuria		
Reproductive system and breast disorders	Azoospermia Amenorrhoea Vaginal haemorrhage	Menopausal symptoms Infertility female Infertility male		
General disorders and administration site conditions	Pyrexia Asthenia Chills Generalised oedema Injection site inflammation Injection site pain Mucosal inflammation	Multi-organ failure Pain		
Investigations	Weight increased Blood bilirubin increased Transaminases increased Blood amylase increased	Blood creatinine increased Blood urea increased Gamma-glutamyltransferase increased Blood alkaline phosphatase increased Aspartate aminotransferase increased		

Paediatric population

The adverse reactions considered at least possibly related to conditioning treatment including thiotepa, reported in paediatric patients as more than an isolated case, are listed below by system organ class and by frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	**Very common**	**Common**	**Not known**
Infections and infestations	Infection susceptibility increased Sepsis	Thrombocytopenic purpura	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Treatment related second malignancy	
Blood and lymphatic system disorders	Thrombocytopenia Febrile neutropenia Anaemia Pancytopenia Granulocytopenia		
Immune system disorders	Acute graft versus host disease Chronic graft versus host disease		
Endocrine disorders	Hypopituitarism Hypogonadism Hypothyroidism		
Metabolism and nutrition disorders	Anorexia Hyperglycaemia		
Psychiatric disorders	Mental status changes	Mental disorder due to a general medical condition	
Nervous system disorders	Headache Encephalopathy Convulsion Cerebral haemorrhage Memory impairment Paresis	Ataxia	Leukoencephalopathy
Ear and labyrinth disorders	Hearing impaired		
Cardiac disorders	Cardiac arrest	Cardiovascular insufficiency Cardiac failure	
Vascular disorders	Haemorrhage	Hypertension	
Respiratory, thoracic and mediastinal disorders	Pneumonitis	Idiopathic pneumonia syndrome Pulmunary haemorrage Pulmonary oedema Epistaxis	Pulmonary arterial hypertension

		Hypoxia Respiratory arrest	
Gastrointestinal disorders	Nausea Stomatitis Vomiting Diarrhoea Abdominal pain	Enteritis Intestinal obstruction	
Hepatobiliary disorders	Venoocclusive liver disease	Liver failure	
Skin and subcutaneous tissue disorders	Rash Erythema Desquamation Pigmentation disorder		Severe toxic skin reactions including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Growth retardation		
Renal and urinary disorders	Bladder disorders	Renal failure Cystitis haemorrhagic	
General disorders and administration site conditions	Pyrexia Mucosal inflammation Pain Multi-organ failure		
Investigations	Blood bilirubin increased Transaminases increased Blood creatinine increased Aspartate aminotransferase increased Alanine aminotransferase increased	Blood urea increased Blood electrolytes abnormal Prothrombin time ratio increased	

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents, ATC code: L01AC01

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

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

Autologous HPCT
Haematological diseases
Engraftment: Conditioning treatments including thiotepa have proved to be myeloablative.
Disease free aurvival (DFS): An estimated 43% at five years has been reported, confirming that conditioning treatments containing thiotepa following autologous HPCT are effective therapeutic strategies for treating patients with haematological diseases.
Relapse: In all conditioning treatments containing thiotepa, relapse rates at more than 1 year have been reported as being 60% or lower, which was considered by the physicians as the threshold to prove efficacy. In some of the conditioning treatments evaluated, relapse rates lower than 60% have also been reported at 5 years.
Overall survival (OS): OS ranged from 29% to 87% with a follow-up ranging from 22 up to 63 months.
Regimen related mortality (RRM) and *Transplant related mortality (TRM)*: RRM values ranging from 2.5% to 29% have been reported. TRM values ranged from 0% to 21% at 1 year, confirming the safety of the conditioning treatment including thiotepa for autologous HPCT in adult patients with haematological diseases.
Solid tumours
Engraftment: Conditioning treatments including thiotepa have proved to be myeloablative.
Disease free survival (DFS): Percentages reported with follow-up periods of more than 1 year confirm that conditioning treatments containing thiotepa following autologous HPCT are effective choices for treating patients with solid tumours.
Relapse: In all conditioning treatments containing thiotepa, relapse rates at more than 1 year have been reported as being lower than 60%, which was considered by the physicians as the threshold to prove efficacy. In some cases, relapse rates of 35% and of 45% have been reported at 5 years and 6 years respectively.
Overall survival: OS ranged from 30% to 87% with a follow-up ranging from 11.7 up to 87 months.
Regimen related mortality (RRM) and *Transplant related mortality (TRM)*: RRM values ranging from 0% to 2% have been reported. TRM values ranged from 0% to 7.4% confirming the safety of the conditioning treatment including thiotepa for autologous HPCT in adult patients with solid tumours.

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

GvHD (graft versus host disease): all conditioning treatments evaluated assured a low incidence of acute GvHD grade III-IV (from 4% to 24%).
D*isease free survival (DFS):* Percentages reported with follow-up periods of more than 1 year and up to 5 years confirm that conditioning treatments containing thiotepa following allogeneic HPCT are effective choices for treating patients with haematological diseases.
Relapse: In all conditioning treatments containing thiotepa, relapse rates at more than 1 year have been reported as being lower than 40% (which was considered by the physicians as the threshold to prove efficacy). In some cases, relapse rates lower than 40% have also been reported at 5 years and 10 years.
Overall survival: OS ranged from 31% to 81% with a follow-up ranging from 7.3 up to 120 months.
Regimen related mortality (RRM) and *Transplant related mortality* (*TRM)*: low values have been reported, confirming the safety of the conditioning treatments including thiotepa for allogeneic HPCT in adult patients with haematological diseases.

Paediatric population

Autologous HPCT
Solid tumours
Engraftment: It has been achieved with all reported conditioning regimens including thiotepa.
Disease free survival (DFS): With a follow-up of 36 to 57 months, DFS ranged from 46% to 70% in the reported studies. Considering that all patients were treated for high risk solid tumours, DFS results confirm that conditioning treatments containing thiotepa following autologous HPCT are effective therapeutic strategies for treating paediatric patients with solid tumours.
Relapse: In all the reported conditioning regimens containing thiotepa, relapse rates at 12 to 57 months ranged from 33% to 57%. Considering that all patients suffer of recurrence or poor prognosis solid tumours, these rates support the efficacy of conditioning regimens based on thiotepa.
Overall survival (OS): OS ranged from 17% to 84% with a follow-up ranging from 12.3 up to 99.6 months.
Regimen related mortality (RRM) and *Transplant related mortality* (*TRM)*: RRM values ranging from 0% to 26.7% have been reported. TRM values ranged from 0% to 18% confirming the safety of the conditioning treatments including thiotepa for autologous HPCT in paediatric patients with solid tumours.

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

5.2 Pharmacokinetic properties

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

Distribution

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

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

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

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

Special populations

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

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

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

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
The expiry date of the product is indicated on the packaging materials.

After reconstitution
Chemical and physical in-use stability after reconstitution has been demonstrated for 80 hours when stored at 2°C-8°C.

After dilution
Chemical and physical in-use stability after dilution has been demonstrated for up to 48 hours when stored at 2°C-8°C and for up to 6 hours when stored at 25°C.

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

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

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

Reconstitution
TEPADINA must be reconstituted with 1.5 ml of sterile water for injections.
Using a syringe fitted with a needle, aseptically withdraw 1.5 ml of sterile water for injections.

Inject the content of the syringe into the vial through the rubber stopper.
Remove the syringe and the needle and mix manually by repeated inversions.
Only colourless solutions, without any particulate matter, must be used. Reconstituted solutions may occasionally show opalescence; such solutions can still be administered.

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

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

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

7. RIGHTS HOLDER AND MANUFACTURER

ADIENNE SA
Via Zurigo 46,
6900 Lugano, Switzerland

8. LICENSE HOLDER

MBI Pharma Ltd.
P.O.B 5061, Kadima
Israel

9. REGISTRATION NUMBER

154-17-34234

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