Scottish Medicines Consortium

plerixafor, 20mg/ml solution for injection (Mozobil®) No. (594/09)
Genzyme Therapeutics Limited

04 December 2009

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

plerixafor (Mozobil®) is accepted for use within NHSScotland in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly.

Significantly more patients treated with plerixafor than with placebo achieved their target collection of CD 34+ cells required for autologous stem cell transplantation with subsequent sustained engraftment.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

In combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly.

Dosing information

By subcutaneous injection, 0.24mg/kg body weight daily, 6 to 11 hours prior to initiation of apheresis following four days pre-treatment with granulocyte-colony stimulating factor (G-CSF).

Plerixafor therapy should be initiated and supervised by a physician experienced in oncology and/or haematology. The mobilisation and apheresis procedures should be performed in collaboration with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

Product availability date

5 August 2009. This product is designated an orphan medicinal product.

Summary of evidence on comparative efficacy

Autologous stem cell transplantation (ASCT) after high dose chemotherapy (HDT) is an important treatment option for patients with lymphoma and multiple myeloma (MM). Mobilisation into the peripheral blood of sufficient CD34+ stem cells is necessary before proceeding to transplant. Plerixafor is an inhibitor of the CXCR4 chemokine receptor and blocks binding of its ligand, CXCL12, preventing the homing and retention of stem cells in the bone marrow resulting in them entering the systemic circulation. Plerixafor has been designated an orphan medicinal product in Europe.

The submitting company propose that plerixafor be considered a second-line treatment option, in patients who have previously failed one mobilisation attempt. This positioning is supported by compassionate use in both Scotland and the US but not by the phase lll studies which are in first-line use.

Two double-blind, randomised phase lll studies have compared the efficacy of plerixafor to placebo in 298 non Hodgkin's lymphoma (NHL) and 302 MM patients. In both studies, patients were 18 years or over, had a biopsy confirmed diagnosis and an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1. Patients who had received a prior autologous or allogeneic transplant and those who had failed previous stem cell collections or attempts were excluded.

Treatment was initiated with G-CSF 10microgram/kg/day for up to eight days. Randomisation was stratified by study centre in the NHL study and by study centre, platelet count and type of planned transplant (single or tandem) in the MM study. After four days, randomised patients received either subcutaneous plerixafor 240 microgram/kg or placebo on the evening before each day of apheresis. Patients continued apheresis for up to four days until ≥ 5 x 10^6 CD34+cells/kg in the NHL study and ≥ 6 x 10^6 CD34+cells/kg in the MM study,

had been collected for transplantation. A rescue protocol was available in both studies for patients who failed to mobilise sufficient CD34+ cells. Following a rest period of at least seven days, patients were treated with open-label plerixafor and G-CSF for up to a total of four days or until ≥ 5 x 10^6 CD34+ cells/kg were collected, whichever occurred first.

The primary outcome was the proportion of patients reaching the target number of CD34+ cells within the predefined number of apheresis sessions for each study (≤4 days in the NHL and ≤2 days in the MM study). An efficacy objective specific to the European Medicines Agency (EMEA) was a composite endpoint including the target number of CD34+ cells and successful polymorphonuclear (PMN) cell and platelet (PLT) engraftment. A number of other secondary endpoints were defined including engraftment endpoints and graft durability. All randomised patients were included in the intention to treat (ITT) population.

In the NHL study, significantly more patients in the plerixafor group, 59% (89/150), than in the placebo group, 20% (29/148), achieved the primary endpoint, collection of ≥5 x 10^6CD34+ cells/kg in ≤4 days of apheresis. Significantly more patients in the plerixafor group achieved the two EMEA-specific endpoints: the proportions of patients with ≥2 and with ≥5 x 10^6 CD34+cells/kg in ≤4 days of apheresis plus successful PMN and PLT engraftment, 84% versus 43%, and 57% versus 19%, respectively. In the plerixafor group, 90% of patients proceeded to transplant compared with 55% of placebo patients.

Of 62 patients entering the rescue procedure, 4/10 patients in the plerixafor group achieved ≥ 2 x 10^6 CD34+ cells/kg in up to four days of apheresis compared with 33/52 patients in the placebo group. In addition, seven placebo patients achieved ≥5 x 10^6 cells/kg in ≤4 days of apheresis.

In the MM study, the primary endpoint, collection of ≥6 x 10^6CD34+ cells/kg in ≤2 days of apheresis, was achieved by significantly more plerixafor patients than placebo patients (72% [106/148] and 34% [53/154], respectively). Significantly more patients in the plerixafor group achieved the EMEA-specific endpoint of the proportion of patients with ≥6 x 10^6 CD34+ cells/kg ≤2 days of apheresis and successful PMN and PLT engraftment, 70% and 34%, respectively. In the plerixafor group, 96% of patients proceeded to transplant compared to 88% of placebo patients.

All seven placebo patients entering the rescue procedure achieved ≥2 x 10^6 CD34+ cells/kg in ≤4 days of apheresis.

The median time to engraftment was similar in the plerixafor and placebo groups in both studies, as were the proportions of patients maintaining a durable graft at 100 days, 6 and 12 months. There was no difference between the groups in overall survival, an exploratory efficacy endpoint.

There have been a number of published reports of the compassionate use programme. The largest of these was in 98 MM and NHL patients. Patients included had previously failed to mobilise sufficient cells for transplant. The primary endpoint of ≥2 x 10^6CD34+ cells/kg was achieved by 60% and 71% of NHL and MM patients, respectively. More than 73% of patients proceeded to transplant.

In the Scottish compassionate use programme, 20 patients (12 MM and 8 NHL patients) who had undergone at least one previous attempt at stem cell mobilisation that failed or resulted in an insufficient cell dose for transplant, were treated with G-CSF and plerixafor. Nineteen of the 20 patients achieved a transplantable stem cell dose of >2.5 x 10^6 CD34+ cells/kg, 18 of these patients after one course. At the time of publication, 10 patients had progressed to transplant and all 10 had achieved sustained engraftment.

Summary of evidence on comparative safety

In the two phase lll studies, the incidence of related adverse events was higher in the plerixafor group, 65% versus 41% in the NHL study and 65% versus 45% in the MM study. In the NHL study three patients had a serious adverse event related to treatment, two in the plerixafor group (one patient with hypotension and dizziness and one patient with thrombocytopenia post-apheresis). The most common treatment-related adverse events were gastrointestinal disorders (diarrhoea, 32% and 18% in the plerixafor groups compared with 4.1% and 5.3% in the placebo groups; nausea, 17% and 16% in the plerixafor groups and 5.5% and 7.3% in the placebo groups) and injection site reactions (erythema, 29% and 20% in the plerixafor groups and 6.9% and 3.3% in the placebo groups).

There is a theoretical risk of tumour cell mobilisation in MM and lymphoma patients. To assess the clinical relevance of this, the long-term follow up of the two phase lll studies has been extended to five years with the compilation of a registry.

Summary of clinical effectiveness issues

There are no active comparator studies with plerixafor plus G-CSF against other chemotherapy plus G-CSF mobilisation regimens. G-CSF in combination with chemotherapy, especially in NHL patients, is the usual remobilisation regimen in Scotland.

The submitting company have proposed that plerixafor be considered for use in a subset of the licensed indication, as second-line use in patients who have previously failed one mobilisation attempt. The evidence for this positioning comes only from the compassionate use programme as in both phase lll studies patients with a prior autologous or allogeneic transplant and failed previous stem cell collections or attempts were excluded. However, evidence from the Scottish programme supports this use, with 18 of the 20 patients achieving a transplantable stem cell dose, although the numbers of patients were small and adverse events were not reported.

There is a theoretical risk that plerixafor might promote the mobilisation of tumour cells into the circulation and contaminate the transplant. At present, there is no definitive clinical evidence that supports or refutes this hypothesis and therefore it will be assessed through extension of the long-term follow up of the two phase lll studies to five years. This potential risk meant that the risk-benefit ratio in the broader population was not favourable and the licensed indication was restricted to poor mobilisers.

The administration of plerixafor allows the collection of sufficient CD34+ cells for autologous stem cell transplant in patients who previously have been unable to mobilise sufficient cells. It reduces the number of days required to collect the target number of cells and the time of collection of the cells is more predictable making the process more manageable. The lower toxicity of plerixafor compared to cyclophosphamide, which is commonly used in combination with G-CSF, is an advantage. However, no overall survival advantage was shown after 12 months follow-up for patients treated with plerixafor.

Clinical experts gave strong support for the use of plerixifor in patients with multiple myeloma and lymphoma whose CD34+ cells mobilise poorly.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis of the use of plerixafor for mobilisation in multiple myeloma and non-Hodgkin's lymphoma patients who had failed at least one previous mobilisation attempt. The comparator mobilisation treatments were G-CSF and G-CSF in combination with cyclophosphamide. These were appropriate comparators.

Rates of successful mobilisation were drawn from a range of sources, data from the compassionate use programme being used for plerixafor while a retrospective analysis was used for G-CSF and G-CSF + cyclophosphamide. Successful mobilisation was followed by autologous transplantation, while those not mobilising were largely assumed to undergo chemotherapy. The effectiveness, survival estimates and utility estimates for these were taken from the literature. Adverse events during mobilisation were not considered.

The key results in multiple myeloma patients were as follows:

- the cost per successful mobilisation gained was £12,768 compared to G-CSF
- the cost per successful mobilisation gained was £11,074 compared to G-CSF + cyclophosphamide
- a gain of 0.47 QALYs at a cost of £18,832 compared to G-CSF, to yield a cost per QALY of £39,649
- a gain of 0.41 QALYs at a cost of £15,561 compared to G-CSF + cyclophosphamide, to yield a cost per QALY of £38,278

The key results in non-Hodgkin's lymphoma patients were as follows:

- the cost per successful mobilisation gained was the same as among multiple myeloma patients
- a gain of 1.22 QALYs at a cost of £23,950 compared to G-CSF, to yield a cost per QALY of £19,586
- a gain of 1.06 QALYs at a cost of £20,054 compared to G-CSF + cyclophosphamide, to yield a cost per QALY of £18,874 compared to G-CSF + cyclophosphamide

Weaknesses of the analysis included:

- The base case analysis assumed that cyclophosphamide would be administered in an in-patient setting and plerixafor in a nurse-led clinic. Sensitivity analysis indicated that when these assumptions were changed to out-patient and in-patient administration respectively, the combined effect was to increase the base case ICERs by 3-4%.
- There was some sensitivity in the results when different sources of mobilisation rates were used.

The economic case was considered demonstrated in the NHL indication. In the MM indication, the cost-effectiveness ratios were comparatively high, but the economic case was considered demonstrated when viewed in light of SMC orphan drug modifiers, particularly

the ability of the treatment to allow patients to bridge to an effective treatment (autologous bone marrow transplant).

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Leukaemia CARE
- Lymphoma Association
- Myeloma UK

Additional information: guidelines and protocols

There are a number of guidelines describing high dose chemotherapy treatment and autologous stem cell transplant but none of these include recommendation of specific treatment.

Additional information: comparators

G-CSF alone, G-CSF plus cyclophosphamide. In Scotland specialists advise that chemotherapy using combination regimens with ifosfamide-etoposide-epirubicin (IVE) and with dexamethasone-cytarabine-cisplatinum (DHAP) both in combination with G-CSF are used for remobilisation.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
Plerixafor plus G-CSF	**0.24milligram/kilogram body weight daily for 2 to 4days plus 10microgram/kg/day for 8 days**	**10388 to 20524**
Ifosfamide Etoposide Epirubicin plus G-CSF	3000mg/m^2 IV Day 1 to 3 200mg/m^2 IV Day 1 to 3 50mg/m^2 IV on Day 1 5 to 10 microgram/kg/daily for 10 days	 1438 to 1808
Cisplatin Cytarabine Dexamethasone Plus G-CSF	100mg/m^2 IV Day 1 2g/m^2 12 hourly IV Day 2 40mg orally Day 1 to 4 5 to 10microgram/kg/daily for 10 days	 927 to 1298
Cyclophosphamide plus G-CSF	1.5 to 3g/m^2 Day 1 5 to 10microgram/kg for 10 days	 646 to 1288
G-CSF	10microgram/kg body weight daily for up to10 days	993

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 5 and 7 October 2009 and the BNF 58. Costs were calculated based on an adult weight of 70kg and body surface area of 1.8m^2. G-CSF doses have been rounded to the nearest unit dose (i.e. 300microgram or 600microgram)

Additional information: budget impact

The manufacturer estimated that given a patient population for secondary mobilisation of 21 per annum and a 100% market share that the gross direct drug cost of mobilising with G-CSF + plerixafor would be £231k per annum. The net drug cost was estimated as £184k.

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 13 November 2009.

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. The reference shaded grey is additional to those supplied with the submission.

Calandra G, McCarty J, McGuirk J et al. AMD3100 plus G-CSF can successfully mobilize CD34+ cells from non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma patients previously failing mobilization with chemotherapy and/or cytokine treatment: compassionate use data. Bone Marrow Transplant 2008; 41(4):331-338.

Gordon W, Johnson P, Roddie P et al. Plerixafor is highly effective in the mobilisation of PBSC for autologous transplantation from patients failing to mobilise by conventional means: the initial Scottish experience in three transplant centres. 35th Annual Meeting of the European Group for Blood and Marrow Transplantation, Goteberg, Sweden March 2009. 2009.

Dipersio JF, Micallef IN, Stiff PJ et al. A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Phase III Study Designed to Assess the Safety and Efficacy of Plerixafor (AMD3100) Plus G-CSF Compared to Placebo Plus GCSF in Mobilization and Transplantation of Patients With Non-Hodgkin's Lymphoma (NHL): OPTOMIZE I. 2007.

Dipersio JF, Stadtmauer EA, Nademanee A et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. Blood 2009; 113(23):5720-5726.

The European Medicines Agency (EMEA). European Public Assessment Report (EPAR) for plerixafor (Mozobil®), EMEA/H/C/001030. www.emea.europa.eu