BUSULFAN Injection

Please see full prescribing information, including boxed warning, for BUSULFAN Injection, enclosed.
BUSULFAN Injection

INNOVATOR PRODUCT NAME: BUSULFEX®
(Busulfex is a registered trademark of Otsuka Pharmaceutical Company, Ltd.)

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Description</th>
<th>Strength</th>
<th>Fill Volume</th>
<th>Concentration</th>
<th>Closure</th>
<th>Unit of Sale</th>
<th>Bar Coded</th>
</tr>
</thead>
<tbody>
<tr>
<td>25021-241-10</td>
<td>Glass Vial</td>
<td>60 mg</td>
<td>10 mL</td>
<td>6 mg per mL</td>
<td>13 mm</td>
<td>8 Vials</td>
<td>✓</td>
</tr>
</tbody>
</table>

This SAGENT product meets stringent FDA requirements and is AP rated, preservative-free and not made with natural rubber latex.

To order, or for more information about how to Discover Injectables Excellence® with SAGENT, contact your sales representative, call 1-866-625-1618 or visit www.SagentPharma.com.

CONTRAINDICATIONS
Busulfan Injection is contraindicated in patients who have a history of hypersensitivity to any of its components.

WARNINGS AND PRECAUTIONS
• Myelosuppression: The most frequent serious consequence of treatment with Busulfan Injection at the recommended dose and schedule is prolonged myelosuppression, occurring in all patients (100%). Use antibiotic therapy and platelet and red blood cell support when medically indicated.
• Seizures: Seizures have been reported in patients receiving high-dose oral busulfan at doses producing plasma drug levels similar to those achieved following the recommended dosage of Busulfan Injection. Initiate phenytoin therapy or any other alternative anti-convulsant prophylactic therapy (e.g., benzodiazepines, valproic acid or levetiracetam) prior to Busulfan Injection treatment. Use caution when administering the recommended dose of Busulfan Injection to patients with a history of a seizure disorder or head trauma or who are receiving other potentially epileptogenic drugs.
• Hepato Veno-Occlusive Disease (HVOD): High busulfan area under the plasma concentration versus time curve (AUC) values (greater than 1,500 µM•min) may be associated with an increased risk of developing HVOD. Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or a prior progenitor cell transplant may be at an increased risk of developing HVOD. Monitor serum transaminases, alkaline phosphatase, and bilirubin daily through bone marrow transplant (BMT) Day +28 to detect hepatotoxicity, which may herald the onset of HVOD.
• Embryo-fetal Toxicity: Busulfan Injection can cause fetal harm when administered to a pregnant woman based on animal data. Advise pregnant women of the potential risk to a fetus, and advise females and males of reproductive potential to use effective contraception during and after treatment with Busulfan Injection.
• Cardiac Tamponade: Cardiac tamponade has been reported in pediatric patients with thalassemia who received high doses of oral busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation. Abdominal pain and vomiting preceded the tamponade in most patients. Monitor for signs and symptoms, promptly evaluate and treat if cardiac tamponade is suspected.
• Bronchopulmonary Dysplasia: Bronchopulmonary dysplasia with pulmonary fibrosis is a rare but serious complication following chronic busulfan therapy. The average onset of symptoms is 4 years after therapy (range 4 months to 10 years).
• Busulfan may cause cellular dysplasia in many organs. This cytologic dysplasia may be severe enough to cause difficulty in the interpretation of exfoliative cytologic examinations of the lungs, bladder, breast and the uterine cervix.
• Lactation: Discontinue breastfeeding during treatment with Busulfan Injection.

ADVERSE REACTIONS
The most common adverse reactions (incidence greater than 60%) were:
• Myelosuppression, nausea, stomatitis, vomiting, anorexia, diarrhea, insomnia, fever, hypomagnesemia, abdominal pain, anxiety, headache, hyperglycemia and hypokalemia.

OVERDOSAGE
There is no known antidote to Busulfan Injection other than hematopoietic progenitor cell transplantation. In the absence of hematopoietic progenitor cell transplantation, the recommended dosage for Busulfan Injection would constitute an overdose of busulfan. The principal toxic effect is profound bone marrow hypoplasia/aplasia and pancytopenia, but the central nervous system, liver, lungs, and gastrointestinal tract may be affected. Monitor hematologic status closely and institute vigorous supportive measures as medically indicated. Dialysis should be considered in the case of an overdose.

To report SUSPECTED ADVERSE REACTIONS, contact Sagent Pharmaceuticals, Inc. at 1-866-625-1618 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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**INDICATIONS AND USAGE**

Busulfan Injection is indicated in adults and pediatric patients for use in combination with cyclophosphamide as a conditioning regimen to prepare patients for allogeneic hematopoietic progenitor cell transplantation. It is indicated in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation. Six of the eight children who received busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation. Six of the eight children who received busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation. Six of the eight children who received busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation. Six of the eight children who received busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation.
Simulations based on a pediatric population pharmacokinetic model indicate that approximately 60% of pediatric patients will achieve or platelet count less than 20,000/mm³. Seventy-nine percent (19/24) of patients experienced lymphopenia (absolute lymphocyte count <0.7×10⁹/L), mostly during the first 7 days after the start of treatment. Busulfan can cause neutropenia, which may be severe enough to require hospitalization or blood transfusion. The median time to neutropenia was 4 days. All evaluable patients (60/60) engrafted at a median of 5 days after the start of treatment.

Itraconazole decreases busulfan clearance by 15% or more, possibly due to the induction of glutathione S-transferase. Since the coadministration of busulfan and itraconazole may increase the risk of myelosuppression, it is recommended to adjust the dose of busulfan in patients receiving concomitant itraconazole.

Because busulfan is eliminated from the body via conjugation with glutathione, use of acetaminophen prior to (less than 72 hours) or during busulfan administration (on the same day) may not be advisable to prevent conjugation and thereby reduce the clearance of busulfan. Phenytoin increases the clearance of busulfan by 15% or more, possibly due to the induction of glutathione-S-transferase. Since the concomitant use of busulfan and phenytoin may increase the risk of myelosuppression, it is recommended to adjust the dose of busulfan in patients receiving concomitant phenytoin.

Patients received Busulfan Injection doses every six hours as a two-hour infusion over four days for a total of 16 doses, followed by a single dose of 0.5 mg/kg. The target area under the plasma concentration-time curve (AUC) of 900 to 1,350 µM•min with an initial dose of 0.8 mg per kg was confirmed in a Phase I/II study in healthy female volunteers. The AUC can be calculated as:

\[ \text{AUC} (\mu M\cdot min) = C_{\text{last}} \times t_{\text{last}} + C_{\text{inf}} \times t_{\text{inf}} \]

where \( C_{\text{last}} \) is the last measurable circulatory concentration, \( t_{\text{last}} \) is the time of that measurement, \( C_{\text{inf}} \) is the concentration at the end of infusion, and \( t_{\text{inf}} \) is the duration of infusion.

Busulfan Injection has not been administered to patients with hepatic insufficiency. Following administration of a greater than normal dose of oral busulfan (2.1 mg per kg; total dose of 23.3 mg per kg) occurred in a 2-year-old child with acute lymphoblastic leukemia. Two thirds of the dose was recovered unchanged in the urine, and the child experienced febrile neutropenia. The median duration of neutropenia was 11 days, and bone marrow aspiration performed on day 14 and at 1 and 2 months showed normal granulopoiesis.

In patients treated in the Busulfan Injection clinical trial who were age 60 years or older and who had renal dysfunction (creatinine clearance <60 ml/min), the AUC of busulfan was not significantly different compared to younger patients. However, there was a significant increase in the clearance of busulfan in patients with creatinine clearance >60 ml/min compared to those with creatinine clearance ≤60 ml/min. Therefore, it is recommended to adjust the dose of busulfan in patients with renal impairment to achieve the target AUC.

Based on the results of the current study, it is recommended to administer busulfan as a two-hour intravenous infusion over four days for a total of 16 doses. The AUC can be calculated as:

\[ \text{AUC} (\mu M\cdot min) = C_{\text{last}} \times t_{\text{last}} + C_{\text{inf}} \times t_{\text{inf}} \]

where \( C_{\text{last}} \) is the last measurable circulatory concentration, \( t_{\text{last}} \) is the time of that measurement, \( C_{\text{inf}} \) is the concentration at the end of infusion, and \( t_{\text{inf}} \) is the duration of infusion.

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Busulfan Injection has not been studied in patients with renal impairment.