PACKAGE LEAFLET

Package leaflet: Information for the user

Busulfan Tillomed 6 mg/ml concentrate for solution for infusion

Busulfan

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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Busulfan is and what it is used for

Busulfan 6 mg/ml concentrate for solution for infusion contains the active substance busulfan, which belongs to a group of medicines called alkylating agents. Busulfan destroys the original bone marrow before the transplant.

Busulfan is used in adults, new-born infants, children and adolescents as a **treatment prior to transplantation**.

In adults, Busulfan is used in combination with cyclophosphamide or fludarabine.

In new-born infants, children and adolescents, Busulfan is used in combination with cyclophosphamide or melphalan.

You will receive this medicine before receiving a transplant of either bone marrow or haematopoietic progenitor cells.

The name of your medicine is Busulfan Tillomed 6 mg/ml concentrate for solution for infusion but will be referred to as Busulfan throughout this leaflet.

2. What you need to know before you use Busulfan

Do not use Busulfan:

- if you are allergic to busulfan or any of the other ingredients of this medicine listed in section 6,
- if you are pregnant or think you may be pregnant.

Warnings and precautions

Busulfan is a potent cytotoxic medicine that results in a profound decrease of blood cells. At the recommended dose, this is the desired effect. Therefore careful monitoring will be performed. It is possible that use of Busulfan may increase the risk of suffering another malignancy in the future. You should tell your doctor:

- if you have a liver, kidney, heart or lung problem,
- if you have a history of seizures,
- if you are currently taking any other medicines.

Cases of formation of blood clots in the small blood vessels may appear after haematopoietic cell transplantation (HCT) with high-dose of your treatment in combination with other medicines.

Other medicines and Busulfan

Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. Busulfan may interact with other medicines.

In particular, tell your doctor or pharmacist if you are taking the following:
• Deferasirox (a medicine used to remove excess iron from your body).

Particular caution should be taken if you use itraconazole and metronidazole (used for certain types of infections) or ketobemidone (used to treat pain), because these may increase the side-effects.

The use of paracetamol during the 72 hours prior to or with Busulfan administration should be used with caution.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor before you receive treatment with Busulfan. Women must not be pregnant during treatment with Busulfan and up to 6 months after treatment.

Women must stop breast-feeding before starting their treatment with Busulfan.

Adequate contraceptive precautions should be used when either partner is receiving Busulfan.

It may no longer be possible for you to achieve pregnancy (infertility) after treatment with Busulfan. If you are concerned about having children, you should discuss this with your doctor before treatment. Busulfan can also produce symptoms of menopause and in pre-adolescent girls, it can prevent the onset of puberty.

Men treated with Busulfan are advised not to father child during and up to 6 months after treatment.

3. How to use Busulfan

Dose and administration:

The dose of Busulfan will be calculated according to your body weight.

<u>In adults:</u>

Busulfan in combination with cyclophosphamide:

- The recommended dose of Busulfan is 0.8 mg/kg.
- Each infusion will last 2 hours.
- Busulfan will be administered every 6 hours, during 4 consecutive days, prior to transplant.

Busulfan in combination with fludarabine:

- The recommended dose of Busulfan is 3.2 mg/kg.
- Each infusion will last 3 hours.

- Busulfan will be administered once daily, during 2 or 3 consecutive days, prior to transplant.

In new-born infants, children and adolescents (0 to 17 years):

The recommended dose of Busulfan, in combination with cyclophosphamide or melphalan, is based on your body weight, varying between 0.8 and 1.2 mg/kg.

- Each infusion will last 2 hours.
- Busulfan will be administered every 6 hours during 4 consecutive days prior to transplant.

Medicines before you receive Busulfan:

Before receiving Busulfan, you will be treated with:

- anticonvulsive medicines to prevent seizures (fits) (phenytoin or benzodiazepines) and
- antiemetic medicines to prevent you from being sick (vomiting).

4. Possible side effects

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

Serious side effects:
The most serious side effects of Busulfan therapy, or the transplant procedure, may include a 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, graft versus host disease (the graft attacks your body) and lung (pulmonary) complications. Your doctor will monitor your blood counts and liver enzymes regularly to detect and manage these events.

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

- a decrease in the number of blood circulating cells (red and white) and platelets
- infections
- insomnia, anxiety, dizziness and depression
- loss of appetite, a decrease in magnesium, calcium, potassium, phosphate, albumin in the blood, and an increase in blood sugar
- an increase in heart rate, an increase or decrease in blood pressure, vasodilation (widening of the blood vessels) and blood clots
- shortness of breath, nasal secretion (rhinitis), sore throat, cough, hiccups, nosebleeds, abnormal breathing
- nausea, inflammation of the membrane of the mouth (mucosa), vomiting, abdominal pain, diarrhoea, constipation, heartburn, discomfort in the opening of the bottom (anus), fluid in the abdomen
- enlarged liver, jaundice (yellowing of the skin or whites of the eyes), blocking of a liver vein
- rash, itching, loss of hair
- back pain, muscle pain and joint pain
- an increase in removal of a chemical waste product, creatinine, that passes through kidneys to be filtered and eliminated in urine, (creatinine elimination), discomfort when passing urine, a decrease in urine output and bloody urine

- fever, headache, weakness, chills, pain, allergic reaction, oedema (fluid build up), general pain or inflammation at the injection site, chest pain, inflammation of the membrane which lines bodily organs
- high levels of liver enzymes and weight increase
- paralysis of the gut

Common (may affect up to 1 in 10 people):

- confusion, nervous system disorders
- low blood sodium (salt) levels
- changes and abnormalities in heart rhythm, fluid retention or inflammation around the heart, a decrease in the amount of blood that the heart pumps to the circulatory system (heart output)
- an increase in breathing rate, respiratory failure, bleeding from the air-filled sacs within the lungs called alveoli (alveolar haemorrhages), asthma, collapsing of small parts of the lung, fluid around the lungs
- inflammation of the gullet (oesophagus) membrane, paralysis (loss of movement) of the gut, vomiting blood (sick)
- skin discolouration, redness of the skin, scaley skin (desquamation)
- an increase in the amount of nitrogen within the blood stream, moderate kidney insufficiency, kidney disorder

Uncommon (may affect up to 1 in 100 people):

- delirium (severe confusion), nervousness, hallucination (seeing things that are not there), agitation (anxiety or nervousness), abnormal brain function, brain haemorrhage, and seizure
- clotting of the artery in the thigh (femoral artery), increased heartbeat, a decrease in heart rate, fluid leakage from the capillaries (small blood vessels)
- decrease in blood oxygen levels
- bleeding in the stomach and/or the gut

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

- Sex glands dysfunction
- Eye disorders, including the clouding of the lens of the eye (cataract), and blurred vision (corneal thinning)
- Menopausal symptoms and female infertility
- Brain abscess, inflammation of the skin, general infection
- Liver disorders
- An increase in the enzyme called lactate dehydrogenase
- An increase of uric acid and urea in the blood
- Incomplete development of teeth
- Increased blood pressure in the blood vessels of the lungs (pulmonary hypertension)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the 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 Busulfan

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 vial label and the carton after EXP. The expiry date refers to the last day of that month.

Unopened vials:

Store in a refrigerator (2°C – 8°C).

Diluted solution:

Chemical and physical in-use stability has been demonstrated for 8 hours (including infusion time) after dilution in glucose 5% or sodium chloride 9 mg/ml (0.9%) solution for injection, when stored at 20 °C ± 5 °C, or for 6 hours after dilution in sodium chloride 9 mg/ml (0.9%) solution for injection, when stored at 2 °C-8 °C followed by 3 hours stored at 20 °C ± 5 °C (including infusion time).

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Do not freeze.

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

6. Contents of the pack and other information

What Busulfan 6 mg/ml concentrate for solution for infusion contains

- The active ingredient is busulfan. One ml of concentrate contains 6 mg busulfan (60 mg of busulfan in the vial). After dilution: one ml of solution contains approximately 0.5 mg of busulfan.
- The other ingredients are N, N-Dimethylacetamide, Macrogol 400 and citric acid anhydrous.

What Busulfan 6 mg/ml concentrate for solution for infusion looks like and contents of the pack

Busulfan consists of a concentrate for solution for infusion and is supplied in colourless glass vials, each vial containing 60 mg of busulfan.

Busulfan is available in single packs of 1 vial or multipacks comprising 8 vials. When diluted, Busulfan is a clear colourless solution.

Vials may or may not be sleeved with plastic shrink sleeve/bottom (puck). This plastic sleeving is not in contact with the drug product and is there to provide additional protection during transportation. This improves the safe handling of the medicinal product by both healthcare professionals and pharmaceutical personnel.

Marketing Authorisation Holder and Manufacturer

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The following information is intended for medical or healthcare professionals only.

PREPARATION GUIDE Busulfan 6 mg/ml concentrate for solution for infusion

Busulfan

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

1. PRESENTATION

Busulfan is supplied as a clear, colourless solution in clear glass vials (Type I). Busulfan must be diluted prior to administration.

2. RECOMMENDATION FOR SAFE HANDLING

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 should be exercised in handling and preparing the Busulfan solution:

- The use of gloves and protective clothing is recommended.
- If Busulfan or diluted Busulfan solution contacts the skin or mucosa, wash them thoroughly with water immediately.

Calculation of the quantity of Busulfan to be diluted and of the diluent

Busulfan must be diluted prior to use with either sodium chloride 9 mg/ml (0.9%) solution for injection or glucose solution for injection 5%.

The quantity of the diluent must be 10 times the volume of Busulfan, ensuring the final concentration of busulfan remains at approximately 0.5 mg/ml.

The amount of Busulfan and diluent to be administered would be calculated as follows:

For a patient with a Y kg body weight:

- Quantity of Busulfan:

$$\frac{Y\ (kg) \times D\ (mg/kg)}{6\ (mg/ml)} = A \text{ ml of Busulfan to be diluted}$$

Y: body weight of the patient in kg

D: dose of Busulfan (see SPC section 4.2)

- Quantity of diluent:

(A ml Busulfan) x (10) = B ml of diluent

To prepare the final solution for infusion, add (A) ml of Busulfan to (B) ml of diluent (sodium chloride 9 mg/ml (0.9%) solution for injection or glucose solution for injection 5%).

Preparation of the solution for infusion

Busulfan must be prepared by a healthcare professional using sterile transfer techniques.

- Using a non-polycarbonate syringe fitted with a needle:
  - The calculated volume of Busulfan must be removed from the vial.
  - The contents of the syringe must be dispensed into an intravenous bag (or syringe) which already contains the calculated amount of the selected diluent. Busulfan must always be added to the diluent, not the diluent Busulfan. Busulfan must not be put into an intravenous bag that does not contain sodium chloride 9 mg/ml (0.9%) solution for injection or glucose solution for injection 5%.
- The diluted solution must be mixed thoroughly by inverting several times.

  After dilution, 1 ml of solution for infusion contains 0.5 mg of busulfan.

  Diluted Busulfan is a clear colourless solution.

Instructions for use

Prior to and following each infusion, flush the indwelling catheter line with approximately 5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or glucose (5%) solution for injection.

The residual medicinal product must not be flushed in the administration tubing, as rapid infusion of busulfan has not been tested and is not recommended.

The entire prescribed Busulfan dose should be delivered over two or three hours depending on the conditioning regimen.

Small volumes may be administered over 2 hours using electric syringes. In that case, infusion sets with minimal priming space should be used (i.e. 0.3-0.6 ml), primed with medicinal product solution prior to beginning the actual Busulfan infusion and then flushed with sodium chloride 9 mg/ml (0.9%) solution for injection or glucose (5%) solution for injection.

Busulfan must not be infused concomitantly with another intravenous solution.

Polycarbonate syringes must not be used with Busulfan.

For single use only. Only a clear solution without particles should be used.

Storage conditions *Unopened*

vials:

Store in a refrigerator (2°C – 8°C).

Diluted solution:

Chemical and physical in-use stability has been demonstrated for 8 hours (including infusion time) after dilution in glucose 5% or sodium chloride 9 mg/ml (0.9%) solution for injection, when stored at 20 °C ± 5 °C, or for 6 hours after dilution in sodium chloride 9 mg/ml (0.9%) solution for injection, when stored at 2 °C-8 ° C followed by 3 hours stored at 20 °C ± 5 °C (including infusion time).

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

3. PROCEDURE FOR PROPER DISPOSAL

Any unused medicinal product or waste should be disposed of in accordance with local requirements for cytotoxic medicinal products.