

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 15 mg powder for concentrate for solution for infusion
TEPADINA 100 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TEPADINA 15 mg powder for concentrate for solution for infusion
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).

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TEPADINA is indicated, in combination with other chemotherapy medicinal products:

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

4.2 Posology and method of administration

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

Posology

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

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

Adults

AUTOLOGOUS HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA

The recommended dose is 185 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

Solid tumours

The recommended dose in solid tumours ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

BREAST CANCER

The recommended dose ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

OVARIAN CANCER

The recommended dose is 250 mg/m²/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/m² (13.51 mg/kg), during the time of the entire conditioning treatment.

GERM CELL TUMOURS

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (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/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose in lymphoma is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose is 185 mg/m²/day (5 mg/kg/day) as a single daily infusion before allogeneic HPCT, without exceeding the total maximum cumulative dose of 185 mg/m² (5 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose ranges from 185 mg/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (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/m²/day (6 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (42 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 250 mg/m²/day (10 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (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/m²/day (5 mg/kg/day) to 250 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose ranges from 200 mg/m²/day (8 mg/kg/day) to 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

REFRACTORY CYTOPENIA

The recommended dose is 125 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

GENETIC DISEASES

The recommended dose is 125 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

SICKLE CELL ANAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (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 vial must be reconstituted with 1.5 mL (TEPADINA 15 mg) or 10 mL (TEPADINA 100 mg) 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 embryofetal 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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		

System organ class	Very common	Common	Uncommon	Not known
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		

System organ class	Very common	Common	Uncommon	Not known
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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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	

System organ class	Very common	Common	Not known
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 Pulmonary haemorrhage Pulmonary oedema Epistaxis Hypoxia Respiratory arrest	Pulmonary arterial hypertension
Gastrointestinal disorders	Nausea Stomatitis Vomiting Diarrhoea Abdominal pain	Enteritis Intestinal obstruction	
Hepatobiliary disorders	Venoocclusive liver disease	Liver failure	
Skin and subcutaneous tissue disorders	Rash Erythema Desquamation Pigmentation disorder		Severe toxic skin reactions including cases of Stevens- Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Growth retardation		
Renal and urinary disorders	Bladder disorders	Renal failure Cystitis haemorrhagic	
General disorders and administration site conditions	Pyrexia Mucosal inflammation Pain Multi-organ failure		

System organ class	Very common	Common	Not known
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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

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

There is no known antidote for thiotepa.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Clinical safety and efficacy

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

Autologous HPCT

Haematological diseases

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

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

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

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

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

Solid tumours

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

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

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

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

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

Allogeneic HPCT

Haematological diseases

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

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

Disease 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/m² to 75 l/m², 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 (triethylenephosphoramidate). 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-mercaptopurine.

Elimination

The total clearance of thiotepa ranged from 11.4 to 23.2 l/h/m². The elimination half-life varied from 1.5 to 4.1 hours. The identified metabolites TEPA, monochlorotepa and thiotepa-mercaptopurine 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-mercaptopurine.

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/m² 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

TEPADINA 15 mg powder for concentrate for solution for infusion

Unopened vial

30 months.

TEPADINA 100 mg powder for concentrate for solution for infusion

Unopened vial

3 years.

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

TEPADINA 15 mg powder for concentrate for solution for infusion

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

Pack size of 1 vial.

TEPADINA 100 mg powder for concentrate for solution for infusion

Type I clear glass vial with a rubber stopper (butyl or chlorobutyl), containing 100 mg thiotepa.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Preparation of TEPADINA

Procedures for proper handling and disposal of anticancer medicinal products must be considered. All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood.

As with other cytotoxic compounds, caution needs to be exercised in handling and preparation of TEPADINA solutions to avoid accidental contact with skin or mucous membranes. Topical reactions associated with accidental exposure to thiotepa may occur. In fact, the use of gloves is recommended in preparing the solution for infusion. If thiotepa solution accidentally contacts the skin, the skin must be immediately and thoroughly washed with soap and water. If thiotepa accidentally contacts mucous membranes, they must be flushed thoroughly with water.

Reconstitution TEPADINA 15 mg

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.

Reconstitution of TEPADINA 100 mg

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

Further dilution in the infusion bag

The reconstituted solution is hypotonic and must be further diluted prior to administration with 500 mL sodium chloride 9 mg/mL (0.9%) solution for injection (1 000 mL if the dose is higher than 500 mg) or with an appropriate volume of sodium chloride 9 mg/mL (0.9%) in order to obtain a final TEPADINA concentration between 0.5 and 1 mg/mL.

Administration

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

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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adienne@adienne.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/622/001
EU/1/10/622/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 17 November 2014

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 200 mg powder and solvent for solution for infusion

TEPADINA 400 mg powder and solvent for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TEPADINA 200 mg powder and solvent for solution for infusion

One bag contains 200 mg thiotepa.

After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

Excipient with known effect

When reconstituted, each bag contains 709 mg (30.8 mmol) of sodium.

TEPADINA 400 mg powder and solvent for solution for infusion

One bag contains 400 mg thiotepa.

After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

Excipient with known effect

When reconstituted, each bag contains 1 418 mg (61.6 mmol) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

Powder: white powder.

Solvent: clear solution, essentially free from visible particulates, pH 4.5-7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TEPADINA is indicated, in combination with other chemotherapy medicinal products:

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

4.2 Posology and method of administration

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

Posology

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

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

Adults

AUTOLOGOUS HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA

The recommended dose is 185 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

Solid tumours

The recommended dose in solid tumours ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

BREAST CANCER

The recommended dose ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

OVARIAN CANCER

The recommended dose is 250 mg/m²/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/m² (13.51 mg/kg), during the time of the entire conditioning treatment.

GERM CELL TUMOURS

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (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/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose in lymphoma is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose is 185 mg/m²/day (5 mg/kg/day) as a single daily infusion before allogeneic HPCT, without exceeding the total maximum cumulative dose of 185 mg/m² (5 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose ranges from 185 mg/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (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/m²/day (6 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (42 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 250 mg/m²/day (10 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (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/m²/day (5 mg/kg/day) to 250 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose ranges from 200 mg/m²/day (8 mg/kg/day) to 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

REFRACTORY CYTOPENIA

The recommended dose is 125 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

GENETIC DISEASES

The recommended dose is 125 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

SICKLE CELL ANAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (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 is for intravenous use only. It must be administered by a qualified healthcare professional as a 2-4 hours intravenous infusion via a central venous catheter.

The bag must only be removed from the aluminum wrapper immediately before the use.

TEPADINA 200 mg

If necessary, dose adjustment of TEPADINA must be operated as per specific application.

In case the calculated dose required is higher than 200 mg but less than a multiple thereof, the user is requested to add the required mg from TEPADINA vials by using a dedicated port of TEPADINA 200 mg.

In case the calculated dose required is lower than 200 mg, the user is requested to remove the unnecessary mg of fully reconstituted 1 mg/mL solution or to set an infusion pump with the amount of medicinal product to be administered in mL.

TEPADINA 400 mg

If necessary, dose adjustment of TEPADINA must be operated as per specific application.

In case the calculated dose required is higher than 400 mg but less than a multiple thereof, the user is requested to add the required mg from TEPADINA vials by using a dedicated port of TEPADINA 400 mg.

In case the calculated dose required is lower than 400 mg, the user is requested to remove the unnecessary mg of fully reconstituted 1 mg/mL solution or to set an infusion pump with the amount of medicinal product to be administered in mL.

For instructions on reconstitution 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).

TEPADINA 400 mg contains 1 418 mg (61.6 mmol) sodium per bag, equivalent to 70.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

TEPADINA 200 mg contains 709 mg (30.8 mmol) sodium per bag, equivalent to 35.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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	Hypersensitivity		

System organ class	Very common	Common	Uncommon	Not known
	Chronic graft versus host disease			
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

System organ class	Very common	Common	Uncommon	Not known
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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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	

System organ class	Very common	Common	Not known
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 Pulmonary haemorrhage Pulmonary oedema Epistaxis Hypoxia Respiratory arrest	Pulmonary arterial hypertension
Gastrointestinal disorders	Nausea Stomatitis Vomiting Diarrhoea Abdominal pain	Enteritis Intestinal obstruction	
Hepatobiliary disorders	Venoocclusive liver disease	Liver failure	

System organ class	Very common	Common	Not known
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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

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

There is no known antidote for thiotepa.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Thiotepa is a polyfunctional cytotoxic agent related chemically and pharmacologically to the nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylene

imine radicals that, as in the case of irradiation therapy, disrupt the bonds of DNA, e.g. by alkylation of guanine at the N-7, breaking the linkage between the purine base and the sugar and liberating alkylated guanine.

Clinical safety and efficacy

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

The results of published clinical studies supporting the efficacy of thiotepa are summarised:

Autologous HPCT

Haematological diseases

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

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

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

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

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

Solid tumours

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

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

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

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

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

Allogeneic HPCT

Haematological diseases

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

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

Disease 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/m² to 75 l/m², 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 (triethylenephosphoramidate). 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-mercaptopurine.

Elimination

The total clearance of thiotepa ranged from 11.4 to 23.2 l/h/m². The elimination half-life varied from 1.5 to 4.1 hours. The identified metabolites TEPA, monochlorotepa and thiotepa-mercaptopurine 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-mercaptopurine.

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/m² 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

Powder

None

Solvent

Sodium chloride

Water for injections

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

Inactivated bag

2 years.

After activation of the bag and reconstitution

From a microbiological point of view, the product should be used immediately after activation and reconstitution.

Chemical and physical stability of the reconstituted product in the activated bag has been demonstrated for up to 48 hours when stored at 2 °C-8 °C and for up to 6 hours at 25 °C temperature.

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.

6.4 Special precautions for storage

Store and transport refrigerated (2°C - 8°C).

Do not freeze.

Keep the bag in the aluminum wrapper in order to protect from activation.

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

6.5 Nature and contents of container

TEPADINA 200 mg

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

TEPADINA 400 mg

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

The bag of TEPADINA 200 mg and 400 mg 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 or thermoplastic elastomer);
- 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.

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.

Activation and reconstitution

TEPADINA bag must be reconstituted with sodium chloride 9 mg/mL (0.9%) solution for injection. 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 calculated according to posology (section 4.2)

TEPADINA 200 mg

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)*
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 in the package leaflet) 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)*
the appropriate volume of the reconstituted solution from TEPADINA 15 mg or 100 mg vials (10 mg/mL) should be transferred into the infusion bag of TEPADINA 200 mg through the dedicated luer port (Step 5 of the Instruction for Use in the package leaflet).

TEPADINA 400 mg

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 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 in the package leaflet) or set an infusion pump with the amount of medicinal product to be administered in mL;
- *addition (if the required dose is greater than 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 infusion bag of TEPADINA 400 mg through the dedicated luer port (Step 5 of the Instruction for Use in the package leaflet).

Administration

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

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

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

Disposal

TEPADINA is for single use only.

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

7. MARKETING AUTHORISATION HOLDER

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB) Italy
Tel: +39-02 40700445
adienne@adienne.com

8. MARKETING AUTHORISATION NUMBER

EU/1/10/622/003
EU/1/10/622/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 17 November 2014

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB) Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 15 mg powder for concentrate for solution for infusion
thiotepa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic.

8. EXPIRY DATE

EXP
After reconstitution, use within 80 hours when stored in a refrigerator.
After dilution, use within 48 hours when stored in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

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

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB) Italy
adienne@adienne.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/622/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TEPADINA 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

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

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

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

15 mg

6. OTHER

ADIENNE S.r.l. S.U.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 100 mg powder for concentrate for solution for infusion
thiotepa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic.

8. EXPIRY DATE

EXP
After reconstitution, use within 80 hours when stored in a refrigerator.
After dilution, use within 48 hours when stored in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

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

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB) Italy
adienne@adienne.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/622/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TEPADINA 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

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

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

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg

6. OTHER

ADIENNE S.r.l. S.U.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 200 mg powder and solvent for solution for infusion
thiotepa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains 200 mg thiotepa.

After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

3. LIST OF EXCIPIENTS

Solvent: sodium chloride and water for injections.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion

One bag contains 200 mg thiotepa and 200 mL solvent

1 bag

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.

Activate seal and gently mix powder and solvent.

Read the package leaflet before use for further instructions and recommended dose.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

After activation of the bag and reconstitution: See the leaflet for further information.

9. SPECIAL STORAGE CONDITIONS

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

Keep the bag in the aluminum wrapper in order to protect from activation.

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB) Italy
adienne@adienne.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/622/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TEPADINA 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Aluminum wrapper

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 200 mg powder and solvent for solution for infusion
thiotepa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains 200 mg thiotepa.
After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

3. LIST OF EXCIPIENTS

Solvent: sodium chloride and water for injections
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion
One bag contains 200 mg thiotepa and 200 mL solvent
1 bag

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Activate seal and gently mix powder and solvent.

Read the package leaflet before use for further instructions and recommended dose.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP
After activation of the bag and reconstitution: See the leaflet for further information.

9. SPECIAL STORAGE CONDITIONS

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

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB) Italy
adienne@adienne.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/622/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Inner label bag

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 200 mg powder and solvent for solution for infusion
thiotepa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains 200 mg thiotepa.

After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

3. LIST OF EXCIPIENTS

Solvent: sodium chloride and water for injections

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion

One bag contains 200 mg thiotepa and 200 mL solvent

1 bag

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.

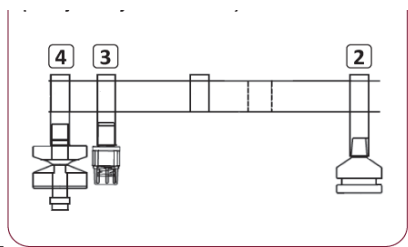
Activate seal and gently mix powder and solvent.

Read the package leaflet before use for further instructions and recommended dose.

2 – Blind Port (NEVER use this port)

3 – Luer Port (For dose adjustment and infusion of the medication)

4 – Twist off Port (For infusion of the medication)



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

After activation of the bag and reconstitution: See the leaflet for further information.

9. SPECIAL STORAGE CONDITIONS

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

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

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

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EU/1/10/622/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE****17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 400 mg powder and solvent for solution for infusion
thiotepa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains 400 mg thiotepa.

After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

3. LIST OF EXCIPIENTS

Solvent: sodium chloride and water for injections.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion

One bag contains 400 mg thiotepa and 400 mL solvent

1 bag

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.

Activate seal and gently mix powder and solvent.

Read the package leaflet before use for further instructions and recommended dose.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

After activation of the bag and reconstitution: See the leaflet for further information.

9. SPECIAL STORAGE CONDITIONS

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

Keep the bag in the aluminum wrapper in order to protect from activation.

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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adienne@adienne.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/622/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TEPADINA 400 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Aluminum wrapper

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 400 mg powder and solvent for solution for infusion
thiotepa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains 400 mg thiotepa.
After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

3. LIST OF EXCIPIENTS

Solvent: sodium chloride and water for injections
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion
One bag contains 400 mg thiotepa and 400 mL solvent
1 bag

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.
Activate seal and gently mix powder and solvent.

Read the package leaflet before use for further instructions and recommended dose.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP
After activation of the bag and reconstitution: See the leaflet for further information.

9. SPECIAL STORAGE CONDITIONS

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

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

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

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Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Inner label bag

1. NAME OF THE MEDICINAL PRODUCT

TEPADINA 400 mg powder and solvent for solution for infusion
thiotepa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains 400 mg thiotepa.

After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

3. LIST OF EXCIPIENTS

Solvent: sodium chloride and water for injections

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion

One bag contains 400 mg thiotepa and 400 mL solvent

1 bag

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution.

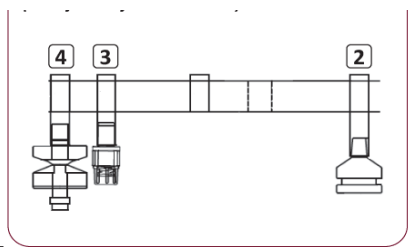
Activate seal and gently mix powder and solvent.

Read the package leaflet before use for further instructions and recommended dose.

2 – Blind Port (NEVER use this port)

3 – Luer Port (For dose adjustment and infusion of the medication)

4 – Twist off Port (For infusion of the medication)



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

After activation of the bag and reconstitution: See the leaflet for further information.

9. SPECIAL STORAGE CONDITIONS

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

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

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

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE****17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

B. PACKAGE LEAFLET

Package leaflet: Information for the user

TEPADINA 15 mg powder for concentrate for solution for infusion thiotepa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What TEPADINA is and what it is used for

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

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

TEPADINA can be used in adults and children and adolescents.

2. What you need to know before you use TEPADINA

Do not use TEPADINA

- if you are allergic to thiotepa,
- if you are pregnant or think you may be pregnant,
- if you are breast-feeding,
- if you are receiving yellow fever vaccination, live virus and bacterial vaccines.

Warning and precautions

You should tell your doctor if you have:

- liver or kidney problems,
- heart or lung problems,
- seizures/fits (epilepsy) or have had them in the past (if treated with phenytoin or fosphenytoin).

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

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

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

Other medicines and TEPADINA

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

Pregnancy, breast-feeding and fertility

You must tell your doctor if you are pregnant or you think you may be pregnant before you receive TEPADINA. You must not use TEPADINA during pregnancy.

Both women and men using TEPADINA must use effective contraceptive methods during treatment. Men should not father a child while treated with TEPADINA and during the year after cessation of treatment.

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

TEPADINA can impair male and female fertility. Male patients should seek advice for sperm preservation before therapy is started.

Driving and using machines

It is likely that certain adverse reactions of thiotepa like dizziness, headache and blurred vision could affect your ability to drive and use machines. If you are affected, do not drive or use machines.

3. How to use TEPADINA

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

How TEPADINA is given

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

Frequency of administration

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

4. Possible side effects

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

The most serious side effects of TEPADINA therapy or the transplant procedure may include

- decrease in circulating blood cell counts (intended effect of the medicine to prepare you for your transplant infusion)
- infection
- liver disorders including blocking of a liver vein
- the graft attacks your body (graft versus host disease)
- respiratory complications

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

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

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

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

Common side effects (may affect up to 1 in 10 people)

- anxiety, confusion
- abnormal bulging outward of one of the arteries in the brain (intracranial aneurysm)
- creatinine elevated
- allergic reactions
- occlusion of a blood vessel (embolism)

- heart rhythm disorder
- heart inability
- cardiovascular inability
- oxygen deficiency
- fluid accumulation in the lungs (pulmonary oedema)
- pulmonary bleeding
- respiratory arrest
- blood in the urine (haematuria) and moderate renal insufficiency
- inflammation of the urinary bladder
- discomfort in urination and decrease in urine output (disuria and oliguria)
- increase in the amount of nitrogen components in the blood stream (BUN increase)
- cataract
- inability of the liver
- cerebral haemorrhage
- cough
- constipation and upset stomach
- obstruction of the bowel
- perforation of stomach
- changes in muscle tone
- gross lack of coordination of muscle movements
- bruises due to a low platelet count
- menopausal symptoms
- cancer (second primary malignancies)
- abnormal brain function
- male and female infertility

Uncommon side effects (may affect up to 1 in 100 people)

- inflammation and exfoliation of the skin (erythrodermic psoriasis)
- delirium, nervousness, hallucination, agitation
- gastrointestinal ulcer
- inflammation of the muscular tissue of the heart (myocarditis)
- abnormal heart condition (cardiomyopathy)

Not known (frequency cannot be estimated from the available data)

- increased blood pressure in the arteries (blood vessels) of the lungs (pulmonary arterial hypertension)
- severe skin damage (e.g. severe lesions, bullae, etc.) potentially involving the full body surface which can be even life-threatening
- damage to a component of the brain (the so-called white matter) which can be even life-threatening (leukoencephalopathy).

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store TEPADINA

Keep this medicine out of the sight and reach of children.

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

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

After reconstitution the product is stable for 80 hours when stored at 2°C -8°C.

After dilution the product is stable 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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What TEPADINA contains

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

What TEPADINA looks like and contents of the pack

TEPADINA is a white crystalline powder supplied in a glass vial containing 15 mg thiotepa. Each carton contains 1 vial.

Marketing Authorisation Holder and Manufacturer

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB) Italy
Tel: +39 02 40700445
adienne@adienne.com

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

Accord Healthcare bv
Tél/Tel: +32 51 79 40 12

България

Accord Healthcare Polska Sp. z o.o.
Тел.: +48 22 577 28 00

Česká republika

Accord Healthcare Polska Sp. z o.o.
Tel: +48 22 577 28 00

Danmark

Accord Healthcare AB
Tlf: + 46 8 624 00 25

Deutschland

Accord Healthcare GmbH
Tel: +49 89 700 9951 0

Eesti

Accord Healthcare AB
Tel: +46 8 624 00 25

Ελλάδα

Accord Healthcare Italia Srl

Lietuva

Accord Healthcare AB
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Luxembourg/Luxemburg

Accord Healthcare bv
Tél/Tel: +32 51 79 40 12

Magyarország

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Accord Healthcare GmbH

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France

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This leaflet was last revised in

Other sources of information

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

The following information is intended for healthcare professionals only.

PREPARATION GUIDE

TEPADINA 15 mg powder for concentrate for solution for infusion

Thiotepa

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

1. PRESENTATION

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

2. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

General

Procedures for proper handling and disposal of anticancer medicinal products should be considered. All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood.

As with other cytotoxic compounds, caution need to be exercised in handling and preparation of TEPADINA solutions to avoid accidental contact with skin or mucous membranes. Topical reactions associated with accidental exposure to thiotepa may occur. In fact, the use of gloves is recommended in preparing the solution for infusion. If thiotepa solution accidentally contacts the skin, immediately the skin must be thoroughly washed with soap and water. If thiotepa accidentally contacts mucous membranes, they must be flushed thoroughly with water.

Calculation of dose of TEPADINA

TEPADINA is administered at different doses in combination with other chemotherapeutic medicinal products in patients prior to conventional haematopoietic progenitor cell transplantation (HPCT) for haematological diseases or solid tumours.

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

Posology in adults

AUTOLOGOUS HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA

The recommended dose is 185 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

Solid tumours

The recommended dose in solid tumours ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

BREAST CANCER

The recommended dose ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

OVARIAN CANCER

The recommended dose is 250 mg/m²/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/m² (13.51 mg/kg), during the time of the entire conditioning treatment.

GERM CELL TUMOURS

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (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/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose in lymphoma is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose is 185 mg/m²/day (5 mg/kg/day) as a single daily infusion before allogeneic HPCT, without exceeding the total maximum cumulative dose of 185 mg/m² (5 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose ranges from 185 mg/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

Posology in paediatric patients

AUTOLOGOUS HPCT

Solid tumours

The recommended dose in solid tumours ranges from 150 mg/m²/day (6 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (42 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 250 mg/m²/day (10 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (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/m²/day (5 mg/kg/day) to 250 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose ranges from 200 mg/m²/day (8 mg/kg/day) to 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

REFRACTORY CYTOPENIA

The recommended dose is 125 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

GENETIC DISEASES

The recommended dose is 125 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

SICKLE CELL ANAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

Reconstitution

TEPADINA must be reconstituted with 1.5 mL of sterile water for injections.

Using a syringe fitted with a needle, aseptically withdraw 1.5 mL of sterile water for injections.

Inject the content of the syringe into the vial through the rubber stopper.

Remove the syringe and the needle and mix manually by repeated inversions.

Only colourless solutions, without any particulate matter, must be used. Reconstituted solutions may occasionally show opalescence; such solutions can still be administered.

Further dilution in the infusion bag

The reconstituted solution is hypotonic and must be further diluted prior to administration with 500 mL sodium chloride 9 mg/mL (0.9%) solution for injection (1 000 mL if the dose is higher than 500 mg) or with an appropriate volume of sodium chloride 9 mg/mL (0.9%) in order to obtain a final TEPADINA concentration between 0.5 and 1 mg/mL.

Administration

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

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

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

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

Disposal

TEPADINA is for single use only.

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

Package leaflet: Information for the user

TEPADINA 100 mg powder for concentrate for solution for infusion thiotepa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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

1. What TEPADINA is and what it is used for

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

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

TEPADINA can be used in adults and children and adolescents.

2. What you need to know before you use TEPADINA

Do not use TEPADINA

- if you are allergic to thiotepa,
- if you are pregnant or think you may be pregnant,
- if you are breast-feeding,
- if you are receiving yellow fever vaccination, live virus and bacterial vaccines.

Warning and precautions

You should tell your doctor if you have:

- liver or kidney problems,
- heart or lung problems,
- seizures/fits (epilepsy) or have had them in the past (if treated with phenytoin or fosphenytoin).

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

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

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

Other medicines and TEPADINA

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

Pregnancy, breast-feeding and fertility

You must tell your doctor if you are pregnant or you think you may be pregnant before you receive TEPADINA. You must not use TEPADINA during pregnancy.

Both women and men using TEPADINA must use effective contraceptive methods during treatment. Men should not father a child while treated with TEPADINA and during the year after cessation of treatment.

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

TEPADINA can impair male and female fertility. Male patients should seek advice for sperm preservation before therapy is started.

Driving and using machines

It is likely that certain adverse events of thiotepa like dizziness, headache and blurred vision could affect your ability to drive and use machines. If you are affected, do not drive or use machines.

3. How to use TEPADINA

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

How TEPADINA is given

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

Frequency of administration

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

4. Possible side effects

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

The most serious side effects of TEPADINA therapy or the transplant procedure may include

- decrease in circulating blood cell counts (intended effect of the medicine to prepare you for your transplant infusion)
- infection
- liver disorders including blocking of a liver vein
- the graft attacks your body (graft versus host disease)
- respiratory complications

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

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

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

- increased susceptibility to infection
- whole-body inflammatory state (sepsis)
- decreased counts of white blood cells, platelets and red blood cells (anaemia)
- the transplanted cells attack your body (graft versus host disease)

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

Common side effects (may affect up to 1 in 10 people)

- anxiety, confusion
- abnormal bulging outward of one of the arteries in the brain (intracranial aneurysm)
- creatinine elevated
- allergic reactions
- occlusion of a blood vessel (embolism)
- heart rhythm disorder
- heart inability
- cardiovascular inability
- oxygen deficiency
- fluid accumulation in the lungs (pulmonary oedema)

- pulmonary bleeding
- respiratory arrest
- blood in the urine (haematuria) and moderate renal insufficiency
- inflammation of the urinary bladder
- discomfort in urination and decrease in urine output (disuria and oliguria)
- increase in the amount of nitrogen components in the blood stream (BUN increase)
- cataract
- inability of the liver
- cerebral haemorrhage
- cough
- constipation and upset stomach
- obstruction of the bowel
- perforation of stomach
- changes in muscle tone
- gross lack of coordination of muscle movements
- bruises due to a low platelet count
- menopausal symptoms
- cancer (second primary malignancies)
- abnormal brain function
- male and female infertility

Uncommon side effects (may affect up to 1 in 100 people)

- inflammation and exfoliation of the skin (erythrodermic psoriasis)
- delirium, nervousness, hallucination, agitation
- gastrointestinal ulcer
- inflammation of the muscular tissue of the heart (myocarditis)
- abnormal heart condition (cardiomyopathy)

Not known (frequency cannot be estimated from the available data)

- increased blood pressure in the arteries (blood vessels) of the lungs (pulmonary arterial hypertension)
- severe skin damage (e.g. severe lesions, bullae, etc.) potentially involving the full body surface which can be even life-threatening
- damage to a component of the brain (the so-called white matter) which can be even life-threatening (leukoencephalopathy).

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store TEPADINA

Keep this medicine out of the sight and reach of children.

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

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

After reconstitution the product is stable for 80 hours when stored at 2°C -8°C.

After dilution the product is stable 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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What TEPADINA contains

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

What TEPADINA looks like and contents of the pack

TEPADINA is a white crystalline powder supplied in a glass vial containing 100 mg thiotepa. Each carton contains 1 vial.

Marketing Authorisation Holder and Manufacturer

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Via Galileo Galilei, 19
20867 Caponago (MB) Italy
Tel: +39 02 40700445
adienne@adienne.com

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only.

PREPARATION GUIDE

TEPADINA 100 mg powder for concentrate for solution for infusion

Thiotepa

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

1. PRESENTATION

TEPADINA is supplied as 100 mg powder for concentrate for solution for infusion.

TEPADINA must be reconstituted and diluted prior to administration.

2. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

General

Procedures for proper handling and disposal of anticancer medicinal products should be considered. All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood.

As with other cytotoxic compounds, caution need to be exercised in handling and preparation of TEPADINA solutions to avoid accidental contact with skin or mucous membranes. Topical reactions associated with accidental exposure to thiotepa may occur. In fact, the use of gloves is recommended in preparing the solution for infusion. If thiotepa solution accidentally contacts the skin, immediately the skin must be thoroughly washed with soap and water. If thiotepa accidentally contacts mucous membranes, they must be flushed thoroughly with water.

Calculation of dose of TEPADINA

TEPADINA is administered at different doses in combination with other chemotherapeutic medicinal products in patients prior to conventional haematopoietic progenitor cell transplantation (HPCT) for haematological diseases or solid tumours.

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

Posology in adults

AUTOLOGOUS HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA

The recommended dose is 185 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

Solid tumours

The recommended dose in solid tumours ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

BREAST CANCER

The recommended dose ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

OVARIAN CANCER

The recommended dose is 250 mg/m²/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/m² (13.51 mg/kg), during the time of the entire conditioning treatment.

GERM CELL TUMOURS

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (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/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose in lymphoma is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose is 185 mg/m²/day (5 mg/kg/day) as a single daily infusion before allogeneic HPCT, without exceeding the total maximum cumulative dose of 185 mg/m² (5 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose ranges from 185 mg/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

Posology in paediatric patients

AUTOLOGOUS HPCT

Solid tumours

The recommended dose in solid tumours ranges from 150 mg/m²/day (6 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (42 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 250 mg/m²/day (10 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (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/m²/day (5 mg/kg/day) to 250 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose ranges from 200 mg/m²/day (8 mg/kg/day) to 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

REFRACTORY CYTOPENIA

The recommended dose is 125 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

GENETIC DISEASES

The recommended dose is 125 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

SICKLE CELL ANAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

Reconstitution

TEPADINA must be reconstituted with 10 mL of sterile water for injections.

Using a syringe fitted with a needle, aseptically withdraw 10 mL of sterile water for injections.

Inject the content of the syringe into the vial through the rubber stopper.

Remove the syringe and the needle and mix manually by repeated inversions.

Only colourless solutions, without any particulate matter, must be used. Reconstituted solutions may occasionally show opalescence; such solutions can still be administered.

Further dilution in the infusion bag

The reconstituted solution is hypotonic and must be further diluted prior to administration with 500 mL sodium chloride 9 mg/mL (0.9%) solution for injection (1 000 mL if the dose is higher than 500 mg) or with an appropriate volume of sodium chloride 9 mg/mL (0.9%) in order to obtain a final TEPADINA concentration between 0.5 and 1 mg/mL.

Administration

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

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

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

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

Disposal

TEPADINA is for single use only.

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

Package leaflet: Information for the user

TEPADINA 200 mg powder and solvent for solution for infusion thiotepa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What TEPADINA is and what it is used for

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

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

TEPADINA can be used in adults and children and adolescents.

2. What you need to know before you use TEPADINA

Do not use TEPADINA

- if you are allergic to thiotepa,
- if you are pregnant or think you may be pregnant,
- if you are breast-feeding,
- if you are receiving yellow fever vaccination, live virus and bacterial vaccines.

Warning and precautions

You should tell your doctor if you have:

- liver or kidney problems,
- heart or lung problems,
- seizures/fits (epilepsy) or have had them in the past (if treated with phenytoin or fosphenytoin).

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

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

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

Other medicines and TEPADINA

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

Pregnancy, breast-feeding and fertility

You must tell your doctor if you are pregnant or you think you may be pregnant before you receive TEPADINA. You must not use TEPADINA during pregnancy.

Both women and men using TEPADINA must use effective contraceptive methods during treatment. Men should not father a child while treated with TEPADINA and during the year after cessation of treatment.

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

TEPADINA can impair male and female fertility. Male patients should seek advice for sperm preservation before therapy is started.

Driving and using machines

It is likely that certain adverse reactions of thiotepa like dizziness, headache and blurred vision could affect your ability to drive and use machines. If you are affected, do not drive or use machines.

TEPADINA contains sodium

This medicine contains 709 mg (30.8 mmol) sodium (main component of cooking/table salt) in each bag. This is equivalent to 35, 5% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use TEPADINA

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

How TEPADINA is given

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

Frequency of administration

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

4. Possible side effects

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

The most serious side effects of TEPADINA therapy or the transplant procedure may include

- decrease in circulating blood cell counts (intended effect of the medicine to prepare you for your transplant infusion)
- infection
- liver disorders including blocking of a liver vein
- the graft attacks your body (graft versus host disease)
- respiratory complications

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

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

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

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

Common side effects (may affect up to 1 in 10 people)

- anxiety, confusion
- abnormal bulging outward of one of the arteries in the brain (intracranial aneurysm)
- creatinine elevated
- allergic reactions
- occlusion of a blood vessel (embolism)

- heart rhythm disorder
- heart inability
- cardiovascular inability
- oxygen deficiency
- fluid accumulation in the lungs (pulmonary oedema)
- pulmonary bleeding
- respiratory arrest
- blood in the urine (haematuria) and moderate renal insufficiency
- inflammation of the urinary bladder
- discomfort in urination and decrease in urine output (disuria and oliguria)
- increase in the amount of nitrogen components in the blood stream (BUN increase)
- cataract
- inability of the liver
- cerebral haemorrhage
- cough
- constipation and upset stomach
- obstruction of the bowel
- perforation of stomach
- changes in muscle tone
- gross lack of coordination of muscle movements
- bruises due to a low platelet count
- menopausal symptoms
- cancer (second primary malignancies)
- abnormal brain function
- male and female infertility

Uncommon side effects (may affect up to 1 in 100 people)

- inflammation and exfoliation of the skin (erythrodermic psoriasis)
- delirium, nervousness, hallucination, agitation
- gastrointestinal ulcer
- inflammation of the muscular tissue of the heart (myocarditis)
- abnormal heart condition (cardiomyopathy)

Not known (frequency cannot be estimated from the available data)

- increased blood pressure in the arteries (blood vessels) of the lungs (pulmonary arterial hypertension)
- severe skin damage (e.g. severe lesions, bullae, etc.) potentially involving the full body surface which can be even life-threatening
- damage to a component of the brain (the so-called white matter) which can be even life-threatening (leukoencephalopathy).

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store TEPADINA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, label on aluminum wrapper and bag, after EXP. The expiry date refers to the last day of that month.

Store and transport refrigerated (2°C-8°C).

Do not freeze.

Keep the bag in the aluminum wrapper in order to protect from activation.

After the activation and reconstitution of the bag, the product is stable 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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What TEPADINA contains

- The active substance is thiotepa.

One bag contains 200 mg thiotepa.

After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

- The other ingredients are sodium chloride and water for injections (see section 2 “TEPADINA contains sodium”).

What TEPADINA looks like and contents of the pack

TEPADINA is supplied in a dual chamber bag containing 200 mg thiotepa and 200 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

After reconstitution, the bag contains a clear and colourless solution for infusion.

Each bag is packed in an aluminum wrapper.

Each carton contains 1 bag.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only.

PREPARATION GUIDE

TEPADINA 200 mg powder and solvent for solution for infusion

Thiotepa

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

1. PRESENTATION

One bag contains 200 mg thiotepa.

After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

TEPADINA must be reconstituted prior to administration.

2. POSOLOGY AND METHOD OF ADMINISTRATION

Calculation of dose of TEPADINA

TEPADINA is administered at different doses in combination with other chemotherapeutic medicinal products in patients prior to conventional haematopoietic progenitor cell transplantation (HPCT) for haematological diseases or solid tumours.

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

If necessary, dose adjustment of TEPADINA must be operated as per specific application.

In case the calculated dose required is higher than 200 mg but less than a multiple thereof, the user is requested to add the required mg from TEPADINA vials by using a dedicated port (luer port) of TEPADINA 200 mg (Step 5 of the Instruction for Use in the package leaflet).

In case the calculated dose required is lower than 200 mg the user is requested to remove the unnecessary mg of fully reconstituted 1 mg/mL solution or to set an infusion pump with the amount of medicinal product to be administered in mL.

Posology in adults

AUTOLOGOUS HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA

The recommended dose is 185 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

Solid tumours

The recommended dose in solid tumours ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

BREAST CANCER

The recommended dose ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

OVARIAN CANCER

The recommended dose is 250 mg/m²/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/m² (13.51 mg/kg), during the time of the entire conditioning treatment.

GERM CELL TUMOURS

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (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/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose in lymphoma is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose is 185 mg/m²/day (5 mg/kg/day) as a single daily infusion before allogeneic HPCT, without exceeding the total maximum cumulative dose of 185 mg/m² (5 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose ranges from 185 mg/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

Posology in paediatric patients

AUTOLOGOUS HPCT

Solid tumours

The recommended dose in solid tumours ranges from 150 mg/m²/day (6 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (42 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 250 mg/m²/day (10 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (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/m²/day (5 mg/kg/day) to 250 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose ranges from 200 mg/m²/day (8 mg/kg/day) to 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

REFRACTORY CYTOPENIA

The recommended dose is 125 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

GENETIC DISEASES

The recommended dose is 125 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

SICKLE CELL ANAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

Activation of the bag and reconstitution

TEPADINA 200 mg must be reconstituted with 200 mL sodium chloride 9 mg/mL (0.9%) solution for injection. 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.
Do not use this medicine if you notice any visible signs of deterioration.

Administration

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

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

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

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

3. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

General

Procedures for proper handling and disposal of anticancer medicinal products should be considered. All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood.

As with other cytotoxic compounds, caution need to be exercised in handling and preparation of TEPADINA solutions to avoid accidental contact with skin or mucous membranes. Topical reactions associated with accidental exposure to thiotepa may occur. In fact, the use of gloves is recommended in preparing the solution for infusion. If thiotepa solution accidentally contacts the skin, immediately the skin must be thoroughly washed with soap and water. If thiotepa accidentally contacts mucous membranes, they must be flushed thoroughly with water.

Disposal

TEPADINA is for single use only.

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

Figure A

1 - Overpouch Notch

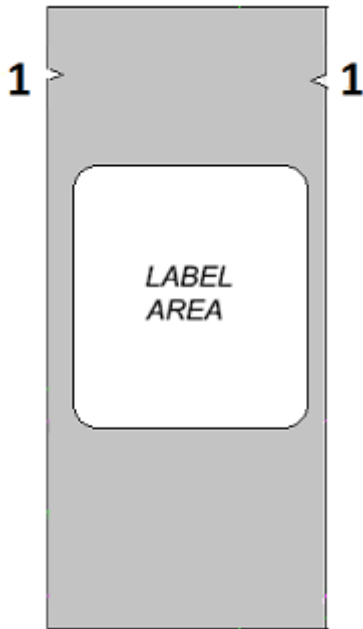
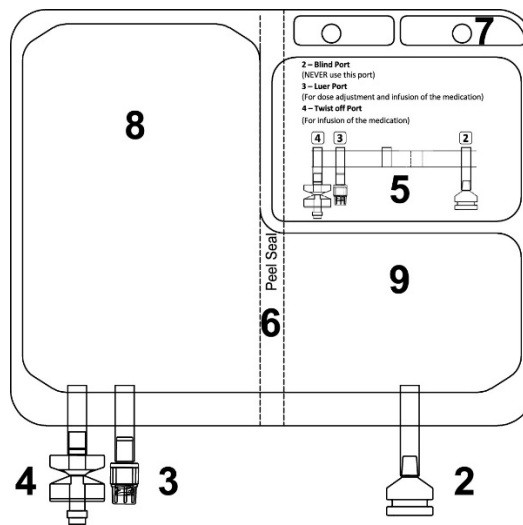


Figure B

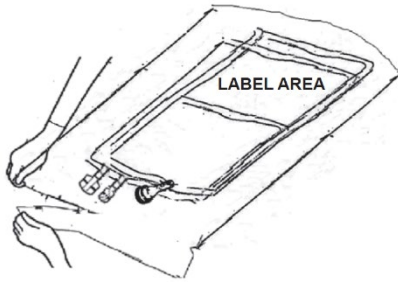
- 2 – Blind Port (NEVER use this port)**
- 3 – Luer Port**
- 4 – Twist off Port**
- 5 – Label Area**
- 6 – Peel Seal (Must break to activate)**
- 7 – Hole (For hanging the bag)**
- 8 – Solvent chamber**
- 9 – Powder chamber**



1 – REMOVE OVERPOUCH

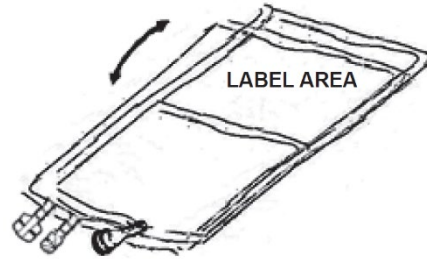
- a) Place bag on a clean, stable surface before opening.
- b) Tear from Overpouch Notch located close to the ports (**Figure A – point 1**).
- c) Tear short sides open to access the inner bag as per **Figure C**.

Figure C



- d) Remove the dual chamber flexible bag from the aluminum secondary packaging and unfold the bag **Figure D**.

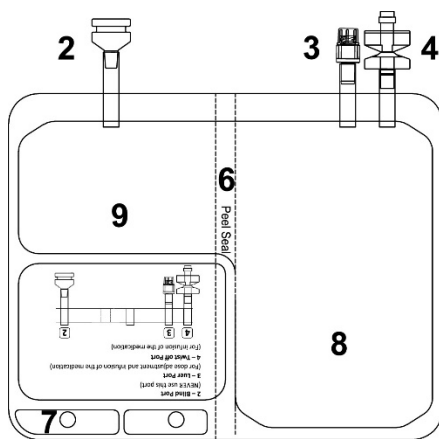
Figure D



2 - INSPECT BAG PRIOR TO ACTIVATION.

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**.

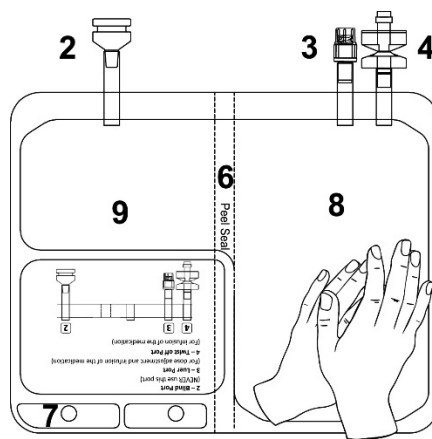
Figure E

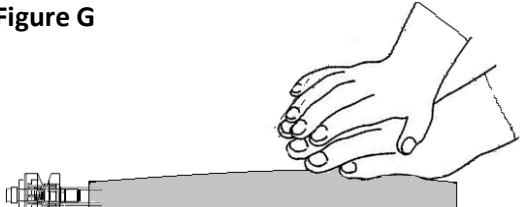
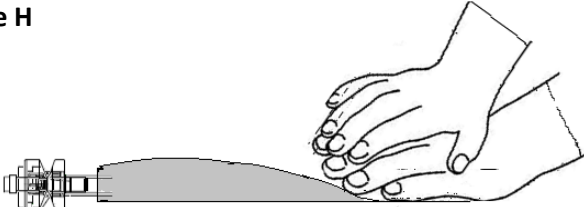



3 – ACTIVATE THE BAG

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

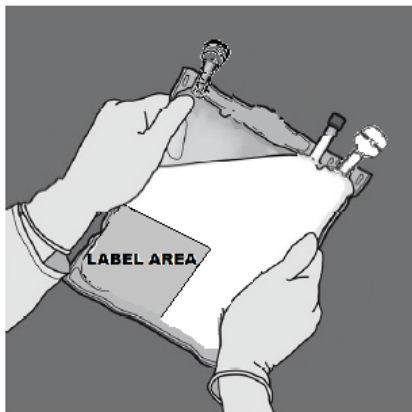


BAG BEFORE ACTIVATION	BAG AFTER ACTIVATION
<p>Figure G</p> 	<p>Figure H</p> 
<p>Do NOT squeeze or press strongly.</p>	<p>Figure I</p> 

4 – INSPECT BAG TO CONFIRM ACTIVATION.

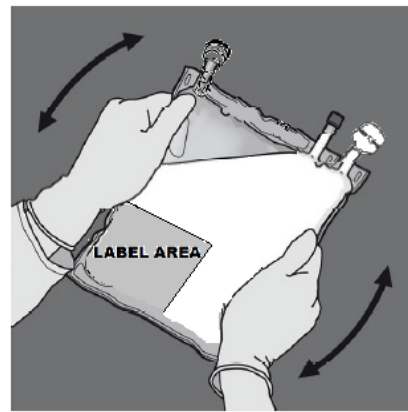
Check the peel seal **6** is now completely activated.
Chamber **8** and **9** are merged.

Figure J



Mix gently until complete dissolution of product.

Figure K



5– DOSE ADJUSTMENT - Please refer to the sections 2. “Posology and method of administration” and 3. “Special precautions for disposal and other handling”

Identify the Luer Port **3** if correcting dose is needed.
Remove the plastic cap from Luer Port.

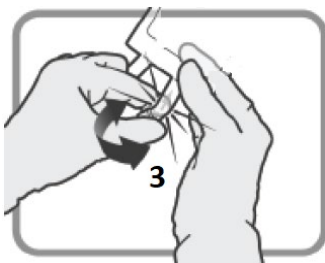


Figure L

Screw the luer lock device as per **Figure M**.
Do not use improper non luer lock devices on port **3**.

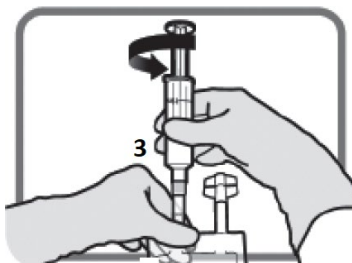


Figure M

Ensure that the connection is fully seated and tighten.

Operate dose adjustment as per sections **2** and **3**

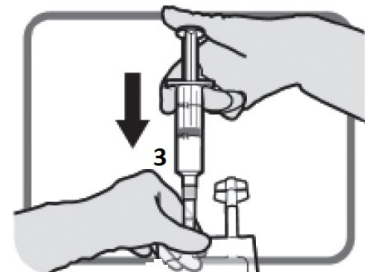


Figure N

Unscrew the device once finished.

Put the plastic cap on Luer Port **3** before proceeding with infusion

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

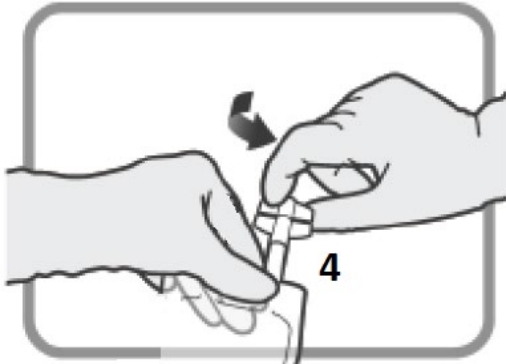


Figure O

Insert the spike connector.

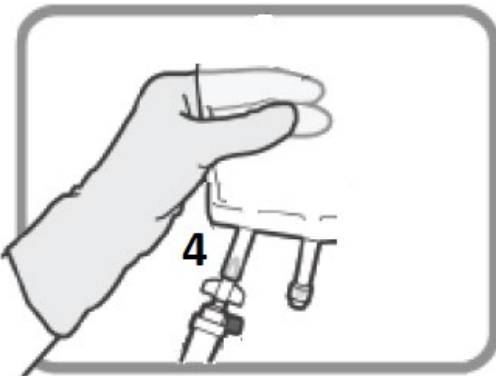


Figure P

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.

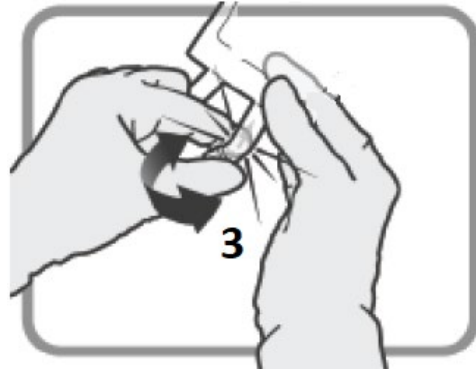


Figure Q

Insert the luer connector.

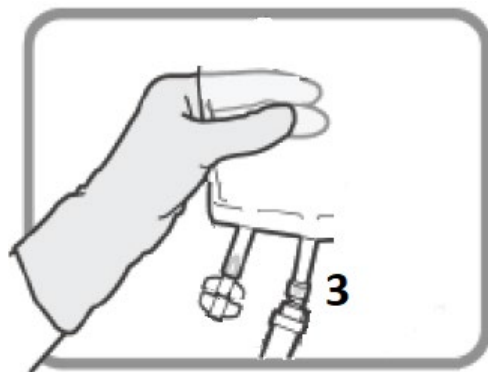


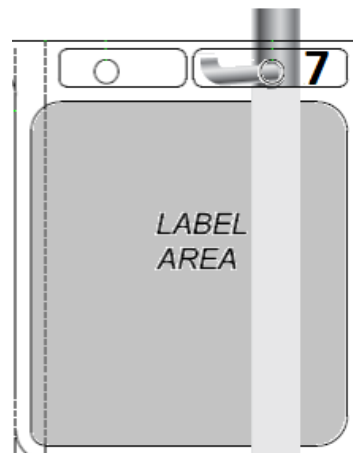
Figure R

Ensure that the connection is fully seated and tighten.

7- HANG THE BAG

Hang the bag by the hole 7.

Figure S



Package leaflet: Information for the user

TEPADINA 400 mg powder and solvent for solution for infusion thiotepa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What TEPADINA is and what it is used for

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

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

2. What you need to know before you use TEPADINA

Do not use TEPADINA

- if you are allergic to thiotepa,
- if you are pregnant or think you may be pregnant,
- if you are breast-feeding,
- if you are receiving yellow fever vaccination, live virus and bacterial vaccines.

Warning and precautions

You should tell your doctor if you have:

- liver or kidney problems,
- heart or lung problems,
- seizures/fits (epilepsy) or have had them in the past (if treated with phenytoin or fosphenytoin).

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

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

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

Other medicines and TEPADINA

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

Pregnancy, breast-feeding and fertility

You must tell your doctor if you are pregnant or you think you may be pregnant before you receive TEPADINA. You must not use TEPADINA during pregnancy.

Both women and men using TEPADINA must use effective contraceptive methods during treatment. Men should not father a child while treated with TEPADINA and during the year after cessation of treatment.

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

TEPADINA can impair male and female fertility. Male patients should seek advice for sperm preservation before therapy is started.

Driving and using machines

It is likely that certain adverse reactions of thiotepa like dizziness, headache and blurred vision could affect your ability to drive and use machines. If you are affected, do not drive or use machines.

TEPADINA contains sodium

This medicine contains 1 418 mg (61.6 mmol) sodium (main component of cooking/table salt) in each bag. This is equivalent to 70.9% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use TEPADINA

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

How TEPADINA is given

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

Frequency of administration

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

4. Possible side effects

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

The most serious side effects of TEPADINA therapy or the transplant procedure may include

- decrease in circulating blood cell counts (intended effect of the medicine to prepare you for your transplant infusion)
- infection
- liver disorders including blocking of a liver vein
- the graft attacks your body (graft versus host disease)
- respiratory complications

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

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

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

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

Common side effects (may affect up to 1 in 10 people)

- anxiety, confusion
- abnormal bulging outward of one of the arteries in the brain (intracranial aneurysm)
- creatinine elevated
- allergic reactions
- occlusion of a blood vessel (embolism)

- heart rhythm disorder
- heart inability
- cardiovascular inability
- oxygen deficiency
- fluid accumulation in the lungs (pulmonary oedema)
- pulmonary bleeding
- respiratory arrest
- blood in the urine (haematuria) and moderate renal insufficiency
- inflammation of the urinary bladder
- discomfort in urination and decrease in urine output (disuria and oliguria)
- increase in the amount of nitrogen components in the blood stream (BUN increase)
- cataract
- inability of the liver
- cerebral haemorrhage
- cough
- constipation and upset stomach
- obstruction of the bowel
- perforation of stomach
- changes in muscle tone
- gross lack of coordination of muscle movements
- bruises due to a low platelet count
- menopausal symptoms
- cancer (second primary malignancies)
- abnormal brain function
- male and female infertility

Uncommon side effects (may affect up to 1 in 100 people)

- inflammation and exfoliation of the skin (erythrodermic psoriasis)
- delirium, nervousness, hallucination, agitation
- gastrointestinal ulcer
- inflammation of the muscular tissue of the heart (myocarditis)
- abnormal heart condition (cardiomyopathy)

Not known (frequency cannot be estimated from the available data)

- increased blood pressure in the arteries (blood vessels) of the lungs (pulmonary arterial hypertension)
- severe skin damage (e.g. severe lesions, bullae, etc.) potentially involving the full body surface which can be even life-threatening
- damage to a component of the brain (the so-called white matter) which can be even life-threatening (leukoencephalopathy).

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store TEPADINA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, label on aluminum wrapper and bag, after EXP. The expiry date refers to the last day of that month.

Store and transport refrigerated (2°C-8°C).

Do not freeze.

Keep the bag in the aluminum wrapper in order to protect from activation.

After the activation and reconstitution of the bag, the product is stable 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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What TEPADINA contains

- The active substance is thiotepa.

One bag contains 400 mg thiotepa.

After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

- The other ingredients are sodium chloride and water for injections (see section 2 “TEPADINA contains sodium”).

What TEPADINA looks like and contents of the pack

TEPADINA is supplied in a dual chamber bag containing 400 mg thiotepa and 400 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

After reconstitution, the bag contains a clear and colourless solution for infusion.

Each bag is packed in an aluminum wrapper.

Each carton contains 1 bag.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only.

PREPARATION GUIDE

TEPADINA 400 mg powder and solvent for solution for infusion

Thiotepa

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

1. PRESENTATION

One bag contains 400 mg thiotepa.

After reconstitution with the solvent, each mL of solution contains 1 mg of thiotepa.

TEPADINA must be reconstituted prior to administration.

2. POSOLOGY AND METHOD OF ADMINISTRATION

Calculation of dose of TEPADINA

TEPADINA is administered at different doses in combination with other chemotherapeutic medicinal products in patients prior to conventional haematopoietic progenitor cell transplantation (HPCT) for haematological diseases or solid tumours.

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

If necessary, dose adjustment of TEPADINA must be operated as per specific application.

In case the calculated dose required is higher than 400 mg but less than a multiple thereof, the user is requested to add the required mg from TEPADINA vials by using a dedicated port (luer port) of TEPADINA 400 mg (Step 5 of the Instruction for Use in the package leaflet).

In case the calculated dose required is lower than 400 mg the user is requested to remove the unnecessary mg of fully reconstituted 1 mg/mL solution or to set an infusion pump with the amount of medicinal product to be administered in mL.

Posology in adults

AUTOLOGOUS HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 300 mg/m²/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m² (24.32 mg/kg), during the time of the entire conditioning treatment.

CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA

The recommended dose is 185 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

Solid tumours

The recommended dose in solid tumours ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

BREAST CANCER

The recommended dose ranges from 120 mg/m²/day (3.24 mg/kg/day) to 250 mg/m²/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/m² (21.62 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 125 mg/m²/day (3.38 mg/kg/day) to 250 mg/m²/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/m² (20.27 mg/kg), during the time of the entire conditioning treatment.

OVARIAN CANCER

The recommended dose is 250 mg/m²/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/m² (13.51 mg/kg), during the time of the entire conditioning treatment.

GERM CELL TUMOURS

The recommended dose ranges from 150 mg/m²/day (4.05 mg/kg/day) to 250 mg/m²/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/m² (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/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LYMPHOMA

The recommended dose in lymphoma is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA

The recommended dose is 185 mg/m²/day (5 mg/kg/day) as a single daily infusion before allogeneic HPCT, without exceeding the total maximum cumulative dose of 185 mg/m² (5 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose ranges from 185 mg/m²/day (5 mg/kg/day) to 481 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose is 370 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 370 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

Posology in paediatric patients

AUTOLOGOUS HPCT

Solid tumours

The recommended dose in solid tumours ranges from 150 mg/m²/day (6 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (42 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS

The recommended dose ranges from 250 mg/m²/day (10 mg/kg/day) to 350 mg/m²/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 1 050 mg/m² (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/m²/day (5 mg/kg/day) to 250 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

LEUKAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA

The recommended dose ranges from 200 mg/m²/day (8 mg/kg/day) to 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

REFRACTORY CYTOPENIA

The recommended dose is 125 mg/m²/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/m² (15 mg/kg), during the time of the entire conditioning treatment.

GENETIC DISEASES

The recommended dose is 125 mg/m²/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/m² (10 mg/kg), during the time of the entire conditioning treatment.

SICKLE CELL ANAEMIA

The recommended dose is 250 mg/m²/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m² (10 mg/kg), during the time of the entire conditioning treatment.

Activation of the bag and reconstitution

TEPADINA 400 mg must be reconstituted with 400 mL sodium chloride 9 mg/mL (0.9%) solution for injection. 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.
Do not use this medicine if you notice any visible signs of deterioration.

Administration

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

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

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

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

3. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

General

Procedures for proper handling and disposal of anticancer medicinal products should be considered. All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood.

As with other cytotoxic compounds, caution need to be exercised in handling and preparation of TEPADINA solutions to avoid accidental contact with skin or mucous membranes. Topical reactions associated with accidental exposure to thiotepa may occur. In fact, the use of gloves is recommended in preparing the solution for infusion. If thiotepa solution accidentally contacts the skin, immediately the skin must be thoroughly washed with soap and water. If thiotepa accidentally contacts mucous membranes, they must be flushed thoroughly with water.

Disposal

TEPADINA is for single use only.

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

Figure A

1 - Overpouch Notch

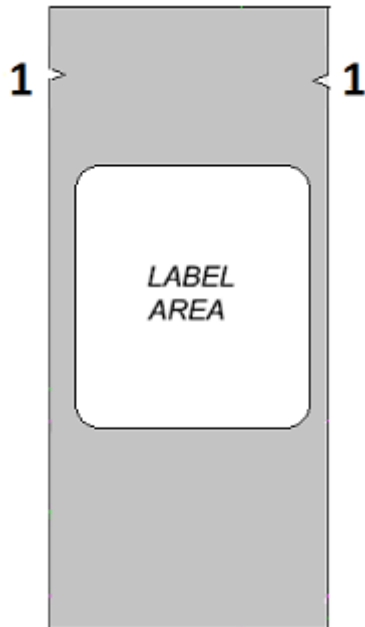
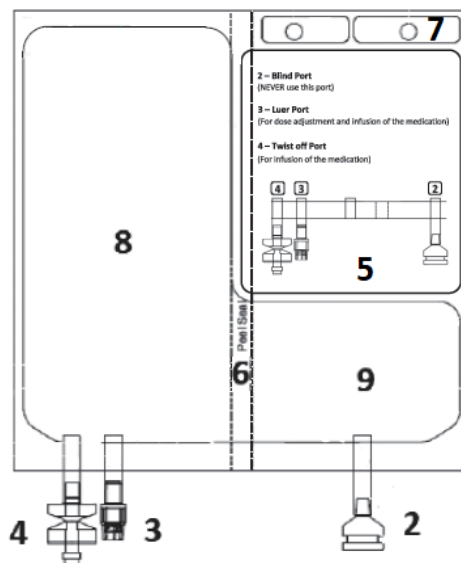


Figure B

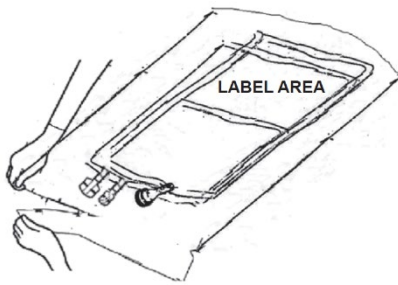
- 2 – Blind Port (NEVER use this port)**
- 3 – Luer Port**
- 4 – Twist off Port**
- 5 – Label Area**
- 6 – Peel Seal (Must break to activate)**
- 7 – Hole (For hanging the bag)**
- 8 – Solvent chamber**
- 9 – Powder chamber**



1 – REMOVE OVERPOUCH

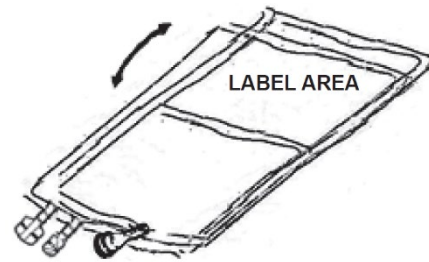
- e) Place bag on a clean, stable surface before opening.
- f) Tear from Overpouch Notch located close to the ports (**Figure A – point 1**).
- g) Tear short sides open to access the inner bag as per **Figure C**.

Figure C



- h) Remove the dual chamber flexible bag from the aluminum secondary packaging and unfold the bag **Figure D**.

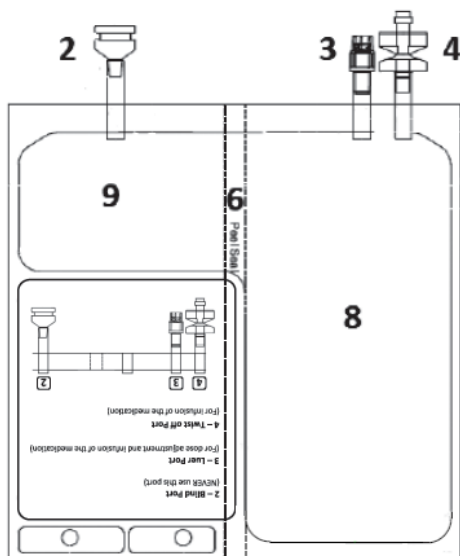
Figure D



2 - INSPECT BAG PRIOR TO ACTIVATION.

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**.

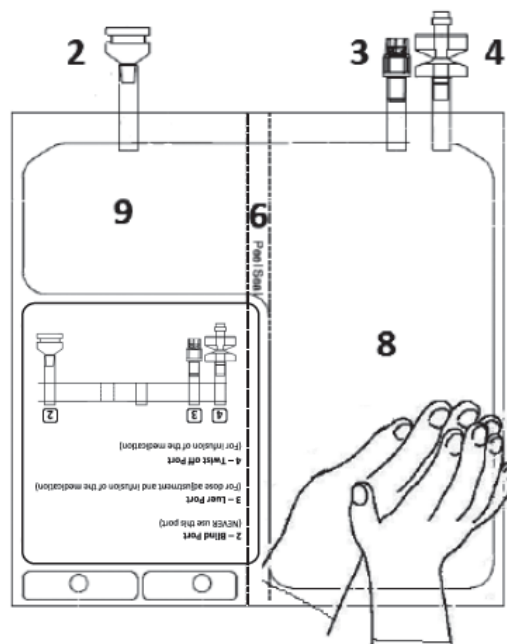
Figure E

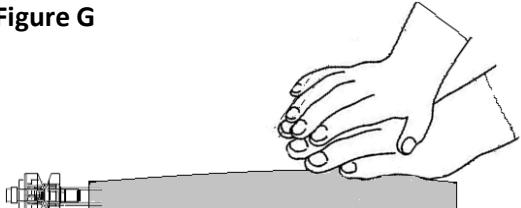
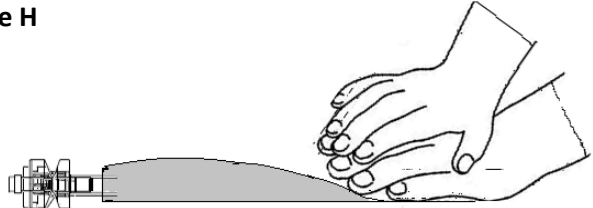

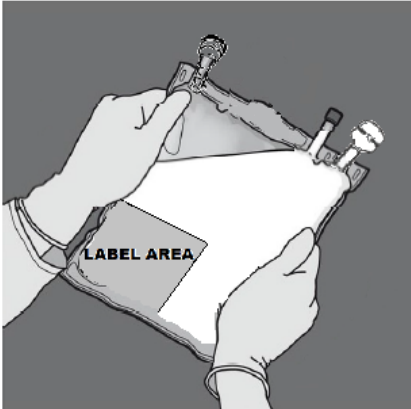
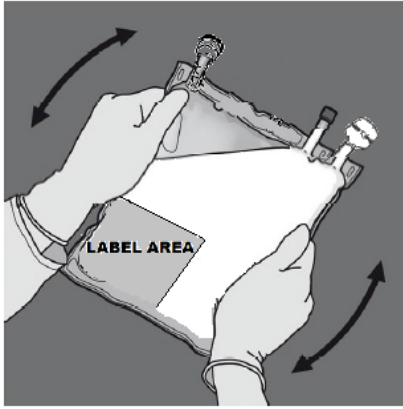
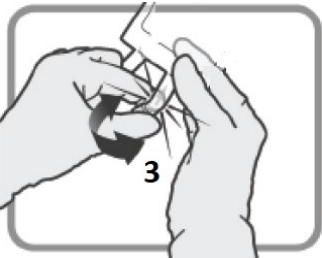
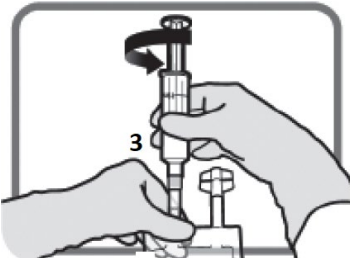
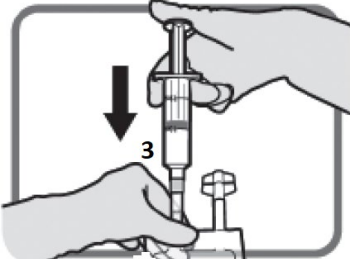


3 – ACTIVATE THE BAG

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



BAG BEFORE ACTIVATION	BAG AFTER ACTIVATION	
<p>Figure G</p> 	<p>Figure H</p> 	
<p>Do NOT squeeze or press strongly.</p>	<p>Figure I</p> 	
4 – INSPECT BAG TO CONFIRM ACTIVATION.		
<p>Check the peel seal 6 is now completely activated. Chamber 8 and 9 are merged.</p> <p>Figure J</p> 	<p>Mix gently until complete dissolution of product.</p> <p>Figure K</p> 	
5– DOSE ADJUSTMENT - Please refer to the sections 2. “Posology and method of administration” and 3. “Special precautions for disposal and other handling”		
<p>Identify the Luer Port 3 if correcting dose is needed. Remove the plastic cap from Luer Port.</p> <p>Figure L</p> 	<p>Screw the luer lock device as per Figure M. Do not use improper non luer lock devices on port 3.</p> <p>Figure M</p>  <p>Ensure that the connection is fully seated and tighten.</p>	<p>Operate dose adjustment as per sections 2 and 3</p> <p>Figure N</p>  <p>Unscrew the device once finished. Put the plastic cap on Luer Port 3 before proceeding with infusion</p>

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

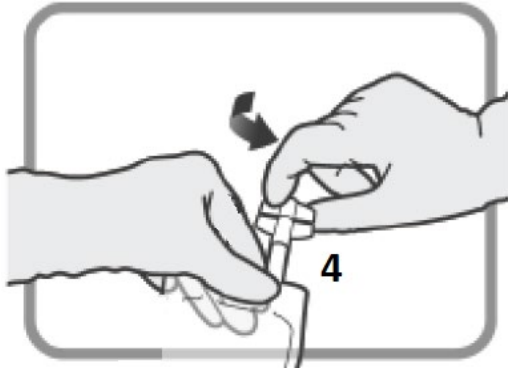


Figure O

Insert the spike connector.

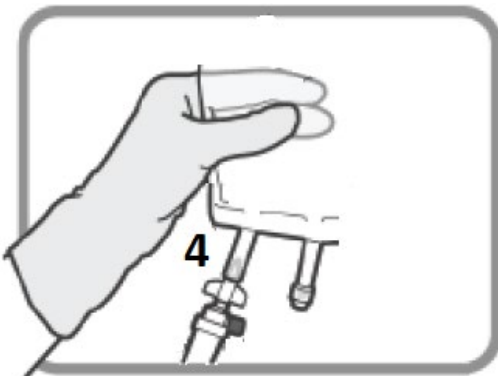


Figure P

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.

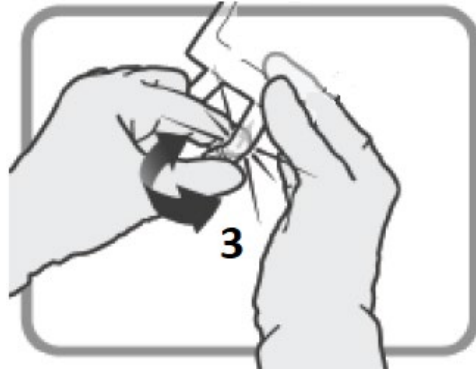


Figure Q

Insert the luer connector.

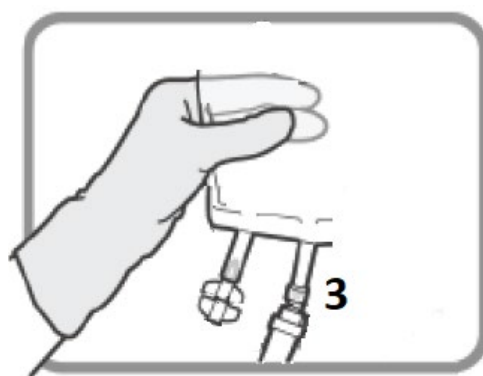


Figure R

Ensure that the connection is fully seated and tighten.

7- HANG THE BAG

Hang the bag by the hole 7.

Figure S

