URGENT – THIOTEPA UPDATE

April 5, 2011

Dear Healthcare Professional,

Due to the current critical shortage of Thiotepa for Injection, USP (Bedford 15 mg/vial; NDC 55390-0030-10) in the United States (US) market, ADIENNE Srl is coordinating with the Food and Drug Administration (FDA) to increase the availability of Thiotepa for Injection, USP. In conjunction with the FDA, ADIENNE Srl has initiated temporary importation into the US market TEPADINA®, an international (EU) Thiotepa for Injection, USP.

TEPADINA® contains the same active ingredient as the US registered Thiotepa for Injection, USP. However, TEPADINA® is provided in two different size vials, 15 mg/vial and 100 mg/vial. The 15 mg vial contains the same amount of active ingredient as the FDA approved Thiotepa for Injection, USP that has been available in the US market. The 100 mg vial has the same active ingredient as the 15 mg vial, but contains 85 mg more Thiotepa per vial than the 15 mg vial. Both vial sizes of TEPADINA® are a clinically acceptable substitute to the Thiotepa for Injection, USP marketed in the US. The choice of vial size will depend on the dosage required for the specific indication and patient.

There are some key differences in the labeling between the US marketed Thiotepa for Injection, USP, and the European ADIENNE TEPADINA® (please see the comparison table). In the US, the labeling for Thiotepa for Injection, USP includes: i) treatment of adenocarcinoma of the breast and ovarian cancer; ii) for controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities; iii) for the treatment of superficial papillary carcinoma of the urinary bladder; and iv) lymphomas, such as lymphosarcoma and Hodgkin's disease. The label in EU is for the use as part of conditioning therapy prior to autologous or allogeneic hematopoietic progenitor cell transplantation for the treatment of malignant and non-malignant disease. In the US package insert, the recommended dose of Thiotepa for the indications listed for intravenous use is 0.3 to 0.4mg/kg and the recommended dose of Thiotepa for intravesical instillation in the US package insert is 0.6 to 0.8mg/ml. **These doses are less than one tenth of the TEPADINA® dose recommended for conditioning therapy in the EU label that accompanies TEPADINA®.** Please refer to the TEPADINA® package insert for more information. TEPADINA® can be safely substituted for any indication that you are currently using the FDA approved Thiotepa for Injection, USP. **Please be sure that you prescribe proper dose for the indication.** The label for TEPADINA® 15 mg/vial and TEPADINA® 100 mg/vial are identical except for the amount of Thiotepa for Injection in the vial -15 mg versus 100 mg respectively. Do not use the trade name when ordering the drug in the US. Please use Thiotepa for Injection, USP.

The Thiotepa in TEPADINA® 15 mg/vial and 100 mg/vial is manufactured at IDT Australia Limited with an active Drug Master File on file with the FDA. The facility that manufactures Thiotepa for TEPADINA is in compliance with FDA current good manufacturing practices.

The packaging for TEPADINA® differs from the FDA approved labeling for Thiotepa for Injection, USP supplied by Bedford. TEPADINA® has no bar code or NDC number. Additionally, the box label will be in English plus two other languages (either French and German or Spanish and Italian). The label on the vial and the package insert is in English.

To order TEPADINA®, please contact Customer Service: Stefano Berardi by phone **+39.035.264206**, fax **+39 035.258.672** or e-mail **stefano.berardi@adienne.com**. Because the drug will be shipped from Italy by a specialize courier in cool temperature box (between +2 and +8ºC), shipments will only be made on Monday, Tuesday and Wednesday in order to ensure receipt prior to the weekend. If TEPADINA® is required urgently; ADIENNE Srl will do everything possible to meet the needs of clinical team. TEPADINA® should be handled exactly as you have handled the FDA approved Thiotepa for Injection, USP. TEPADINA® vials should be stored between +2 and +8ºC, once reconstituted; and the reconstituted drug should be used within 8 hours.

To report adverse events or medication errors among patients administered TEPADINA®, please contact Pharmacovigilance: Daniela Rota, Biotech D. by phone: **+39.035.199.640.47**; fax: **+39.035.432.9792** or e-mail: **daniela.rota@adienne.com**. ADIENNE will ensure that the FDA is aware of the adverse event. Adverse events that may be related to the use of this product may also be reported using the FDA's MedWatch Adverse Event Reporting Program either online, by regular mail or by fax:

- Online: www.fda.gov/medwatch/report.htm
- Regular Mail: use postage-paid FDA form 3500 available at www.fda.gov/MedWatch/getforms.htm. Mail to: MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787
- Fax: +1-800-FDA-0178

At this time, no other entity except ADIENNE Srl is authorized by the FDA to import or distribute TEPADINA® (thiotepa for injection 15mg and 100mg vials) in the United States. Any sales of TEPADINA® 15mg or 100mg vials from any entity other than ADIENNE Srl. will be considered a violation of the Federal Food, Drug and Cosmetic Act and will be subject to enforcement by FDA.

Thank you,

RJ Tesi, MD, Chief Medical Officer, ADIENNE Srl

Bedford Thiotepa for Injection USP (FDA approved)	**ADIENNE TEPADINA® (thiotepa for injection)**	**What does this mean to you as a Healthcare Professional**
Contains 15 mg/vial	Two Strengths are available: 15 mg/vial and 100 mg/vial	Take note of the strength vial you have been provided. The amount of diluent required differs depending on the vial strength. Dilute 15 mg/vial with 1.5 mL of sterile water for injection. Dilute 100 mg/vial with 10 mL of sterile water for injection. **Care must be taken to ensure that TEPADINA® is reconstituted with the appropriate amount of solution prior to intravenous infusion to yield a thiotepa concentration of approximately 10 mg/mL. Care should be taken in calculating the specific dose of thiotepa based on mg/kg, not by vials/dose.**
Reconstitute with 1.5 mL of Sterile Water for Injection resulting in concentration of approximately 10 mg/mL. The reconstituted solution should be further diluted in 500 mL of Normal Saline (0.9% Saline) prior to administration.	**15 mg/vial:** Reconstitute with **1.5 mL** of Sterile Water for Injection resulting in concentration of approximately 10 mg/mL. The reconstituted solution should be further diluted in 500 mL of Normal Saline (0.9% Saline) prior to administration. **100mg/vial:** Reconstitute with **10 mL** of Sterile Water for Injection resulting in concentration of approximately 10 mg/mL. The reconstituted solution should be further diluted in 500 mL of Normal Saline (0.9% Saline) prior to administration.	Thiotepa is a potent alkylating agent used to treat cancer. The drug should be handled and used by experienced health care professionals.
Is indicated for palliation of a variety of neoplastic diseases in adults for: • Adenocarcinoma of the breast • Adenocarcinoma of the ovary • For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases • For treatment of superficial papillary carcinoma of the urinary bladder • while now largely superseded by other treatments, thiotepa has been effective against other lymphomas, such as lymphosarcoma and Hodgkin's disease	In all Europe, 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 hematopoietic progenitor cell transplantation (HPCT) in hematological diseases in adult and pediatric patients • When high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumors in adult and pediatric patients	The labeling you receive will contain all indications approved in Europe. Ensure you are referring to the dosage and administration instructions that refer to the indication you are intending to use. In the United States, thiotepa is approved only for the indications specified in the Bedford thiotepa package insert. ADIENNE is currently in discussions with the FDA regarding the approval process for TEPADINA® for some of the indications for which it is approved in Europe.
In the US package insert, the	The total dose of TEPADINA® in	TEPADINA® can be safely substituted

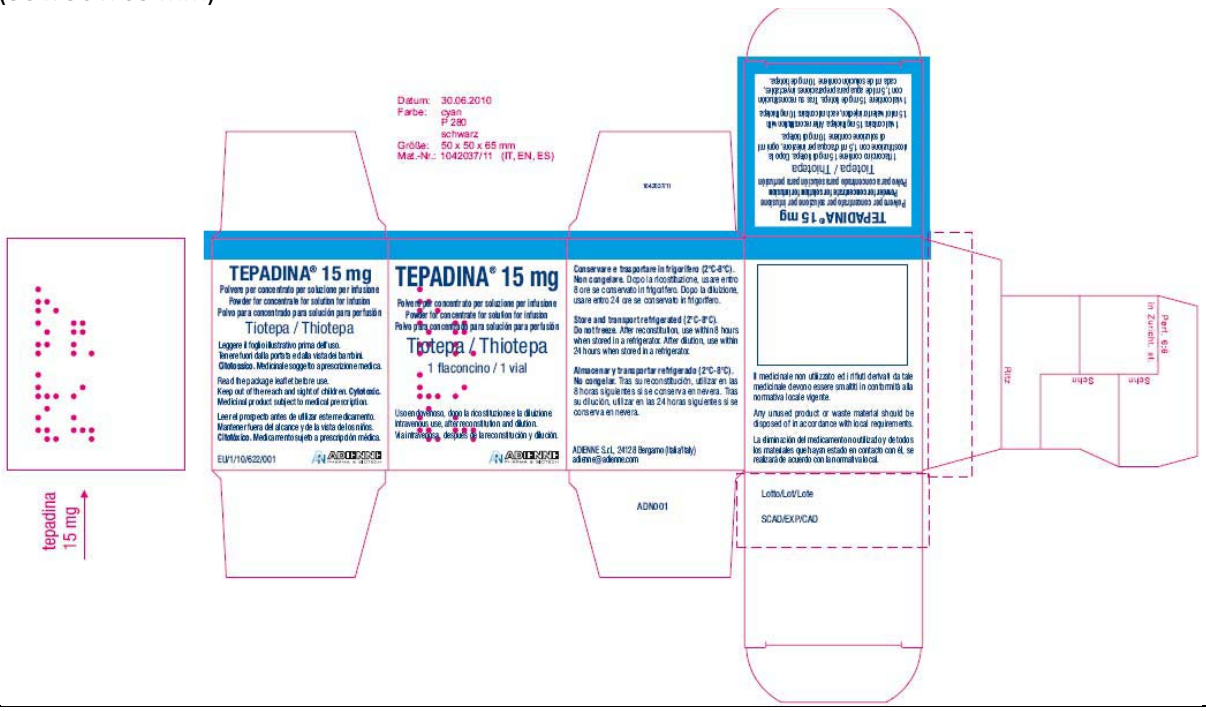
recommended dose is 0.3 to 0.8 mg/kg depending on the indication	Europe is often 10 mg/kg (range: 5 to 42 mg/kg) as part of conditioning therapy prior to hematopoietic progenitor cell transplantation using autologous or allogeneic cells for non-malignant or malignant disease. Please refer to package insert for dosing based on indication.	for thiotepa for injection, USP. The dose of TEPADINA® should be identical to the dose of thiotepa for the indication that you intend to use it for.
Product has a NDC number and a barcode on packaging.	No barcode or NDC number	No barcode is available for TEPADINA®. Other means of confirming the correct drug is being prepared and administered to the correct patient should be utilized.
Manufactured by BenVenue for Bedford Laboratories	Manufactured by IDT Australia Limited, for ADIENNE Srl	No impact to Healthcare Professionals – Both facilities have been inspected by regulatory authorities and are in compliance with local requirements.

EU TEPADINA® Powder for Solution for Infusion

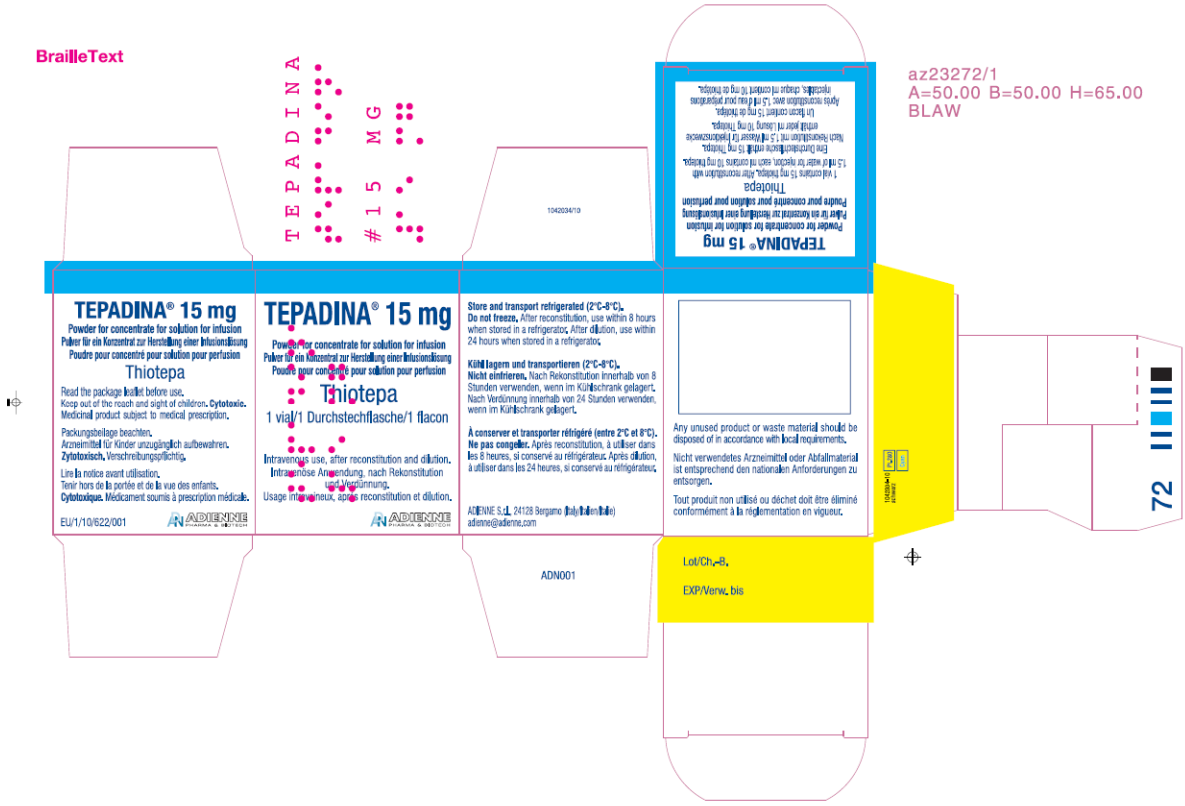
TEPADINA® 15 mg

Bottle label – EN
(60 x 16 mm)

Carton label – IT/EN/ES
(50 x 50 x 65 mm)



Carton label – EN/DE/FR
(50 x 50 x 65 mm)



Leaflet – EN

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.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

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.

2. BEFORE YOU USE TEPADINA®

Do not use TEPADINA®
- if you are allergic (hypersensitive) to thiotepa,
- if you are pregnant or think you may be pregnant (see below),
- if you are breast-feeding,
- if you are receiving yellow fever vaccination.

Take special care with TEPADINA®
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.

You will have to take regular blood tests during treatment to check your blood cell counts.

You will have to use anti-infectives to prevent and manage infections.

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

Pregnancy and breast-feeding
You must tell your doctor if you are or 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.

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 for sperm preservation before therapy is started and should not father while treated and during the year after cessation of treatment.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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 3 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: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Very common side effects
- 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 (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
- 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

Uncommon side effects
- 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)
- male and female infertility

If any of the side effects gets serious, or if you notice any side effects not mentioned in this leaflet, please tell your doctor or nurse.

5. HOW TO STORE TEPADINA®

Keep out of the reach and sight 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 8 hours when stored at 2 °C - 8 °C.

After dilution the product is stable for 24 hours when stored at 2 °C - 8 °C. From a microbiological point of view, the product should be used immediately.

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

6. FURTHER INFORMATION

What TEPADINA® contains
- The active substance is thiotepa. One vial contains 15 mg thiotepa. After recorstitution, 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
ADIENNE S.r.l.
Via Broseta 64/B
24128 Bergamo
Italy

+39 035 19964047
adienne@adienne.com

Manufacturer
RIEMSER Arzneimittel AG
7 An der Wiek
17493 Greifswald
Insel Riems
Germany

This leaflet was last approved in: 03/2010

Detailed information on this medicine is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu

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The following information is intended for medical or 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.
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 autologous 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.
LEUKEMIA
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 1050 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 1050 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.
LEUKEMIA
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 clear colourless solutions, without any particulate matter, must be used.

Further dilution in the infusion bag
The reconstituted solution is hypotonic and should be further diluted prior to administration with 500 ml sodium chloride 9 mg/ml (0.9 %) solution for injection.

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

It is recommended that the infusion solution be administered to patients using an infusion set equipped with a 0.2 µm in-line filter.

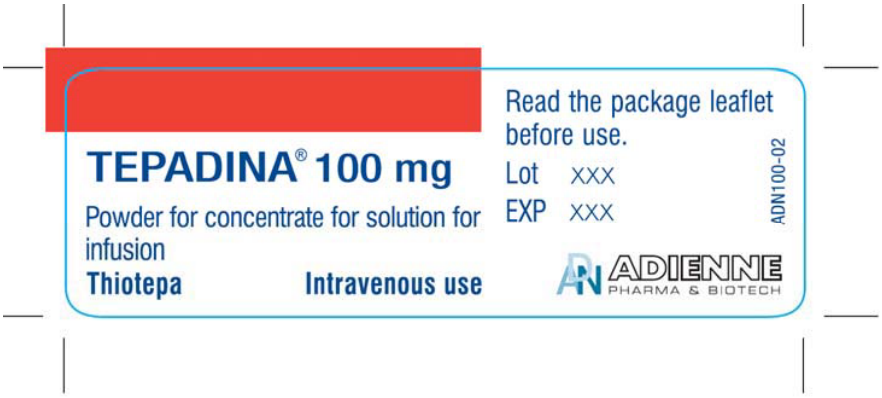
TEPADINA® should be aseptically administered as a 2-4 hours infusion under room temperature and normal light conditions.

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.

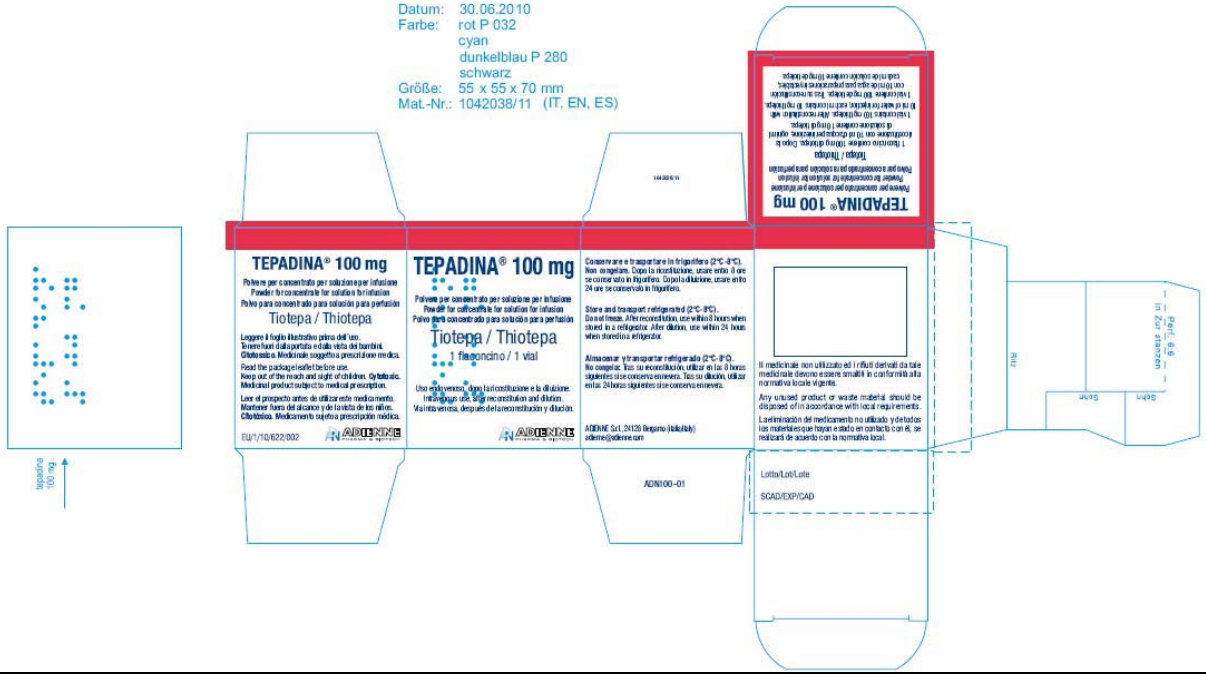
Disposal
TEPADINA® is for single use only.
Any unused product or waste material should be disposed of in accordance with local requirements.

TEPADINA® 100 mg

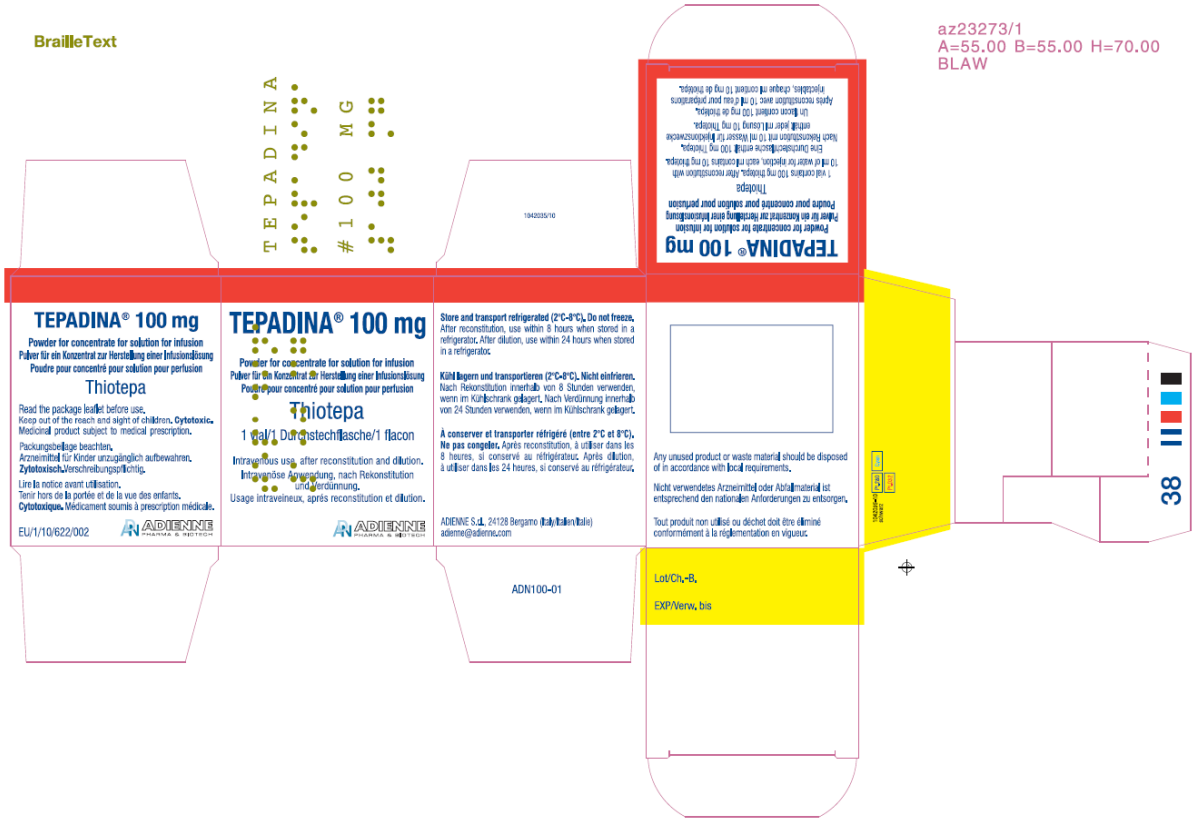
Bottle label – EN
(73 x 24 mm)



Carton label – IT/EN/ES
(55 x 55 x 70 mm)



Carton label – EN/DE/FR
(55 x 55 x 70 mm)



Leaflet – EN

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.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

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.

2. BEFORE YOU USE TEPADINA®

Do not use TEPADINA®
- if you are allergic (hypersensitive) to thiotepa,
- if you are pregnant or think you may be pregnant (see below),
- if you are breast-feeding,
- if you are receiving yellow fever vaccination.

Take special care with TEPADINA®
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.

You will have to take regular blood tests during treatment to check your blood cell counts.

You will have to use anti-infectives to prevent and manage infections.

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

Pregnancy and breast-feeding
You must tell your doctor if you are or 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.

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 for sperm preservation before therapy is started and should not father while treated and during the year after cessation of treatment.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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 3 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 those events.

Side effects of TEPADINA® may occur with certain frequencies, which are defined as follows:
- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Very common side effects
- 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 (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
- 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 (dysuria 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

Uncommon side effects
- 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)
- male and female infertility

If any of the side effects gets serious, or if you notice any side effects not mentioned in this leaflet, please tell your doctor or nurse.

5. HOW TO STORE TEPADINA®

Keep out of the reach and sight 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 8 hours when stored at 2 °C - 8 °C.

After dilution the product is stable for 24 hours when stored at 2 °C - 8 °C. From a microbiological point of view, the product should be used immediately.

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

6. FURTHER 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.

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Detailed information on this medicine is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu

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The following information is intended for medical or 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.
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 autologous 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.
LEUKEMIA
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 1050 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 1050 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.
LEUKEMIA
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 clear colourless solutions, without any particulate matter, must be used.

Further dilution in the infusion bag
The reconstituted solution is hypotonic and should be further diluted prior to administration with 500 ml sodium chloride 9 mg/ml (0.9 %) solution for injection.

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

It is recommended that the infusion solution be administered to patients using an infusion set equipped with a 0.2 µm in-line filter.

TEPADINA® should be aseptically administered as a 2-4 hours infusion under room temperature 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.