Package leaflet: Information for the user
Thiotepa Seacross 15 mg powder for concentrate for solution for infusion
Thiotepa Seacross 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 Thiotepa Seacross is and what it is used for

Thiotepa Seacross contains the active substance thiotepa, which belongs to a group of medicines called alkylating agents.
Thiotepa Seacross 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.
Thiotepa Seacross can be used in adults and children and adolescents.

2. What you need to know before you use Thiotepa Seacross

Do not use Thiotepa Seacross
- 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.

Warnings 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 Thiotepa Seacross 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.

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

Other medicines and Thiotepa Seacross
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 Thiotepa Seacross. You must not use Thiotepa Seacross during pregnancy.

Both women and men using Thiotepa Seacross must use effective contraceptive methods during treatment. Men should not father a child while treated with Thiotepa Seacross 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 Thiotepa Seacross.

Thiotepa Seacross 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 Thiotepa Seacross

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

How Thiotepa Seacross is given
Thiotepa Seacross 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, Thiotepa Seacross can cause side effects, although not everybody gets them.

The most serious side effects of Thiotepa Seacross 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 Thiotepa Seacross 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Thiotepa Seacross

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

Do not use Thiotepa Seacross 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 72 hours when stored at 2°C-8°C.

After dilution the product is stable for 36 hours when stored at 2°C-8°C and for 6 hours when stored at 25°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. Contents of the pack and other information

What Thiotepa Seacross contains
- The active substance is thiotepa.
- One vial contains 15 mg thiotepa. After reconstitution, each mL contains 10 mg thiotepa (10 mg/mL).
  One vial contains 100 mg thiotepa. After reconstitution, each mL contains 10 mg thiotepa (10 mg/mL).
- Thiotepa Seacross does not contain any other ingredients.

What Thiotepa Seacross looks like and contents of the pack
Thiotepa Seacross is a white or off white powder or cake supplied in a glass vial containing 15 mg thiotepa.
Thiotepa Seacross is a white or off white powder or cake supplied in a glass vial containing 100 mg thiotepa.

Each carton contains 1 vial.

Marketing Authorisation Holder and Manufacturer
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The following information is intended for healthcare professionals only:

PREPARATION GUIDE
Thiotepa Seacross 15 mg powder for concentrate for solution for infusion
Thiotepa Seacross 100 mg powder for concentrate for solution for infusion
Thiotepa

Read this guide prior to the preparation and administration of Thiotepa Seacross.

1. PRESENTATION
Thiotepa Seacross is supplied as 15 mg powder for concentrate for solution for infusion.
Thiotepa Seacross is supplied as 100 mg powder for concentrate for solution for infusion.
Thiotepa Seacross 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 Thiotepa Seacross 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 Thiotepa Seacross
Thiotepa Seacross 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.
Thiotepa Seacross 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/m^2/day (3.38 mg/kg/day) to 300 mg/m^2/day (8.10 mg/kg/day) as a single daily infusion, administered from 2 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 900 mg/m^2 (24.32 mg/kg), during the time of the entire conditioning treatment.

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

CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA
The recommended dose is 185 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 2 consecutive days before autologous HPCT, without exceeding the total maximum cumulative dose of 370 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

MULTIPLE MYELOMA
The recommended dose ranges from 150 mg/m^2/day (4.05 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.

Solid tumours

The recommended dose in solid tumours ranges from 120 mg/m^2/day (3.24 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) divided in one or two daily infusions, administered from 2 up to 5 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 800 mg/m^2 (21.62 mg/kg), during the time of the entire conditioning treatment.

BREAST CANCER
The recommended dose ranges from 120 mg/m^2/day (3.24 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered from 3 up to 5 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without

exceeding the total maximum cumulative dose of 800 mg/m^2 (21.62 mg/kg), during the time of the entire conditioning treatment.

CNS TUMOURS
The recommended dose ranges from 125 mg/m^2/day (3.38 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) divided in one or two daily infusions, administered from 3 up to 4 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.

OVARIAN CANCER
The recommended dose is 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered in 2 consecutive days before autologous HPCT, without exceeding the total maximum cumulative dose of 500 mg/m^2 (13.51 mg/kg), during the time of the entire conditioning treatment.

GERM CELL TUMOURS
The recommended dose ranges from 150 mg/m^2/day (4.05 mg/kg/day) to 250 mg/m^2/day (6.76 mg/kg/day) as a single daily infusion, administered for 3 consecutive days before autologous HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m^2 (20.27 mg/kg), during the time of the entire conditioning treatment.

ALLOGENEIC HPCT

Haematological diseases

The recommended dose in haematological diseases ranges from 185 mg/m^2/day (5 mg/kg/day) to 481 mg/m^2/day (13 mg/kg/day) divided in one or two daily infusions, administered from 1 up to 3 consecutive days before allogeneic HPCT depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 555 mg/m^2 (15 mg/kg), during the time of the entire conditioning treatment.

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

MULTIPLE MYELOMA
The recommended dose is 185 mg/m^2/day (5 mg/kg/day) as a single daily infusion before allogeneic HPCT, without exceeding the total maximum cumulative dose of 185 mg/m^2 (5 mg/kg), during the time of the entire conditioning treatment.

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

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

Posology in paediatric patients

AUTOLOGOUS HPCT

Solid tumours

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

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

ALLOGENEIC HPCT

Haematological diseases

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

LEUKAEMIA
The recommended dose is 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

THALASSEMIA
The recommended dose ranges from 200 mg/m^2/day (8 mg/kg/day) to 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

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

GENETIC DISEASES
The recommended dose is 125 mg/m^2/day (5 mg/kg/day) as a single daily infusion, administered for 2 consecutive days before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

SICKLE CELL ANAEMIA
The recommended dose is 250 mg/m^2/day (10 mg/kg/day) divided in two daily infusions, administered before allogeneic HPCT, without exceeding the total maximum cumulative dose of 250 mg/m^2 (10 mg/kg), during the time of the entire conditioning treatment.

Reconstitution
Thiotepa Seacross 15 mg powder for concentrate for solution for infusion 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.

Thiotepa Seacross 100 mg powder for concentrate for solution for infusion 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 (1000 mL if the dose is higher than 500 mg) or with an appropriate volume of sodium chloride 9 mg/mL (0.9%) in order to obtain a final Thiotepa Seacross concentration between 0.5 and 1 mg/mL.

Administration
Thiotepa Seacross 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.

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