Package leaflet: Information for the user

Busilvex 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.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Busilvex is and what it is used for

Busilvex contains the active substance busulfan, which belongs to a group of medicines called alkylating agents. Busilvex destroys the original bone marrow before the transplant.

Busilvex is used in adults, new-born infants, children and adolescents as a **treatment prior to transplantation.**
In adults Busilvex is used in combination with cyclophosphamide or fludarabine.
In new-born infants, children and adolescents, Busilvex is used in combination with cyclophosphamide or melphalan.
You will receive this preparative medicine before receiving a transplant of either bone marrow or haematopoietic progenitor cell.

2. What you need to know before you use Busilvex

Do not use Busilvex:
- if you are allergic to busulfan or any of the other ingredients of Busilvex listed in section 6,
- if you are pregnant, or think you may be pregnant.

Warnings and precautions
Busilvex is a potent cytotoxic medicine that results in 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 Busilvex 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 other medicines.

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

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

Particular caution should be taken if you use itraconazole and metronidazole (used for certain types of infections) or ketobemidone (used to treat pain) or deferasirox (a medicine used to remove excess iron from your body), because this may increase the side-effects.

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

Pregnancy, breast-feeding and fertility
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 Busilvex. Women must not be pregnant during treatment with Busilvex and up to 6 months after treatment.
Women must stop breast-feeding before starting their treatment with Busilvex.

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

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

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

3. How to use Busilvex

Dose and administration:
The dose of Busilvex will be calculated according to your body weight.

In adults:
Busilvex in combination with cyclophosphamide:
- The recommended dose of Busilvex is 0.8 mg/kg
- Each infusion will last 2 hours
- Busilvex will be administered every 6 hours during 4 consecutive days prior to transplant.

Busilvex in combination with fludarabine
- The recommended dose of Busilvex is 3.2 mg/kg
- Each infusion will last 3 hours
- Busilvex 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 Busilvex 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
- Busilvex will be administered every 6 hours during 4 consecutive days prior to transplant.

Medicines before you receive Busilvex:
Before receiving Busilvex, you will be medicated with
- anticonvulsive medicines to prevent seizures (phenytoin or benzodiazepines) and
- antiemetic medicines to prevent 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 Busilvex 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, graft versus host disease (the graft attacks your body) and 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):
Blood: decrease of blood circulating cells (red and white) and platelets. **Infections**. **Nervous system**: insomnia, anxiety, dizziness, and depression. **Nutrition:** loss of appetite, decrease in magnesium, calcium, potassium, phosphate, albumine in blood, and increase in blood sugar. **Cardiac:** increase in heart rate, increase or decrease of blood pressure, vasodilatation (a state of increased calibre of the blood vessels), and blood clots. **Respiratory:** shortness of breath, nasal secretion (rhinitis), sore throat, cough, hiccup, nosebleeds, abnormal breath sounds. **Gastro-intestinal**: nausea, inflammation of the mucosa of the mouth, vomiting, abdominal pain, diarrhoea, constipation, heart burn, anus discomfort, liquid in the abdomen. **Hepatic:** enlarged liver, jaundice**,** blocking of a liver vein. **Skin**: rash, itching, loss of hairs. **Muscle and bone**: back, muscle and joint pain. **Renal**: increase in creatinine elimination, discomfort in urination, decrease in urine output and bloody urine. **General**: fever, headache, weakness, chills, pain, allergic reaction, oedema, general pain or inflammation at injection site, chest pain, inflammation of the mucosa. **Investigations**: elevated liver enzymes and weight increased.

Common (may affect up to 1 in 10 people):
Nervous system: confusion, nervous system disorders. **Nutrition:** low blood sodium. **Cardiac:** changes and abnormalities in heart rhythm, fluid retention or inflammation around the heart, decrease heart output. **Respiratory:** increase in breath rhythm, respiratory failure, alveolar haemorrhages, asthma, collapse of small portions of the lung, fluid around the lung. **Gastro-intestinal**: inflammation of the mucosa of oesophagus, paralysis of the gut, vomiting blood. **Skin**: Skin colour disorder, redness of the skin, skin desquamation. **Renal**: increase in the amount of nitrogen components in the blood stream, moderate renal insufficiency, renal disorder.

Uncommon (may affect up to 1 in 100 people):
Nervous system: delirium, nervousness, hallucination, agitation, abnormal brain function, cerebral haemorrhage, and seizure. **Cardiac:** clotting of femoral artery, extra heart beats, decrease in heart rate, diffuse leak of fluid from the capillaries (small blood vessels). **Respiratory:** decrease in blood oxygen. **Gastro-intestinal**: bleeding in the stomach and/or the gut.

Not known (frequency cannot be estimated from the available data)
Sex glands dysfunction.
Lens disorders including clouding of the lens of the eye (cataract), and blurred vision (corneal thinning).
Menopausal symptoms and female infertility.
Brain abscess, Inflammation of the skin, generalised infection.
Liver disorders.
Increase of lactate dehydrogenase in the blood.
Increase of uric acid and urea in the blood.
Incomplete development of teeth.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

United Kingdom: Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Ireland: HPRA Pharmacovigilance, Website: www.hpra.ie.

5. How to store Busilvex

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.

Unopened vials:
Store in a refrigerator (2°C – 8°C).

Diluted solution:
Chemical and physical in-use stability after dilution in glucose 5% or sodium chloride 9 mg/ml (0.9%) solution for injection has been demonstrated for 8 hours (including infusion time) after dilution when stored at 20 °C ± 5 °C or 12 hours after dilution when stored at 2 °C-8 °C followed by 3 hours stored at 20 °C ± 5 °C (including infusion time).
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 environment.

6. Contents of the pack and other information

What Busilvex contains
- The active substance is busulfan. One ml of concentrate contains 6 mg busulfan (60 mg in the vial). After dilution: one ml of solution contains approximately 0.5 mg of busulfan.
- The other ingredients are dimethylacetamide and macrogol 400.

What Busilvex looks like and contents of the pack
Busilvex consists of a concentrate for solution for infusion and is supplied in colourless glass vials, each vial containing 60 mg of busulfan.
Busilvex is available in multipacks comprising 2 packs, each containing 4 vials.
When diluted Busilvex is a clear colourless solution.

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For any information about this medicine, please contact the Marketing Authorisation Holder

This leaflet was last revised in {02/2022}

Other sources of information

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

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The following information is intended for medical or healthcare professionals only

PREPARATION GUIDE

Busilvex 6 mg/ml concentrate for solution for infusion
Busulfan

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

1. PRESENTATION

Busilvex is supplied as a clear colourless solution in 10 ml clear glass vials (type I). Busilvex 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 Busilvex solution:
- The use of gloves and protective clothing is recommended.
- If Busilvex or diluted Busilvex solution contacts the skin or mucosa, wash them thoroughly with water immediately.

Calculation of the quantity of Busilvex to be diluted and of the diluent
Busilvex 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 Busilvex ensuring the final concentration of busulfan remains at approximately 0.5 mg/ml.

The amount of Busilvex and diluent to be administered would be calculated as follows:
for a patient with a Y kg body weight:

- Quantity of Busilvex:

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

Y: body weight of the patient in kg
D: dose of Busilvex (see SPC section 4.2)

- Quantity of diluent:

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

To prepare the final solution for infusion, add (A) ml of Busilvex 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
Busilvex must be prepared by a healthcare professional using sterile transfer techniques.

- Using a non polycarbonate syringe fitted with a needle:
  - the calculated volume of Busilvex 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. Busilvex must always be added to the diluent, not the diluent to Busilvex. Busilvex 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 Busilvex 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 Busilvex has not been tested and is not recommended.

The entire prescribed Busilvex 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 Busilvex infusion and then flushed with sodium chloride 9 mg/ml (0.9%) solution for injection or glucose (5%) solution for injection.

Busilvex must not be infused concomitantly with another intravenous solution.

Due to incompatibility, do not use infusion components containing polycarbonate with Bulsivex.

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 after dilution in glucose 5% or sodium chloride 9 mg/ml (0.9%) solution for injection has been demonstrated for 8 hours (including infusion time) after dilution when stored at 20 °C ± 5 °C or 12 hours after dilution when stored at 2 °C-8 °C followed by 3 hours stored at 20 °C ± 5 °C (including infusion time).
For a microbiological point of view, the diluted solution should be used immediately.

3. PROCEDURE FOR PROPER DISPOSAL

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