PATIENT INFORMATION LEAFLET

BUSLERA 60mg/ 10ml Vial Containing Concentrated Solution For IV Infusion

For intravenous usage only.

Sterile, Apyrogen

- ***Active ingredient:*** Each ml of concentrated solution contains 6 mg busulfan.
- ***Excipients:*** dimethyleacetamide, polyethylene glycol 400.

Before use this medicine, please read this PATIENT INFORMATION LEAFLET carefully, because it contains important information for you.

- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, consult your doctor or your pharmacist.*
- *This medicine has been prescribed for you personally; you should not pass it on to others.*
- *During use of this medicine please tell to your doctor that you use this medicine when you go to the doctor or hospital.*
- *Follow the information in the leaflet exactly. Do not use **lower** or **higher** dosages rather than recommended dosages regarding the medicine.*

In this patient information leaflet:

1. What is BUSLERA and what is used for?

BUSLERA belongs to “alkylating agents” group of medicines, contains busulfan as active ingredient and used to clear away present bone-morrow before bone-marrow transplations.

- Each box of BUSLERA 60mg/10ml concentrated solution for IV infusion contains 1 vial.
- BUSLERA concentrated solution for infusion is presented in transparent glass vial. Each vial contains 60 mg busulfan. Diluted BUSLERA is a form of clear, odorless solution.

- BUSLERA is used in adults, new-born infants, children and adolescents as a treatment prior to transplantation.
- BUSLERA is used with cyclophosphamide in adults.
- BUSLERA is used with cyclophosphamide or melphalan in adults, new-born infants, children and adolescents.
- This preparative medicine will be administered to you before receiving hemopoetic progenitor cell transplantation.

2. Precautions before using of BUSLERA

Do not use BUSLERA:

If;

- You are hyper-sensitive to Busulfan or contents of BUSLERA,
- You are pregnant or you think you may be pregnant.

USE BUSLERA CAREFULLY for following conditions:

BUSLERA is a strong cytostatic medicine that results in profound decrease of blood cells. At the recommended doses, this is a desired effect. Therefore careful monitoring will be performed. It is possible that use of BUSLERA may increase the risk of suffering another malignancy in the future.

Before use BUSLERA,

If;

- You have a liver, renal, heart or lung diseases,
- You have history of seizure in the past,
- You are currently taking another medicine.

You must be sure that your doctor knows these.

Please consult your doctor, even if these statements were applicable to you at any time in the past.

- It may no longer be possible for you to achieve a pregnancy after treatment with busulfan (infertility). If you are concerned about having children, please speak to your doctor before treatment. BUSLERA can also produce symptoms of menopause and it can prevent the onset of puberty in pre-adolescent girls.
- Men treated with BUSLERA are advised not to be father during and up to 6 months after treatment. Treatment with BUSLERA may cause irreversible infertility. Because of this,

if you want to have a baby in the future, speak to your doctor before treatment and seek advice on cryopreservation of sperm prior to treatment.

Pregnancy

Before use this medicine, consult your doctor or your pharmacist.

If you are pregnant or you think you may be pregnant, do not use BUSLERA.

If you are pregnant or think you may be pregnant or are planning to have a baby, ask your doctor before you receive treatment.

Women must not be pregnant during treatment with BUSLERA and up to 6 months after treatment.

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

Breast-feeding

Before use this medicine, consult your doctor or your pharmacist.

If you are breast-feeding ask your doctor before you receive treatment with BUSLERA. Women must stop breast-feeding before starting their treatment with BUSLERA.

Driving and using machinery

Not valid.

Usage with other medicines

BUSLERA may interact with other medicines. This is very important because using medicines at same time can increase or decrease the effects of medicines.

If you are taking following medicines, you must be careful;

- Itraconazole (an antifungal),
- Ketobemidone (used to treat pain).

Because usage of BUSLERA with these medicines at same time can increase side effects.

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

If you are taking or have recently taken any other medicines, including medicines obtained without a prescription, please tell your doctor or your pharmacist.

3. How to use BUSLERA

Instuctions for use and for frequency of dosage/administration

Your doctor will decide the dose that is the best for you and will administrate.

Dosage:

In adults:

The dose is calculated according to your body weight.

The recommended dose of BUSLERA in combination with cyclophosphamide, is 0.8 mg for each kilogram of body weight.

In new-borns, children and adolescents (0-17 years of age):

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

Administration route and method:

BUSLERA is administered as central intravenous infusion by experienced health professionals after dilution of each vial. Each infusion will last for 2 hours. BUSLERA will be administered every 6 hours during 4 consecutive days prior to transplant.

Different age groups:

Use in children: BUSLERA is used in new-borns and children.

Use in geriatrics: Dosage adjustment is not necessary for patients below age 50.

Special usage conditions:

In patients with renal impairment: Because of BUSLERA is excreted by urine at medium level, changing these patients' dosage is not recommended. Furthermore, it is recommended to be careful.

In patients with liver impairment: If you have especially heavy liver disabilities, you must be careful.

If you notice that the effects of BUSLERA are too strong or too weak, speak to your doctor or your pharmacist.

If you receive more BUSLERA than you should:

Because of this medicine is administered in hospital by experienced health professionals, this

section is not valid for you.

If you forget to take BUSLERA:

Because of this medicine is administered in hospital by experienced health professional, this section is not valid for you.

Medicines you will use before BUSLERA:

Before administration of BUSLERA, you must use following medicines:

- Anticonvulsant medicines (phenytoin or benzodiazepines) in order to prevent seizures and
- Antiemetic medicines (nausea preventers) in order to prevent vomiting.
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4. What are the possible side effects?

Like all medicines, this medicine can cause side effects on people who are sensitive to contents of BUSLERA.

These side effects are seen at following described frequencies:

- Very common : may affect 1 patient of 10 patients,
- Common :may effect less than 1 of 10 patients, but more than 1 of 100 patients,
- Non-common : may effect less than 1 of 100 patients, but more 1 of 1000 patients,
- Rare : may effect less than 1 of 1000 patients, but more 1 of 10.000 patients,
- Very-rare : may effect more than 1 of 10.000 patients,

Serious side effects:

The most serious side effects of BUSLERA treatment 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.

Very-common side effects:

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 mucose 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 creatine elimination, discomfort in urination, decrease in urine output and bloody urine. **General**: fever, headache, weakness, chills, pain, allergic reaction, oedema, general pain inflammation at injection site, chest pain, inflammation of the mucosa. **Investigations:** elevated liver enzymes and weight increased.

Common side effects:

Nervous sytem: 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 breathe 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 color disorder, redness of the skin, skin desquamation. **Renal**: increase in the amount of nitrogen components in the blood stream, moderate renal insufficiency, renal disorder.

Non-common side effects:

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 stomach and/or the gut. *If you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.*

5. How to store BUSLERA

Keep BUSLERA out of the sight and reach of children and store in the original pack.

Store unopened vials in refrigerator at 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
- 12 hours after dilution when stored at 2°C - 8°C followed by 3 hours stored at 20°C ± 5°C (including of infusion time).

Do not freeze.

Please use BUSLERA in accordance with expiry date.

Do not use BUSLERA after expiry-date stated on the outer pack.

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.

Registration holder : Biem İlaç San. ve Tic. A.Ş.
Anıttepe Mah. Turgut Reis Cad. No: 21
Tandoğan / Çankaya – Ankara

Manufacturing Site : Mustafa Nevzat Pharmaceuticals
Yenibosna/İstanbul

This patient information leaflet is approved on 01/05/2014

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THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONAL WHO WILL ADMINISTER THIS MEDICINE.

PREPARATION GUIDE

BUSLERA 60mg/ 10ml Vial Containing Concentrated Solution For IV Infusion

Busulfan

Please read this guide prior to the preparation and administration of BUSLERA.

1. PHARMACEUTICAL FORM

BUSLERA is supplied as a clear colourless solution in 10 ml clear glass vials (type 1), BUSLERA 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 BUSLERA solution:

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

Calculation of the quantity of BUSLERA to be diluted and of the diluent:

BUSLERA 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 diluent must be 10 times the volume of BUSLERA and ensuring final concentration of busulfan remains at approximately 0.5 mg/ml. For example;

The amount of BUSLERA and diluent to be administrated would be calculated as follows:

For a patient with a Y kg body weight:

- Quantity of BUSLERA

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

6 (mg/ml)

Y: body weight of the patient in kg.
D: dose of BUSLERA (refer to SMPC Section 4.2.)

- Quantity of diluent:

(A ml BUSLERA) x (10) = B ml diluent
To prepare the final solution for infusion, add (A) ml of BUSLERA 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:

- BUSLERA must be prepared by experienced health professional by sterile transfer techniques. Using a non-polycarbonate syringe fitted with a needle:
- the calculated volume of BUSLERA 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. BUSLERA must always be added to the diluent, not the diluent to BUSLERA. BUSLERA **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 infusion solution contains 0.5 mg of busulfan. Diluted BUSLERA is clear, colorless 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 BUSLERA has not been tested and is not recommended.
Prescribed dosage of BUSLERA should be administered completely within 2 hours.
Small volumes may be administered by 2 hours using electric syringes. In this 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 BUSLERA infusion and then flushed with

sodium chloride 9 mg/ml (0.9%) solutişon for injection or glucose (5%) solution for injection.

BUSLERA must not be administered with other intravenous solutions at the same time.
Polycarbonate syringes must not be used with BUSLERA.
For single use only. Only a clear solution without particles should be used.

3. PROCEDURE FOR PROPER DISPOSAL

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