AUSTRALIAN PRODUCT INFORMATION
BUSULFAN APOTEX (BUSULFAN) INJECTION

1 NAME OF THE MEDICINE

Busulfan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL vial of busulfan injection contains 60 mg (6 mg/mL) of busulfan.

For the full list of excipients see section **6.1 List of excipients.**

3 PHARMACEUTICAL FORM

Busulfan APOTEX Injection is supplied as a sterile solution in 10 mL single-use clear glass vials.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Busulfan injection is indicated for use in combination with cyclophosphamide, melphalan or fludarabine in conditioning prior to haematopoietic stem cell transplantation.

4.2 DOSE AND METHOD OF ADMINISTRATION

IV busulfan administration should be supervised by a physician experienced in conditioning treatment prior to HSCT.

It is intended for dilution with 0.9% sodium chloride solution for injection or 5% glucose solution for injection.

Dosage

In adult patients eligible for myeloablative HSCT the proposed dosage recommendation is 3.2 mg/kg body weight/day for four days, giving a total dose of 12.8 mg/kg.

In new-born infants, children and adolescents (0 to 17 years) eligible for myeloablative HSCT it is recommended that dosing is based on a patient's body weight as follows:

Actual body weight (kg)	IV busulfan dose (mg/kg/day)	Total IV busulfan dose (mg/kg)
< 9	4.0	16.0
9 to < 16	4.8	19.2
16 to 23	4.4	17.6
> 23 to 34	3.8	15.2
> 34	3.2	12.8

The IV busulfan daily dose may be given as a single three-hour infusion once daily (od) over 4 consecutive days for a total of 4 doses. Alternatively the daily dose may be divided and given as a two to three hour infusion every 12 hours (bd) for four days, giving a total of 8 doses, or every 6 hours (qid) for four days, giving a total of 16 doses.

In a non-myeloablative conditioning regimen (also known as a reduced-intensity conditioning regimen) a lower IV busulfan daily dose may be administered and/or the dose may be administered for less than four days, resulting in a lower total dose. In clinical trials IV busulfan total doses ranging from 0.8 mg/kg to 6.4 mg/kg in reduced intensity conditioning regimens have been typically used, administered in divided doses over two to four days.

When used in combination with cyclophosphamide or melphalan, dosing of these chemotherapeutic agents should not be initiated for at least 24 hours following the final IV busulfan dose.

Administration

Busulfan injection must be diluted prior to administration. A final concentration of approximately 0.5 mg/mL busulfan should be achieved. Busulfan injection should be administered by intravenous infusion via central venous catheter.

Busulfan injection should not be given by rapid intravenous, *bolus* or peripheral injection.

All patients should be pre-medicated with anticonvulsant medication to prevent seizures reported with the use of high dose busulfan. It is recommended to administer anticonvulsants 12 h prior to Busulfan injection to 24 h after the last dose of Busulfan injection. In adults all studied patients received phenytoin. There is no experience with other anticonvulsant agents such as benzodiazepines. In paediatric studies patients received either phenytoin or benzodiazepines.

Antiemetics should be administered prior to the first dose of Busulfan injection and continued on a fixed schedule according to local practice through its administration.

Therapeutic Drug Monitoring

Therapeutic drug monitoring and dose adjustment following the first dose of Busulfan injection is recommended. The formula for adjustment of subsequent doses to achieve the desired target exposure (AUC), is provided below.

$$\text{Adjusted dose (mg)} = \frac{\text{Actual Dose (mg)} \times \text{Target AUC (µMol-minute)}}{\text{Actual AUC (µMol-minute)}}$$

For example, if a patient received a dose of 50 mg busulfan and if the corresponding AUC measured was 800 µMol-minute, for a target AUC of 1125 µMol-minute, the target mg dose would be:

$$\text{Mg dose} = \frac{50 \text{ mg} \times 1125 \text{ µMol-minute}}{800 \text{ µMol-minute}} = 70 \text{ mg}$$

A minimum of four blood samples should be taken to ensure accurate AUC determinations with the first sample taken at the completion of the infusion (time 0), and subsequent samples 1, 2 and 4 hours after the infusion is completed.

To avoid contamination with infusing drug blood samples for busulfan estimation should be taken either from the other lumen of a double lumen central venous line (after adequate flushing) or from a peripheral IV line.

Obese Patients

Adults

For obese patients, dosing based on adjusted ideal body weight (AIBW) should be considered.

Ideal body weight (IBW) is calculated as follows:

IBW men (kg) = 50 + 0.91 x (height in cm-152);

IBW women (kg) = 45 + 0.91 x (height in cm-152).

Adjusted ideal body weight (AIBW) is calculated as follows:

AIBW = IBW+0.25x (actual body weight - IBW).

New-born infants, children and adolescents

There is no experience in obese children and adolescents with body mass index Weight $(kg)/(m)^2 > 30\ kg/m^2$.

Instruction for handling and disposal

Procedures for proper handling and disposal of anticancer drugs 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 injection or diluted Busulfan injection solution contacts the skin or mucosa, wash them thoroughly with water immediately.

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

Busulfan injection must be diluted prior to use with either sodium chloride (0.9%) solution for injection or glucose (5%) solution for injection. The quantity of the diluent must be 10 times the volume of Busulfan injection ensuring the final concentration of busulfan remains at approximately 0.5 mg/mL.

For example, the amount of Busulfan injection and diluent to be administered would be calculated as follows for a patient with a Y kg body weight receiving Z mg/kg busulfan:

- Quantity of Busulfan injection:

$$\frac{Y\ (kg) \times Z\ (mg/kg)}{6\ (mg/mL)} = A\ mL\ of\ Busulfan\ injection\ to\ be\ diluted$$

Y: body weight of the patient in kg

Z: dose on a mg/kg basis

- Quantity of diluent:

  (A mL busulfan) x (10) = B mL of diluent

To prepare the final solution for infusion, add (A) mL of Busulfan injection 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

Due to incompatibility, do not use any infusion components containing polycarbonate with Busulfan Injection.

- Using a non polycarbonate syringe fitted with a needle:
  - Remove the calculated volume of Busulfan injection from the vial.
  - Dispense the contents of the syringe into an intravenous bag (or syringe) which already contains the calculated amount of the selected diluent. Always add Busulfan injection to the diluent, not the diluent to Busulfan injection. Do not put Busulfan injection into an intravenous bag that does not contain sodium chloride (0.9%) solution for injection or glucose (5%) solution for injection.
- Mix thoroughly by inverting several times.

After dilution, 1 mL of solution for infusion contains 0.5 mg of busulfan. Diluted Busulfan injection 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 (0.9%) solution for injection or glucose (5%) solution for injection.

Do not flush residual drug in the administration tubing as rapid infusion of Busulfan injection has not been tested and is not recommended.

The entire prescribed Busulfan injection dose should be delivered over two or three hours (depending on frequency of dose).

Small volumes may be administered over 2 or 3 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 drug solution prior to beginning the actual Busulfan injection infusion and then flushed with sodium chloride (0.9%) solution for injection or glucose (5%) solution for injection.

A nylon or polyester filter should be used if Busulfan injection is administered via an in-line filter or a filter fitted with an infusion set.

Do not infuse concomitantly with another intravenous solution.

Busulfan injection contains no antimicrobial agent. Product is for single use in one patient only. Only a clear solution without any particles should be used. Opened vials should be used immediately to assure sterility. Discard any residue.

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

Incompatibilities

In the absence of compatibility studies, Busulfan injection must not be mixed with other medicinal products except those mentioned in this section.

4.3 CONTRAINDICATIONS

Busulfan injection is contraindicated in patients with hypersensitivity to the active substance busulfan or to any of the excipients.

Busulfan injection is contraindicated in women who are pregnant and/or lactating.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The consequence of treatment with IV busulfan at the recommended dose and schedule is profound myelosuppression, occurring in all patients. Severe granulocytopenia, thrombocytopenia, anaemia, or any combination thereof may develop. Frequent complete blood counts, including differential white blood cell counts, and platelet counts should be monitored during the treatment and until recovery is achieved. To detect hepatotoxicity, which may herald the onset of hepatic veno-occlusive disease, serum transaminases, alkaline phosphatase and bilirubin should be evaluated daily until transplant day 28. Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) should be considered for the prevention and management of infections during the neutropenic period. Platelet and red blood cell support, as well as the use of growth factors such as G-CSF, should be employed as medically indicated. Documentation on Precautions with IV busulfan use is derived from two uncontrolled clinical trials in adults (trials OMC-BUS-3 and 4) and one uncontrolled clinical trial in children (trial F60002 IN 1 01 G0).

Myelosuppression

In adults, absolute neutrophil counts < 0.5 x 10^9/L at a median of 4 days post transplant occurred in 100% of patients and recovered at median day 10 and 13 days following autologous and allogeneic transplant respectively (median neutropenic period of 6 and 9 days respectively). Thrombocytopenia (< 25 x 10^9/L or requiring platelet transfusion) occurred at a median of 5-6 days in 98% of patients. Anaemia (haemoglobin < 80 g/L) occurred in 69% of patients.

In children, absolute neutrophil counts < 0.5 x 10^9/L at a median of 3 days post transplant occurred in 100% of patients and lasted 5 and 18.5 days in autologous and allogeneic transplant respectively. In children, thrombocytopenia (< 25 x 10^9/L or requiring platelet transfusion) occurred in 100% of patients. Anaemia (haemoglobin < 80 g/L) occurred in 100% of patients.

Infection

In adults, 39% of patients (40/103) experienced one or more episodes of infection, of which 83% (33/40) were rated as mild or moderate. Pneumonia was fatal in 1% (1/103) and life-threatening in 3% of patients. Other infections were considered severe in 3% of patients. Fever was reported in 87% of patients and graded as mild/moderate in 84% and severe in 3%. 47% of patients experienced chills which were mild/moderate in 46% and severe in 1%.

In children, infections (documented and non documented febrile neutropenia) were experienced in 89% of patients (49/55). Mild/moderate fever was reported in 76% of patients.

Fanconi Anaemia

The Fanconi anaemia cells have hypersensitivity to cross-linking agents. There is limited clinical experience of the use of busulfan as component of conditioning regimen prior to HSCT

in children with Fanconi anaemia. Therefore IV busulfan should be used with caution in this type of patients.

Graft versus Host Disease

In adults, the incidence of acute graft versus host disease (a-GVHD) data was collected in OMC-BUS-4 study (allogeneic) (n = 61). A total of 11 patients (18%) experienced a- GVHD. The incidence of a-GVHD grades I-II was 13% (8/61), while the incidence of grade III-IV was 5% (3/61). Acute GVHD was rated as serious in 3 patients. Chronic GVHD (c-GVHD) was reported if serious or the cause of death, and was reported as the cause of death in 3 patients.

In children, the incidence of acute graft versus host disease (a-GVHD) data was collected in allogeneic patients (n = 28). A total of 14 patients (50%) experienced a-GVHD. The incidence of a-GVHD grades I-II was 46.4% (13/28), while the incidence of grade III-IV was 3.6% (1/28). Chronic GVHD was reported only if it is the cause of death: one patient died 13 months post-transplant.

Liver Toxicity

In adults, 15% of serious adverse events involved liver toxicity. HVOD is a recognized potential complication of conditioning therapy post-transplant. Six of 103 patients (6%) experienced HVOD. HVOD occurred in: 8.2% (5/61) allogeneic patients (fatal in 2 patients) and 2.5% (1/42) of autologous patients. Elevated bilirubin (n = 3) and elevated AST (n = 1) were also observed. Two of the above four patients with serious serum hepatotoxicity were among patients with diagnosed HVOD. Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or prior stem cell transplant may be at an increased risk (see section **4.8 Adverse effects (Undesirable effects)**).

In children grade 3 elevated transaminases were reported in 24% of patients. HVOD was reported in 15% (4/27) and 7% (2/28) of the autologous and allogenic transplant respectively. HVOD observed were neither fatal nor severe and resolved in all cases.

Repeated doses of the solvent, DMA, produced signs of liver toxicity, the first being increases in serum clinical enzymes followed by histopathological changes in the hepatocytes. Higher doses can produce hepatic necrosis and liver damage can be seen following single high exposures.

Cardiac Toxicity

Cardiac tamponade has been reported in children with thalassemia (8/400 or 2% in one series) who received high doses of oral busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation. Six of the eight children died and two were saved by rapid pericardiocentesis. Abdominal pain and vomiting preceded the tamponade in most patients. No patients treated in the IV busulfan clinical trials experienced cardiac tamponade or other specific cardiac toxicities related to busulfan. However cardiac function should be monitored regularly in patients receiving IV busulfan (see section **4.8 Adverse effects (Undesirable effects)**).

Pulmonary Toxicity

Occurrence of acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis was reported in section **4.8 Adverse effects (Undesirable effects)** studies in one patient who died, although, no clear etiology was identified. In addition, busulfan might induce pulmonary toxicity that may be additive to the effects produced by other cytotoxic agents. Therefore, attention should be paid to this pulmonary issue in patients with prior history of mediastinal or pulmonary radiation (see section **4.8 Adverse effects (Undesirable effects)**).

Seizures

Seizures have been reported with high dose busulfan treatment. Special caution should be exercised when administering the recommended dose of IV busulfan to patients with a history of seizures. Patients should receive adequate anticonvulsant prophylaxis. In adults all data with IV busulfan have been obtained using phenytoin. There are no data available on the use of other anticonvulsant agents such as benzodiazepines, therefore the effect of other agents on busulfan pharmacokinetics is not known. In paediatric patients data have been obtained using benzodiazepines and phenytoin.

High-Risk Patients

HSCT is generally not recommended in high-risk patients because of poorer outcomes. High-risk patients include those of age > 50 years and those with prior myeloablative transplants, organ dysfunction, poor performance status or extensive prior chemotherapy. Careful consideration of the risks and benefits of IV busulfan is necessary in these patients. Non-myeloablative conditioning regimens, with a reduced dose or reduced duration of IV busulfan, have demonstrated a low rate of regimen related toxicity in high-risk patients but can lead to an increase in the incidence of disease relapse (see section **5.1 Pharmacodynamic properties - Clinical trials**).

Use in hepatic impairment

IV busulfan as well as busulfan has not been studied in patients with hepatic impairment. Since busulfan is mainly metabolized through the liver, caution should be observed when IV busulfan is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. It is recommended when treating these patients that serum transaminase, alkaline phosphatase, and bilirubin should be monitored regularly 28 days following transplant for early detection of hepatotoxicity.

Use in renal impairment

Studies in renally impaired patients have not been conducted, however, as busulfan is moderately excreted in the urine, dose modification is not recommended in these patients. Caution is recommended. In a Phase I study conducted in patients with metastatic renal carcinoma, all of whom had only one functioning kidney, a conditioning regimen of once- daily IV busulfan in combination with fludarabine gave a high incidence of regimen related toxicity.

Use in the elderly

Patients older than 50 years of age have been successfully treated with IV busulfan. Refer to the section **5.1 Pharmacodynamic properties - Clinical trials** for information on the use of IV busulfan in elderly patients in non-myeloablative conditioning regimens. Only limited information is available for the safe use of IV busulfan in patients older than 60 years.

Paediatric use

IV busulfan may be used in children (0-17 years).

Data on the use of IV busulfan in children are limited (see section **5.1 Pharmacodynamic properties - Clinical trials**) and there have been no studies in juvenile animals. The level of DMA in IV busulfan is higher than in other products and this may represent a particular risk to children. Pulmonary thrombosis and vasculitis were seen with DMA alone in clinical trials in adults and hepatoxicity and neurotoxic effects have been reported with DMA in the literature.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No specific clinical trial was carried out to assess drug-drug interaction between IV busulfan and antifungal agents. From published studies in adults, administration of itraconazole to patients receiving high-dose busulfan may result in reduced busulfan clearance. Patients should be monitored for signs of busulfan toxicity when itraconazole is used as an antifungal prophylaxis with IV busulfan.

No interaction was observed when busulfan was combined with fluconazole (antifungal agent) or 5-HT_3 antiemetics such as ondansetron or granisetron.

Metronidazole increases plasma levels of busulfan, which may lead to treatment-related toxicities.

Published studies in adults have described that ketobemidone (analgesic) might be associated with high levels of plasma busulfan; therefore special care is recommended when combining these two drugs.

It has been reported that when using the BuCy2 regimen in adults the time interval between the last oral busulfan administration and the first cyclophosphamide administration may influence the development of toxicities. A reduced incidence of Hepatic Veno-Occlusive Disease (HVOD) and other regimen related toxicity have been observed in patients when the lag time between the last dose of oral busulfan and the first dose of cyclophosphamide is > 24 hours.

It has also been reported that when using the BuMel regimen in paediatric patients the administration of melphalan less than 24 hours after the last oral busulfan administration may influence the development of toxicities.

Paracetamol is described to decrease glutathione levels in blood and tissues, and may therefore decrease busulfan clearance when used in combination. Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with IV busulfan due to a possible decrease in the metabolism of busulfan.

Phenytoin or benzodiazepines were administered for seizure prophylaxis in all patients in the clinical trials conducted with IV busulfan. The concomitant systemic administration of phenytoin to patients receiving high-dose busulfan has been reported to increase busulfan clearance, due to induction of glutathion-S-transferase. However no evidence of this effect has been seen in IV data.

No interaction has been reported when benzodiazepines such as diazepam, clonazepam or lorazepam have been used to prevent seizures with high-dose busulfan. Periodic monitoring

of renal function should be considered during therapy with IV busulfan (see section **4.8 Adverse effects (Undesirable effects)**).

Iron chelating agents

Decreased clearance of busulfan has been observed with deferasirox. The mechanism of this interaction is not fully elucidated. Iron chelating agents should be discontinued well in advance of administration of busulfan to avoid increased exposure to busulfan.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Busulfan can impair fertility. Impotence, sterility, azoospermia, and testicular atrophy have been reported in male patients. Therefore, men treated with IV busulfan are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with IV busulfan. Ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in pre-menopausal patients. Busulfan treatment in a pre-adolescent girl prevented the onset of puberty due to ovarian failure. Busulfan may cause temporary or permanent infertility in females.

Busulfan disrupted spermatogenesis in rats, guinea-pigs, rabbits and monkeys, depleted oocytes and impaired fertility in female mice, and induced sterility in male rats and male hamsters. The solvent dimethylacetamide (DMA) was found to impair fertility in studies with male and female rodents.

Use in pregnancy

Category D

IV busulfan is contraindicated during pregnancy. Busulfan and DMA reduced fetal weight and caused embryofetal lethality and malformations in various animal species in pre- clinical studies. For busulfan, terata were observed in the musculoskeletal system of mice, rats and rabbits, while DMA-induced malformations occurred in the heart, major vessels and oral cavity in the rat. Administration of busulfan to pregnant rats caused sterility in male and female offspring due to the destruction of germinal cells in the testes and ovaries.

There are no adequate and well-controlled studies of either busulfan or DMA in pregnant women. A few cases of congenital abnormalities have been reported with low-dose oral busulfan, not necessarily attributable to the drug, and third trimester exposure may be associated with impaired intrauterine growth.

Women of childbearing potential must use effective contraception during and up to 6 months after treatment.

Use in lactation

Patients who are taking IV busulfan must be advised not to breast-feed. It is not known whether busulfan and DMA are excreted in human milk. Because of the potential for severe adverse effects, including tumourigenicity, breast-feeding should be discontinued at the start of therapy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No relevant effects have been noted.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse event information is derived from two trials in adults in 103 patients (OMC-BUS 3 and 4) and one trial in children in 55 patients (F60002 IN 1 01) in which IV busulfan was used in a four times daily regimen for 4 days in combination with cyclophosphamide or melphalan. Adverse reactions reported as more than an isolated case are listed in Table 1. See section **4.4 Special warnings and precautions for use** for more information on serious adverse reactions. Serious toxicities involving the haematological, hepatic and respiratory systems were considered as expected consequences of the conditioning regimen and transplant process. These include infection and graft-versus-host disease which were the major causes of morbidity and mortality. The safety profile for IV busulfan in once daily and twice daily regimens and in combination with fludarabine appears similar to four times daily in combination with cyclophosphamide or melphalan; however the data are very limited and in small numbers of patients.

Table 1. Adverse Reactions Reported both in Adults and Children (Very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100))

System Organ Class	Very Common	Common	Uncommon
Blood and lymphatic system disorders	Leucopenia Neutropenia Thrombocytopenia Anaemia Pancytopenia Febrile neutropenia		
Immune system disorders	Acute graft-versus-host disease	Chronic graft-versus-host disease	
Infections and infestations	Infection Fever Chills	Pneumonia	
Nervous system disorders	Insomnia Dizziness Depression	Confusion	Delerium Nervousness Hallucination Agitation Encephalopathy Cerebral haemorrhage Seizure
Metabolism and nutrition disorders	Anorexia Hyperglycaemia Hypomagnesaemia Hypokalaemia Hypocalcaemia Hypophosphataemia Oedema	Hyponatraemia	
Psychiatric disorders	Anxiety		
Cardiac disorders	Tachycardia Hypertension Hypotension Vasodilatation Thrombosis	Arrhythmia Atrial fibrillation Cardiomegaly Pericardial effusion Pericarditis Decrease ejection fraction	Femoral artery thrombosis Ventricular extrasystoles Bradycardia Capillary leak syndrome
Respiratory thoracic and mediastinal disorders	Dyspnoea Rhinitis Pharyngitis Cough Hiccup Epistaxis Abnormal breath sounds	Hyperventilation Respiratory failure Alveolar haemorrhages Asthma Atelectasis Pleural effusion	Hypoxia

System Organ Class	Very Common	Common	Uncommon
Gastrointestinal disorders	Nausea Stomatitis Vomiting Diarrhoea Constipation Dyspepsia Anus discomfort Abdominal pain Ascites	Oesophagitis Ileus Haematemesis	Gastrointestinal haemorrhage
Hepato-biliary disorders	Hepatomegaly Jaundice	Hepatic veno-occlusive disease	
Skin and subcutaneous tissue disorders	Rash Pruritis Alopecia	Erythema Pigmentation disorder Skin desquamation	
Musculoskeletal and connective tissue disorders	Back pain Myalgia Arthralgia		
Renal and urinary disorders	Creatinine elevated Dysuria Oliguria	BUN increase Haematuria Moderate renal insufficiency	
General disorders and administration site conditions	Headache Asthenia Pain Allergic reaction Oedema general Pain or inflammation at injection site Chest pain Mucositis		
Investigations	Transaminases increased Bilirubin increased GGT increased Weight increased Alkaline phosphatases increased		

Note: One patient in the IV busulfan trials experienced a fatal case of acute respiratory distress syndrome with subsequent respiratory failure associated with intestinal pulmonary fibrosis. Cardiac tamponade and alterations of cornea and lens of the eye have been reported with oral busulfan.

Post-Marketing Experience

The following adverse reactions (reported as MedDRA terms) have been identified during post-approval use of IV busulfan: febrile neutropenia, tumor lysis syndrome, thrombotic micro-angiopathy (TMA), severe bacterial, viral (eg, cytomegalovirus viraemia) and fungal infections, sepsis and tooth hypoplasia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems and contact Apotex Medical Information Enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

The principal toxic effect is profound myeloablation and pancytopenia but the central nervous system, liver, lungs, and gastrointestinal tract may also be affected.

There is no known antidote to Busulfan injection other than haematopoietic stem cell transplantation. In the absence of haematopoietic progenitor cell transplantation, the recommended dosage of busulfan would constitute an overdose of busulfan. The haematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated.

There have been two reports that busulfan is dialyzable, thus dialysis should be considered in the case of an overdose. Since, busulfan is metabolized through conjugation with glutathione, administration of glutathione might be considered.

It must be considered that overdose of Busulfan injection will also increase exposure to DMA. In human the principal toxic effects were hepatotoxicity and central nervous system effects. CNS changes precede any of the more severe side effects. No specific antidote for DMA overdose is known. In case of overdose, management would include general supportive care.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: Cytotoxic agents (alkylating agents). ATC Code: L01AB01

Busulfan is a potent cytotoxic agent and a bifunctional alkylating agent. In aqueous media, release of the methanesulphonate groups produces carbonium ions which can alkylate DNA, thought to be an important biological mechanism for its cytotoxic effect.

Clinical trials

Clinical trials in adults

Documentation of the safety and efficacy of IV busulfan in combination with cyclophosphamide in myeloablation prior to autologous or allogeneic haematopoietic stem cell transplantation (HSCT) in adults is derived from two uncontrolled clinical trials (trials OMC-BUS 3 and 4 respectively).

The trials were conducted in patients with haematological disease, the majority of whom had advanced disease. Diseases included were acute leukaemia past first remission, in first or subsequent relapse, in first remission (high risk), or induction failures; chronic myelogenous leukaemia in chronic or advanced phase; primary refractory or resistant relapsed Hodgkin's disease or non-Hodgkin's lymphoma, and myelodysplastic syndrome. The age of patients was 18-63 years and 60% were male. Patients received 0.8 mg/kg IV busulfan every 6 hours by intravenous (IV) infusion for 4 days from day 7 to day 4 before HSCT. Cyclophosphamide 60 mg/kg/day once daily IV was given for 2 days from day 3 to 2 before HSCT (BuCy2 regimen).

The primary efficacy parameters in these studies were myeloablation, engraftment, relapse, and survival. IV busulfan with cyclophosphamide was effective in inducing myeloablation and engraftment. Relapse-free and overall survival were similar in the two trials (Table 2).

Table 2. IV busulfan *qid*/Cyclophosphamide – HSCT Conditioning Efficacy in Adults

	OMC-BUS 3 (n = 42)	OMC-BUS-4 (n = 61)
Myeloablation[1]%	100	100
Median time to neutropenia (range) *days*	4 (-7, 6)	4 (-7,5)
Median duration of neutropenia (range) *days*	6 (2, 13)	9 (1, 28)
Engraftment[2]%	100	98[3]
Median time to engraftment (range) *days*	10 (8, 19)	13 (9, 29)
Relapse-free Kaplan-Meier estimate % at 1 yr [95% CI]	56 [40, 72]	51 [35, 67]
Survival Kaplan-Meier estimate % at 1 yr [95% CI]	70 [52, 88]	67 [54, 80]

[1] Absolute neutrophil count (ANC) < 0.5 x 10^9/L, absolute lymphocyte count < 0.1 x 10^9/L or platelet count < 20 x 10^9/L or bleeding requiring platelet transfusion.

[2] ANC > 0.5 x 10^9/L within 100 days of HSCT.

[3] One patient died before engraftment could be determined.

Uncontrolled (Fernandez) and non-randomised controlled trials (Mamlouk) in adults with haematological malignancies showed comparable incidences of engraftment for once daily and twice daily IV busulfan 3.2 mg/kg/day regimens in combination with cyclophosphamide 60 mg/kg/day compared with the four times daily regimen. Short-term survival was above 80% (Table 3). Reproducible busulfan pharmacokinetic parameters were demonstrated for once daily IV busulfan.

Table 3. IV busulfan *od* or *bd*/Cyclophosphamide – HSCT Conditioning Efficacy in Adults

	Fernandez (n = 12)	Mamlouk		
IV busulfan/oral busulfan schedule	*od* (n = 6) or *bd* (n = 6), days -7 to -4[1]	*od* IV 4d (n = 20)	*qid* IV 4d (n = 11)	*qid po* 4d (n = 25)
Cyclophosphamide schedule	daily, days -3 to -2	2 days, start 27 h after IV busulfan	2 days, start 18 h after IV busulfan	2 days, start 18 h after busulfan
Engraftment[2]%	92[3]	100	100	100
Median time to engraftment[3] (range) *days*	11 (10, 20)	12 (11, 17)	14 (12, 18)	13 (10, 26)
Relapse-free at 100 days post-HSCT %	67	90	100	88
Survival at 100 days post-HSCT%	83	95	82	84

[1]Before HSCT.

[2] ANC > 0.5 x 10^9/L.

[3] One patient died before engraftment could be determined.

Two uncontrolled trials in adults with haematological malignancies (Russell, de Lima) showed comparable incidences of engraftment for once daily busulfan 3.2-3.3 mg/kg in combination with fludarabine compared with the four times daily IV busulfan with cyclophosphamide regimen. Two-year survival was 37-88% depending on risk (Table 4). Reproducible busulfan pharmacokinetic parameters were demonstrated for IV busulfan.

Table 4. IV busulfan *od* or *bd*/Fludarabine – HSCT Conditioning Efficacy in Adults

	Russell (n = 70)	**De Lima (n = 96)**
IV busulfan schedule	3.2 mg/kg *od*, days -5 to -2[1]	130 mg/m^2 *od* ≒ 3.3 mg/kg days -6 to -3[1]
Fludarabine schedule	50 mg/m^2/d, days -6 to -2[1]	40 mg/m^2/d days -6 to -3[1]
Engraftment[2]%	94[3]	99
Medium time to engraftment[2] (range) *days*	18 (12, 42)	12 (9, 25)
Relapse-free %	26-74 (depending on risk) (2 yr est)	66
Survival %	37 – 88 (depending on risk) (2 yr est)	65 (1 yr est)

[1] Before HSCT.

[2] ANC > 0.5 x 10^9/L

[3] Two patients failed engraftment because of persistent leukaemia and two died before engraftment could be determined. In unrelated or mismatched donor, anti-thymocyte globulin (ATG) was used.

In a retrospective analysis (Alyea) comparing the outcomes of allogeneic transplant in patients aged > 50 years with haematological malignancies, who received either a non- myeloablative conditioning regimen of once-daily IV busulfan 0.8 mg/kg for 4 days in combination with fludarabine 30 mg/m^2 for 4 days or a myeloablative conditioning regimen of total body irradiation (TBI)/cyclophosphamide or oral busulfan/cyclophosphamide, improved 100-day treatment-related mortality rates and non- relapse mortality rates were noted in patients receiving the non-myeloablative IV busulfan- fludarabine conditioning regimen (Table 5). Although the cumulative incidence of disease relapse was higher in patients receiving the non-myeloablative conditioning regimen, overall survival and progression-free survival were not adversely affected by the reduction in intensity of the conditioning regimen.

Table 5. IV busulfan/Fludarabine – Comparison of Myeloablative and Non-Myeloablative HSCT Conditioning Efficacy in Adults – Alyea

	Non-Myeloablative (n = 71)	**Myeloablative (n = 81)**
Myeloablative/non-myeloablative schedule	IV busulfan 0.8 mg/kg/d, fludarabine 30 mg/m^2/d Days -6 to -3[1]	Cyclophosphamine/ TBI or oral Busulfan/ cyclophosphamine[2]
Treatment related mortality (100 day)	6%	30%
Non-relapse mortality	32%	50%
Cumulative relapse rate	46%	30%
Kaplan-Meier overall survival	39% (2 yr est)	29% (2 yr est)
Kaplan-Meier progression-free survival	27% (2 yr est)	25% (2 yr est)

[1] Before HSCT.

[2] 94% received Cytarabine 1800 mg/m^2/d for 2 days and TBI (total body irradiation) 1400cGy in 7 fractions over 4 days. 6% received oral busulfan 16 mg/kg divided over 4 days and cyclophosphamide.

Clinical trials in Children

Documentation of the safety and efficacy of IV busulfan in combination with cyclophosphamide or melphalan in myeloablation prior to autologous or allogeneic HSCT in children is derived from one uncontrolled clinical trial (trial F60002 IN 1 01 G0). The age of patients was 0.3-17.2 years and 53% were male. The dose of IV busulfan ranged from 3.2-4.8 mg/kg/day depending on weight group. The IV busulfan dose was based on body weight as detailed in the section **4.2 Dose and method of administration** and given in four divided doses daily for 4 days.

In autologous HSCT, IV busulfan was given from day 6 to day 3 before HSCT and melphalan 140 mg/m^2 IV on the day before HSCT (BuMel regimen). In allogeneic HSCT, IV busulfan was given from day 9 to day 6 before HSCT and cyclophosphamide 50 mg/kg IV for 4 days from day 5 to 2 before HSCT (BuCy4 regimen). All patients achieved myeloablation and engraftment. The estimated 2-year survival was almost 80% (Table 6).

Table 6. IV busulfan *qid*/Melphalan (Bu/Mel) or Cyclophosphamide (Bu/Cy) - HSCT Conditioning Efficacy in Children – Trial F60002 IN 1 01

	Bu/Mel (n = 27)	**Bu/Cy (n = 28)**
Myeloablation[1] %	100	100
Median time to neutropenia (range) *days*	5 (3, 8)	5 (3, 8)
Median duration of neutropenia (range) *days*	5 (3, 10)	5 (3, 10)
Engraftment[2] %	100	100
Median time to engraftment (range) *days*	11 (10, 15)	21 (12, 47)
Median follow-up (range) *mths*	16.9 (5.4, 26.9)	13.5 (3.4, 23.5)
Relapse-free Kaplan-Meier estimate % at 2 yrs [95% CI]	72 (66, 73)	88 (84, 91)
Survival Kaplan-Meier estimate % at 2 yrs [95% CI]	77 (73, 82)	79 (73, 85)

[1] Absolute neutrophil count (ANC) < 0.5 x 10^9/L, absolute lymphocyte count < 0.1 x 10^9/L or platelet count < 20 x 10^9/L or bleeding requiring platelet transfusion.

[2] ANC > 0.5 x 10^9/L within 100 days of HSCT.

Four uncontrolled trials in children (Table 7) with malignant and non-malignant conditions showed comparable incidences of engraftment for once daily IV busulfan 4 mg/kg/day for 4 days (Grigull) or with IV busulfan targeted to a steady-state concentration of 900 ng/mL four times daily (approx 3.2 mg/kg/day) for 4 days (Horn) in combination with fludarabine 30- 40 mg/m^2/day, compared with four times daily IV busulfan with cyclophosphamide or melphalan. Lower incidences of engraftment were obtained for reduced intensity conditioning regimens using a reduced dose or reduced duration of IV busulfan (Kletzel, Horn, Jacobsohn). The reduced intensity conditioning was associated with lower incidences of treatment related toxicity.

Table 7. IV busulfan *od* or *bd*/Fludarabine - HSCT Conditioning Efficacy in Children

	Grigull (n = 5)	Horn (n = 19)	Kletzel (n = 30)	Jacobsohn (n = 13)
IV busulfan schedule†	4 mg/kg/d *od*, days -8 to -5	Target C_{ss} 600 ng/mL (n = 16), 900 ng/mL (n = 3) *qid*, days -9 to -6	3.2 mg/kg/d *od*, target 3200-4800 µmol. min days -5 to -4[1]	0.8 mg/kg *qid*, target 3800-4200 µmol. min days -5 to -4
Fludarabine schedule	30 mg/m^2/d days -10 to -5	40 mg/m^2/d days -5 to -2	30 mg/m^2/d days -5 to -2	30 mg/m^2/d days -10 to -5
Engraftment[2] %	100	75% (C_{ss} 600 mg/mL) 100%	87	72
Med time to engraft (range) *days*	16	20 (16, 28)	not stated	18 (14, 25)
Relapse-free %	100	74	63	23
Survival %	100 (med 32 mth F/U)	89 (med 2 yr KM)	60 (2 yr KM)	69 (2 yr KM)

[1]Before HSCT.

[2]ANC > 0.5 x 10^9/L within 100 days of HSCT. KM – Kaplan-Meier.

†Rabbit or equine ATG was also used.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and distribution pharmacokinetics of IV busulfan has been investigated. The information presented on metabolism and elimination is based on oral busulfan.

Absorption

The pharmacokinetics of IV busulfan was studied in 124 evaluable patients following a 2-hour intravenous infusion for a total of 16 doses over four days. Immediate and complete availability of the dose is obtained after intravenous infusion of busulfan. Similar blood exposure was observed when comparing plasma concentrations in patients receiving 1 mg/kg oral and 0.8 mg/kg IV busulfan. Low inter (CV = 21%) and intra (CV = 12%) patient variability on drug exposure was demonstrated through a population pharmacokinetic analysis with IV busulfan, performed on 102 patients.

Distribution

Terminal volume of distribution Vz ranged between 0.62 and 0.85 L/kg. Busulfan concentrations in the cerebrospinal fluid are comparable to those in plasma although these concentrations are probably insufficient for anti-neoplastic activity. Reversible binding to plasma proteins was around 7% while irreversible binding, primarily to albumin, was about 32%.

Metabolism

Busulfan is metabolised mainly through conjugation with glutathione (spontaneous and glutathione-S-transferase mediated). The glutathione conjugate is then further metabolised in the liver by oxidation. None of the metabolites is thought to contribute significantly to either efficacy or toxicity.

Excretion

Total clearance in plasma ranged 2.25 - 2.74 mL/minute/kg. The terminal half-life ranged from 2.8 to 3.9 hours. Approximately 30% of the administered dose is excreted into the urine over 48 hours with 1% as unchanged drug. Elimination in faeces is negligible. Irreversible protein binding may explain the incomplete recovery. Contribution of long- lasting metabolites is not excluded.

Pharmacokinetic linearity

The dose proportional increase of drug exposure was demonstrated following intravenous busulfan up to 1 mg/kg.

Pharmacokinetic/ pharmacodynamics Relationships

The literature on oral busulfan when used in myeloablative conditioning regimens every six hours for four days suggests a therapeutic window between 900 and 1500 -minute for AUC. During clinical trials with IV busulfan administered in this way, 90% of patients AUCs were below the upper AUC limit (1500 µMol-minute) and at least 80 % were within the targeted therapeutic window (900 - 1500 µMol-minute).

Special populations

The effects of renal dysfunction on IV busulfan disposition have not been thoroughly assessed. However busulfan was not well tolerated in a Phase I study conducted in patients with metastatic renal carcinoma where all patients had only one functioning kidney.

The effects of hepatic dysfunction on IV busulfan disposition have not been assessed. Nevertheless the risk of liver toxicity may be increased in this population.

No age effect on busulfan clearance was evidenced from available IV busulfan data in patients over 60 years.

Pharmacokinetics in children

A continuous variation of clearance ranging from 2.49 to 3.92 mL/minute/kg was established in children from < 6 months up to 17 years old. The terminal half life ranged from 2.26 to 2.52 h. The described dosing based on body weight allows achievement of a similar targeted AUC whatever the child’s age, comparable with adult plasma exposure. Inter and intra patient variabilities in plasma exposure were lower than 20% and lower than 10%, respectively.

The successful engraftment achieved in all paediatric patients during the phase II clinical trial suggests the appropriateness of the targeted AUCs of 900 to 1500 µMol-minute. Occurrence of hepatic veno-occlusive disease (HVOD) was not related to overexposure. A pharmacokinetic/pharmacodynamic relationship was observed between stomatitis and AUCs in autologous patients and between bilirubin increase and AUCs in a combined autologous and allogeneic patient analysis.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Busulfan was mutagenic in bacterial (*Salmonella typhimurium* and *E. coli*), insect (*Drosophila melanogaster*) and mammalian (mouse, hamster and human) cells. Busulfan induced chromosomal aberrations *in vitro* (mouse, hamster and human cells) and *in vivo* (mouse, rat, hamster and human).

Carcinogenicity

Busulfan belongs to a class of substances which are potentially carcinogenic based on their mechanism of action. On the basis of human data, busulfan has been classified by the International Agency for Research on Cancer (IARC) as a human carcinogen. The World Health Organisation (WHO) has concluded that there is a causal relationship between busulfan exposure and cancer. The available data in animals support the carcinogenic potential of busulfan. Intravenous administration of busulfan to mice significantly increased the incidences of thymic and ovarian tumours.

The increased risk of a second malignancy should be explained to the patient. Leukaemia patients treated with busulfan developed many different cytological abnormalities, and some developed carcinomas. Busulfan is thought to be leukemogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Dimethylacetamide (DMA)
- macrogol 400

6.2 INCOMPATIBILITIES

Due to incompatibility, do not use any infusion components containing polycarbonate with Busulfan Injection.

In the absence of compatibility studies, Busulfan injection must not be mixed with other medicinal products except those mentioned in the section **4.2 Dose and method of administration**.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials must be stored at 2°-8°C in a refrigerator (Do not freeze).

Busulfan APOTEX Injection must be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose prior to use. To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2°-8°C for not more than 15 hours.

The chemical and physical stability of the diluted solution has been demonstrated for 8 hours at 20±5°C

6.5 NATURE AND CONTENTS OF CONTAINER

Busulfan APOTEX Injection is provided in packages of eight vials (AUST R number 210228).

APO and APOTEX are registered trade marks of Apotex Inc.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

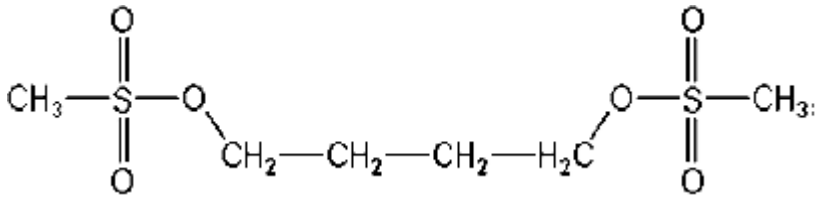
Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic drugs.

6.7 PHYSICOCHEMICAL PROPERTIES

Busulfan injection is an intravenous form of busulfan, a chemotherapeutic agent commonly used as part of a conditioning regimen prior to haematopoietic stem cell transplantation.

Busulfan, the active ingredient of busulfan injection, is a white crystalline solid that is only very slightly soluble in water, sparingly soluble in acetone and slightly soluble in ethanol.

Chemical structure



Chemical Name: Busulfan, 1,4-butanediol dimethanesulfonate

Molecular Formula: $C_6H_{14}O_6S_2$

Molecular Weight: 246.31

CAS number 55-98-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

9 October 2014

10 DATE OF REVISION

2 July 2019

Summary table of changes

Section Changed	Summary of new information
All	Reformatted product information; minor editorial changes
4.2, 4.5, 4.6, 4.8, 6.2	Safety related updates to method of administration, interactions, effects on fertility, adverse effects and incompatibilities.