

busulfan, 6mg/ml, intravenous (Busilvex®)

No. (337/06)

Pierre Fabre Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

busulfan for intravenous infusion (Busilvex®) is accepted for use within NHS Scotland as part of a combination regimen for conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in paediatric and adult patients. The intravenous preparation offers advantages to patients over the oral formulation in terms of convenience of administration and predictability of blood levels.

In adults it should be followed by cyclophosphamide (BuCy2) and in children it should be followed by cyclophosphamide (BuCy4) or by melphalan (BuMel).

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Busulfan for intravenous (IV) infusion followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients, when the combination is considered the best available option.

Busulfan for intravenous (IV) infusion followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional HPCT in paediatric patients

Dosing information

When followed by 2 cycles of 60mg/kg body weight (BW) cyclophosphamide the recommended dosage and schedule of administration is 0.8 mg/kg BW of busulfan as a two-hour infusion every 6 hours over 4 consecutive days for a total of 16 doses prior to cyclophosphamide and conventional haematopoietic progenitor cell transplantation (HPCT).

In children, the busulfan dose/kg is stratified according to actual BW as detailed in a table in the Summary of Product Characteristics (SPC). It is followed by 4 cycles of cyclophosphamide or by one administration of melphalan.

Date of licensing or licence status on date of review

November 2003 (adults) and January 2006 (children).
Orphan drug status designated December 2000.

Summary of evidence on comparative efficacy

A combination of busulfan and cyclophosphamide (BuCy2) is used as a conditioning regimen for patients receiving autologous or allogenic haematopoietic progenitor (stem) cell transplantation (HPCT or HSCT) for a range of malignant and non-malignant conditions. Busulfan is an alkylating agent whose primary purpose in this regimen is to eradicate malignant cells, while cyclophosphamide is given primarily as an immunosuppressant to prevent rejection and permit engraftment of the donor cells.

Conditioning regimens for HSCT involve various combinations of chemotherapy and radiotherapy but can be divided into two categories: those based on total-body irradiation (TBI - most patients) and those based on chemotherapy. Regimens based on busulfan are the most commonly used non-TBI-based conditioning treatments prior to both autologous and allogenic transplantation.

Although oral busulfan is used in these regimens, it is not licensed in this indication. It involves a large pill burden (around 500 tablets over 4 days), and is associated with nausea and vomiting, variable bioavailability and a requirement for plasma level monitoring. An intravenous formulation has been developed to improve patient acceptability and deliver predictable levels. It is the first busulfan product to be licensed in this indication and, because of the small number of patients likely to receive therapy based on busulfan as opposed to other conditioning regimens, it was granted orphan drug status for this indication in December 2000.

Pharmacokinetic studies indicate that the licensed IV regimen in adults should yield a median busulfan area under the plasma busulfan concentration/time curve (AUC) of 1100 to 1200 micromol-min and avoid first-pass hepatic metabolism, and may therefore reduce the risk of hepatic venous occlusive disease (HVOD) and obviate the need to monitor plasma levels of

busulfan. HVOD is a recognised complication of HSCT. High-dose busulfan is associated with an increased risk for HVOD particularly above a threshold AUC of 1500 micromol-min.

Two, phase II studies of similar design have investigated toxicity (particularly hepatic toxicity) and efficacy of busulfan as part of a BuCy2 regimen in adult patients receiving allogenic (n=61) and autologous (n=42) HSCT for haematological malignancies. Patients were eligible provided that they had a physiologic age of 15-55, did not qualify for a protocol of higher institutional priority, and had a Zubrod performance status of <2 and life expectancy of at least 12 weeks.

Profound myelosuppression occurred in all patients in both studies. In patients receiving allogenic HSCT, median time to neutropenia was 4 days (range -7 to +5). The median duration of neutropenia was 9 days (range 1-28 days) and for lymphopenia was 4 days (range 1-19 days). In patients undergoing autologous transplantation, median time to neutropenia was 4 days (range -7 to +6). The median duration of neutropenia and lymphopenia was 6 days (range 2 -13 days) and 3 days (range 1 - 7 days) respectively.

Engraftment (recovery of the neutrophil count) occurred in all evaluable patients in both studies (60 allogenic-transplantation patients and 42 autologous-transplantation patients). On long-term follow-up, about 19 months after transplantation, relapse (disease recurrence) rates were 43% for allogenic-transplantation patients and 69% for autologous, with a median time (range) to relapse of 202 days (36-701) and 181 days (13-716). At the same time point, 33% of allogenic-transplantation patients had died (median time to death 164 days, range 20-831) and the equivalent figures for autologous-transplantation patients were 21% (220 days, range 124-528).

There are no prospective studies comparing oral and IV busulfan. However, data from 61 allogenic-transplantation patients from the phase II study were compared to data from the medical records of patients who had received oral BuCy2 conditioning therapy prior to allogenic transplantation (n=30). This was primarily a safety study; however, mortality at 100 days post-transplantation was 13% in patients receiving IV therapy and 33% for those receiving oral. In a matched pairs analysis comparing IV and oral BuCy2 in patients undergoing allogenic or autologous transplantation, 100-day mortality was 6.2% and 19% respectively.

In one non-comparative study in children, IV busulfan was given at the licensed dose combined with either melphalan (before autologous transplantation, n=27) or cyclophosphamide (before allogenic, n=28). Donor engraftment was documented in all patients, and 26/28 (93%) patients achieved complete chimerism following allogenic transplantation, and 2/28 had mixed chimerism (7.1%). At a median follow-up of 32 months, 70% of patients were surviving following autologous transplantation and 85% were alive at a median follow-up of 28 months after allogenic transplantation.

Summary of evidence on comparative safety

In phase II prospective studies in adults, all suspected cases of HVOD were verified against clinical criteria by an independent reviewer. The incidence of confirmed HVOD was 3/61 (4.9%) in patients undergoing allogeneic transplantation and 3/42 (7.1%) for autologous. In a combined analysis of the two phase II studies (n=103), five of those six cases were reported as serious adverse events (SAE). Two patients had HVOD, which was rated moderate in severity, two had life-threatening HVOD and two had fatal HVOD.

Twenty-six of 103 patients (25%) had a single serious adverse event (SAE), 10/103 (10%) had two SAE, 3/103 (3%) had three SAE and one patient had four SAE. Two SAEs (acute delirium and hypotension) were unexpected and occurred prior to transplantation. The most commonly reported SAE was infection or signs of infection.

The overall mortality and treatment-related mortality rates were 29/103 (28%) and 16/103 (16%) respectively. The incidence of total and non-relapse mortality was higher in the allogeneic than the autologous transplantation groups: 20/61 (33%) and 14/61 (23%) vs 9/42 (21%) and 2/42 (5%) respectively.

Summary of clinical effectiveness issues

The data available to support the efficacy of busulfan IV are limited due to the nature of the condition. However, the IV formulation offers advantages over oral busulfan in terms of convenience of administration and predictability of drug levels. The available evidence also suggests advantages in terms of efficacy and avoidance of HVOD.

In the phase II studies, most patients (95/103 in a combined analysis) were considered to be at high risk for relapse and poor outcome following HSCT.

Data comparing oral and IV busulfan are from indirect studies designed principally to evaluate toxicity, particularly HVOD. HVOD incidence with IV busulfan appears to be lower than that observed with oral busulfan, and in the oral-therapy groups in those studies the incidence of HVOD corresponded to estimates from the literature for oral high-dose busulfan in this indication – about 20%. However, as prospective comparative safety data are lacking, it is not possible definitively to confirm this hypothesis. Patients with hepatic dysfunction, particularly if severe, may be at a higher risk of developing HVOD when receiving the busulfan/ cyclophosphamide preparation, and this is reflected as a warning in the SPC.

The pattern of adverse events and serious adverse events reported in safety data from phase II studies in adults was similar to that reported for high-dose oral busulfan therapy.

Summary of comparative health economic evidence

The manufacturer did not submit a formal health economic model on the basis of the limited information that was available to enable such analysis. The manufacturer instead, using a cost-outcomes approach, described the likely costs and benefits from using IV busulfan compared to oral busulfan as part of the treatment pathway leading to HPCT. IV busulfan was associated with a drug acquisition cost of £3200 per adult or £1600 per child compared to £117 for oral busulfan. However, the reduced incidence of expensive episodes of HVOD with IV busulfan mitigated some of the additional drug costs of the IV regimen; the expected

treatment costs were therefore calculated as being £3772 with IV busulfan or £2326 with oral busulfan in adult patients once the likelihood of HVD costs were taken into account. The manufacturer also indicated that the improved mortality rates with IV busulfan would generate additional QALYs and therefore that IV busulfan was likely to be cost-effective in the context of the small additional cost. The results were not presented in terms of an overall cost per QALY figure.

Costs in the analysis were not always clearly described in terms of how they were derived. It should be noted that the evidence supporting the reduced incidence of HVD and improved mortality rates with IV busulfan originated from retrospective comparative studies.

The benefits of removing the heavy pill burden of oral therapy and the consistency of plasma busulfan levels achieved by the IV route, coupled with possible outcome benefits, justify the relatively small extra costs in the context of the substantial costs of HCST.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

Conditioning regimens for HSCT involve various combinations of chemotherapy and radiotherapy but can be divided into two categories: those based on total-body irradiation (TBI) and those based on chemotherapy. Regimens based on busulfan are the most commonly used non-TBI-based conditioning treatments prior to both autologous and allogenic transplantation.

Additional information: costs

The cost of oral and intravenous therapy with busulfan as part of BUCy2 regimens is given below. However, it should be noted that oral therapy is not licensed for this indication. IV doses in the table are as licensed for adults while oral doses are detailed in the European Public Assessment Report for IV busulfan. Costs are given over the body-weight range of 60-80kg.

Regimen	Cost per patient
Busulfan 0.8mg/kg IV every six hours for a total of 16 doses (Busilvex®).	£3220*
Busulfan 1 mg/kg oral every six hours for a total of 16 doses (Myleran®).	£100-£133

* Doses round to one vial. Costs for IV busulfan from Monthly Index of Medical Specialities, September 2006.

Doses are shown for general comparison and do not imply therapeutic equivalence.

Additional information: budget impact

The manufacturer estimated a gross drug budget impact for busulfan IV of £25,760 per year. It was estimated that the net budget impact would be £24460. These estimates assume that five adult patients and six paediatric patients would receive busulfan IV rather than oral busulfan per year. These estimates represent all eligible patients.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 19 October 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Andersson BS, Kashyap A, Gian V et al. Conditioning Therapy With Intravenous Busulfan and Cyclophosphamide (IV BuCy2) for Hematologic Malignancies Prior to Allogeneic Stem Cell Transplantation: A Phase II Study. *Biology of Blood and Marrow Transplantation*. 2002;8:145-54.

Kashyap A, Wingard J, Cagnoni P et al. Intravenous versus Oral Busulfan as Part of a Busulfan/Cyclophosphamide Preparative Regimen for Allogeneic Hematopoietic Stem Cell Transplantation: Decreased Incidence of Hepatic Venoocclusive Disease (HVD), HVD-Related Mortality, and Overall 100-Day Mortality. *Biology of Blood and Marrow Transplantation*. 2002;8:493-500.