All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Plerixafor (Mozobil®▼)

Genzyme Therapeutics Ltd

Advice No: 0110 – March 2010

Recommendation of AWMSG

Plerixafor (Mozobil®▼) is recommended as an option for restricted use within NHS Wales in combination with granulocyte-colony stimulating factor (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.

Plerixafor (Mozobil®▼) should be restricted for use specifically in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) who have already failed one complete mobilisation attempt.

AWMSG is of the opinion that plerixafor (Mozobil®▼) is not suitable for shared care within NHS Wales.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 3rd March 2010

The recommendation of AWMSG is:

Plerixafor (Mozobil®▼) is recommended as an option for restricted use within NHS Wales in combination with granulocyte-colony stimulating factor (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.

Plerixafor (Mozobil®▼) should be restricted for use specifically in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) who have already failed one complete mobilisation attempt.

AWMSG is of the opinion that plerixafor (Mozobil®▼) is not suitable for shared care within NHS Wales.

Additional notes:

- Tumour cell mobilisation, specifically in poor mobilisers, requires evaluation of progression free survival (as well as other long-term outcomes) by use of a registry, as requested by the Committee for Medicinal Products for Human Use (CHMP).

- AWMSG recommends that Health Boards establish a process to monitor uptake and compliance with this recommendation.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Plerixafor (Mozobil®▼) is licensed in combination with granulocyte-colony stimulating factor (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[1].

Based on company-sought experience of clinical practice in Wales, the company have restricted their submission to the use of plerixafor specifically to patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) who have already failed one mobilisation[2].

2.2 Dosing

The recommended dose of plerixafor is 0.24mg/kg body weight per day. It should be administered by subcutaneous injection, six to 11 hours prior to initiation of apheresis; following four days of pre-treatment with G-CSF. In clinical trials, plerixafor has been commonly used for two to four (and up to seven) consecutive days[1].

Each vial of plerixafor is intended for single use only. Further information regarding administration of plerixafor can be found in the Summary of Product Characteristics (SPC)[1].

2.3 Market authorisation date

31st July 2009[2].

2.4 UK Launch date

5th August 2009[2].

3.0 DECISION CONTEXT

3.1 Background

Autologous haematapoietic stem cell transplantation (ASCT) provides haematopoietic support after high dose chemotherapy (HDT) and is the standard of care for patients with MM or relapsed high grade NHL who are fit enough to undergo this form of treatment[3-7]. HDT and ASCT are associated with higher complete response rates and improvements in survival in patients with MM and NHL[2,8]. To receive HDT, sufficient stem cells must be collected prior to HDT in order to carry out ASCT. Mobilisation is carried out using G-CSF in combination with chemotherapy, or with G-CSF alone. With these treatments, however, a significant proportion of patients (5-30%) fail to collect enough stem cells which necessitates additional mobilisation attempts or prevents patients from receiving ASCT with the subsequent survival benefits[8]. The number generally accepted to be able to proceed is a minimum of 2 $x10^6$ CD34+ stem cells/kg body weight to an optimal level of 5 $x10^6$ CD34+ stem cells/kg body weight[8,9].

Plerixafor is a selective reversible antagonist of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1α, also known as CXCL12, resulting in mobilisation of haematopoietic stem cells positive for surface glycoprotein CD34+ (CD34+ cells) from the bone marrow to the peripheral blood where they can be collected for ASCT[1,10].

Plerixafor was designated by the European Medicines Agency (EMEA) as an orphan medicinal product in 2004. It is given in combination with G-CSF, to enhance mobilisation in patients with MM and lymphoma who mobilise poorly[10]. Given the estimate that 19% of patients with MM and NHL fail to mobilise on first attempt, the company anticipate 12 patients could be eligible for treatment each year[2]. Plerixafor therefore appears to satisfy AWMSG criteria for ultra-orphan drug status, based on the number of patients with MM or NHL receiving autologous transplants per year as highlighted in the company submission. However, based on the full licensed indication, expert opinion raises concerns that prevalence may exceed this threshold within NHS Wales.

3.2 Comparators

The company anticipate that plerixafor would replace the regimens of cyclophosphamide plus G-CSF or G-CSF alone in patients with MM or NHL who had failed current first line mobilisation. The comparison of G-CSF plus plerixafor against G-CSF plus cyclophosphamide is considered to be the most relevant for this submission as company-sought expert opinion suggests G-CSF alone is used infrequently in Wales[2].

There are currently no other clinical comparators to plerixafor for the treatment of this group of failed mobilisers.

3.3 Guidance and related advice

ASCT is considered by the National Comprehensive Cancer Network (NCCN) in their clinical practice guidelines as a category 1 recommendation (see glossary) as follow up treatment to induction therapy for MM[4]. It is also NCCN's treatment of choice for patients with relapsed or refractory diffuse large B-cell lymphoma and is recommended by the Network for other subtypes of NHL[7]. This is in line with the National Institute for Health and Clinical Excellence (NICE) and the British Committee for Standards in Haematology who currently recommend that HDT with autologous stem cell rescue should be available for patients who have MM or recurrent treatment-resistant aggressive lymphomas who are fit enough to undergo this form of treatment[3,5,6].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

A number of studies were provided in the company submission which included patients with NHL and MM treated with plerixafor. The company however highlight that trials for plerixafor have generally excluded those patients where mobilisation has previously failed. Evidence for the use of plerixafor plus G-CSF in those patients who have failed an alternative mobilisation regimen using either G-CSF plus chemotherapy or G-CSF alone, has therefore been obtained from four studies (two available in abstract only) within a compassionate use programme (CUP) and a retrospective analysis. The clinical evidence for the submission population is therefore derived from a relatively small number of patients.

From the data available, plerixafor resulted in the majority of patients who had previously failed stem cell mobilisation (median of two prior attempts) with either G-CSF alone, or G-CSF plus chemotherapy, to subsequently collect enough CD34+ cells to proceed to transplant. G-CSF plus chemotherapy is known to improve collections by two- to five-fold over G-CSF alone. Nevertheless, some patients in the clinical trials presented had previously failed to collect a transplantable dose of stem cells using chemokine mobilisation (i.e. G-CSF alone) rather than G-CSF plus chemotherapy. Further longer-term data regarding evaluation of relapse, progression-free survival, and overall survival from the completion of two phase III trials (first-line therapy) will help to confirm the safety and efficacy of plerixafor plus G-CSF including its use in poor mobilisers.

4.2 Review of the evidence on cost-effectiveness

The company submission describes a cost utility analysis of G-CSF plus plerixafor within its licensed indication. The comparators in the analysis are G-CSF plus chemotherapy or G-CSF alone, although it appears that the former is by far the most commonly used in Wales.

There is consistent evidence that plerixafor increases the probability of patients achieving sufficient peripheral blood stem cell (PBSC) counts to undergo apheresis and subsequent autologous transplant. Compared with G-CSF plus chemotherapy, the incremental cost per quality adjusted life year (QALY) gained with the plerixafor regimen is estimated in the base case analyses to be £36,794 in patients with MM and £20,391 in patients with NHL. However, the base case analyses employ efficacy data derived from small numbers of patients, and which are more favourable in terms of success rates and shorter durations of apheresis when compared with other available sources of data, some of which involve greater patient numbers. Sensitivity analyses indicate the model is sensitive to the assumed rates of successful remobilistaion and duration of apheresis. Other limitations of the economic evidence include the assumption of equal efficacy across patients with MM and NHL, despite some evidence of a differential response. It is, therefore, not clear that the base case analyses presented in the company submission provide the most plausible point estimates of the cost effectiveness of plerixafor.

4.3 Limitations of the evidence

- There are no robust, direct comparative data to inform the economic model. Effectiveness inputs are based on retrospective, observational data.
- It is acknowledged that the safety and efficacy of plerixafor in paediatric patients have not been established in controlled clinical studies[1].

5.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

5.1 Clinical evidence

The company submission highlights four studies (two in abstract only) from a Compassionate Use Programme (CUP) for the use of plerixafor plus G-CSF which include patients with NHL and MM who have failed an alternative mobilisation regimen[11-14]. A retrospective analysis on re-mobilisation[15] and a further two phase III studies[16,17] relating to first line use of plerixafor were also highlighted by the company in their submission as supportive evidence. Although the phase III trials for plerixafor excluded failed mobilisers at trial entry, data from the rescue protocol of these trials were considered relevant[18]. The total study population of the trials included patients with Hodgkin's disease (HD); this information was not considered relevant by the company[2] and is therefore not discussed below.

5.1.1 Compassionate Use Programme (CUP)

Two studies from the CUP investigated the efficacy and safety of plerixafor plus G-CSF[11,12]. The studies included a cohort of 98 patients (study 1) and 16 patients (study 2) diagnosed with either MM or NHL and who had previously failed to mobilise and collect sufficient CD34+ cells for transplant. In both studies, patients received subcutaneous G-CSF 10 micrograms/kg/day for four days followed by subcutaneous plerixafor 240 micrograms/kg (given on the evening of the fourth day; 10-11 hours prior to apheresis). On day 5 G-CSF was administered followed by apheresis. Administration of G-CSF, apheresis and plerixafor were then repeated daily until the patient reached the primary outcome and had collected sufficient cells for transplantation (i.e. a minimum of 2 x 10^6 CD34+ cells/kg).

The primary endpoint (≥2 x 10^6 CD34+ cells/kg) was reached in the first study (n=98) by 60.3% and 71.4% of patients with NHL and MM respectively; with a median of three and four days of apheresis reported for NHL and MM patients respectively[11]. In the second study, 15 (10 NHL and 5 MM) out of the16 patients in the cohort were able to yield sufficient PBSCs with one apheresis procedure to proceed to ASCT. One of the five patients diagnosed with MM required two aphereses procedures, when treated with the combination of plerixafor plus G-CSF[12]. The majority of the cohort in both studies received a transplant. The number of days of apheresis, median time to neutrophil engraftment and also platelet engraftment were similar in both studies[11,12]; data on graft durability up to one year post-transplant was available from one study[11] (see Table 1A, Appendix 1).

Results from two other studies of patients treated following the same CUP protocol (made available in abstract and poster form only[13,14]) also reported an increase in the percentage of patients achieving a transplantable dose of stem cells (the majority of patients reaching the primary endpoint of achieving ≥2 X 10^6 CD34+ cells/kg). Further information can be found in Table 1A, Appendix 1, however it has not been possible to fully assess these studies based on the limited data submitted.

5.1.2 Retrospective Analysis

This study involved retrospective analysis conducted on 1834 patients, of which 1040 met the study inclusion criteria. The analysis included 502 patients with NHL, 401 patients with MM and also 137 with HD, undergoing an initial stem cell mobilisation regime with G-CSF or G-CSF plus chemotherapy[15]. Approximately 19% (n=350) failed mobilisation with G-CSF plus chemotherapy or G-CSF alone. A total of 269 patients then underwent a second mobilisation with G-CSF and/or granulocyte-macrophage stimulating factor (GM-CSF) (n=217), G-CSF plus chemotherapy (n=34) or G-CSF plus plerixafor (n=18). Failure rates were 81.6%, 73.5% and 27.8% respectively. The median number of $CD34^+$ cells/kg yield for each mobilisation regime was 1.2 x 10^6, 0.9 x 10^6 and 4.6 x 10^6 cells/kg following treatment with G-CSF and/or GM-CSF, G-CSF plus chemotherapy or G-CSF plus plerixafor respectively.

5.1.3 Data from the rescue protocol for phase III trials

In the rescue procedure a high proportion of patients who failed to collect ≥ 2 x 10^6 CD34+ cells/kg underwent successful re-mobilisation with plerixafor plus G-CSF[1]. A total of 37/62 (59.7%) of rescue patients with NHL achieved ≥ 2 x 10^6 CD34+ cells/kg in four or fewer days of apheresis (4/10 patients originally treated with plerixafor plus G-CSF and 33/52 patients originally treated with placebo plus G-CSF)[10]. All MM rescue patients collected ≥ 2 x 10^6 cells/kg in four days of apheresis (seven patients from placebo plus G-CSF arm)[2]. During the 12 month follow-up period, there were no differences in graft durability and haematology profiles between groups in either of the phase III trials[2].

5.2 Safety

The most common adverse events considered related to the study drug in the plerixafor trials were gastrointestinal disorders and injection-site reactions, most of which were mild to moderate in severity[10]. It should be noted that diarrhoea was reported very commonly in the phase III trials of plerixafor[1,2] and diarrhoea was responsible for a one-month delay in stem cell harvesting and repeat remobilisation therapy in one of the 20 patients included in one of the CUP study reports[13]. A second treatment with anti-diarrhoeal cover was however successful. The Committee of Medicinal Products for Human Use (CHMP) are satisfied that adverse events including hypotension, cardiac disorders, systemic reactions, leukocytosis, thrombocytopenia, and paraesthesia have been adequately addressed either in the risk management plan or by follow-up procedures[10]. In particular the SPC contains a warning concerning manifestations of vasovagal reactions (including orthostatic hypotension and/or syncope)[1]. Due to the very rare occurrence of splenic rupture following G-CSF administration, individuals receiving plerixafor in conjunction with G-CSF who report left upper abdominal pain and/or scapular or shoulder pain should be evaluated for splenic integrity[1].

The mode of action of plerixafor is such however that binding of the CXCR4 receptor, which is present also on tumour cells, may theoretically enhance mobilisation of the tumour cell itself. In clinical studies of patients with NHL and MM, however, mobilisation of tumour cells has not been observed with plerixafor[1]. The company highlight that an opposite antitumour effect might also be hypothesised[10]. The risk/benefit especially in poor mobilisers, is therefore considered acceptable by CHMP if there are no alternative treatment options for mobilisation[10]. In this population careful long-term follow-up has been recommended in order to rule out detriment in terms of progression-free survival. To address the risk of potential tumour cell mobilisation with plerixafor, the company have extended the long-term follow-up for the two phase III studies from three to five years, including evaluation of relapse, progression-free survival, and overall survival[10](see also section 9.4).

6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- The company highlight that trials for plerixafor have generally excluded those patients where mobilisation has previously failed. The clinical evidence for the submission population is therefore derived from a relatively small number of patients. Further data are needed to confirm the success rates and duration of apheresis in these patients.
- CHMP acknowledge that there is no universally accepted definition of 'poor mobilisers', but suggest that these would be patients that after adequate dosage of G-CSF do not reach CD34+ cells greater than 20 $x10^6$/litre in the peripheral blood or do not reach within four days of apheresis a total of 5 x 10^6/kg CD34+ cells in the harvest[10].
- G-CSF alone is known to be well tolerated but limited by suboptimal PBSC yields. G-CSF plus chemotherapy improves collections by two- to five-fold[8].
- Company-sought expert opinion suggests G-CSF alone is used infrequently in Wales[2]. From the evidence presented however, some patients across the clinical trials had previously failed to collect a transplantable dose of stem cells using chemokine mobilisation (i.e. G-CSF alone) rather than G-CSF plus chemotherapy.
- Two of the CUP studies which had a substantially greater number of patients were available in abstract and as a poster presentation only[13,14].
- Two of the CUP study reports[11,14] indicate a possible differential response to plerixafor treatment in patients with MM and NHL (successful remobilisation rates were numerically greater in patients with MM compared with NHL).

- In the clinical trials available the primary endpoint was the achievement of the minimum CD34+ cell counts required for autologous transplant. Transplantation of 2 x 10^6 CD34+ cells/kg is generally accepted as the minimum cell number required, however it is beneficial to collect a larger cell number[19,20]. Longer term data beyond a year regarding survival will help confirm the benefits of plerixafor in poor mobilisers.
- The long-term follow-up for the two phase III studies, including evaluation of relapse, progression-free survival, and overall survival will help provide further evidence regarding the safety profile of this product beyond 12 months[10].
- It has been reported that after chemomobilisation, the lapse of time before the number of CD34+ cell peaks varies substantially between patients. White blood cell (WBC) counts and CD34+ cell counts need to be monitored over several days to determine when to begin apheresis. Unscheduled apheresis sessions, for example on weekends, may be required necessitating additional resources[8]. The company state that with plerixafor there is an ability to predict when to initiate apheresis since the peripheral blood CD34+ count occurs between 10 and 14 hours after administration.
- G-CSF plus chemotherapy is associated with toxicities, such as febrile neutropenia and haemorrhagic cystitis[21], which puts the patient at considerable risk of infection, and an increased risk of mortality[22]. The company highlight that plerixafor in conjunction with G-CSF does not cause neutropenia. This may be considered an advantage where there is a need for repeated mobilisation attempts.

7.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

7.1 Context

The company submission[2] describes a cost utility analysis of G-CSF plus plerixafor within its licensed indication. The comparators in the analysis are G-CSF plus chemotherapy or G-CSF alone as second-line therapy and the modelled population is patients with MM or NHL who have failed with first-line therapy to achieve sufficient mobilisation of haematopoietic stem cells to undergo autologous stem cell transplantation. The perspective of the analysis is NHS Wales.

7.2 Methods

Modelling approach: A state transition model has reportedly been developed to simulate the lifetime clinical pathway followed by a hypothetical cohort of patients[2] (see Table 2A, Appendix 2 for details). Patients undergo mobilisation therapy with one of the modelled regimens, followed by apheresis and autologous transplant if initial peripheral blood CD34+ cell counts are sufficient (defined as a minimum of 2 x10^6 CD34+ cells/kg). If insufficient CD34+ cell counts are achieved, patients are assumed to undergo other treatment, which may include allogeneic transplant, bone marrow harvest (BMH) followed by transplant, or standard (non-transplant) treatment with chemotherapy (assumed to be R-ICE regimen for NHL, and bortezomib plus dexamethasone for MM) for patients when not in remission. All patients who survive transplant procedures are assumed to achieve successful engraftment and remission[2].

The model permits one attempt at remobilisation. The duration of apheresis is assumed to be two days for those patients modelled to receive G-CSF plus chemotherapy, three days for those receiving G-CSF alone and almost two days (1.95 days) for those receiving G-CSF plus plerixafor. Ultimately, all patients who survive transplant procedures, and those who receive standard treatment, are assumed to experience relapse, undergo relapse treatment, and die from cancer[2].

Inputs: The phase II and III clinical trials of plerixafor relate to first-line use, rather than its licensed indication for second-line use in poor mobilisers[2]. Therefore, the model uses efficacy data obtained from a US compassionate use programme (CUP)[12] and data from a retrospective analysis of US patient records (including patients with NHL and MM) identified from a systematic literature review[15], supplemented with company-sought expert opinion[2].

In the base case analysis, the probabilities of successful remobilisation with G-CSF with or without chemotherapy (27% of 34 patients and 18% of 217 patients respectively), and the mean number of days of apheresis, are based on the retrospective analysis of US patient records[15]. This study also includes data on the use of plerixafor in patients who have previously failed mobilisation attempts (13/18 patients [72%] achieved successful remobilisation over a median of 2.5 apheresis days), but these are not used in the model, which instead uses more favourable data for plerixafor observed in a CUP (17/20 patients [85%] with MM or NHL achieved successful remobilisation over a reported mean of 1.95 apheresis days)[12]. It should be noted that the data for plerixafor used in the base case analysis are based on very small numbers of patients, and under these circumstances a small change in the number of successful remobilisations due to chance could have a dramatic impact on the reported success rates and the mean duration of apheresis. With this in mind, two of the three other CUP study reports included in the company submission, which provide data in relation to greater numbers of patients (98[11] and 251[14] relevant patients, respectively) indicate lower successful remobilisation rates with plerixafor than those used in the base case analysis — in the range 60% to 67% for patients with NHL and 71% to 81% for patients with MM.

The remaining CUP study report discussed in the company submission, which provides data on 20 relevant patients, indicates a successful remobilisation rate with one cycle of plerixafor (which is the scenario modelled for the economic analysis) of 90%, over a median of two apheresis days[13]. Sensitivity analyses have explored the impact of the use of data from these other three CUP study reports[2].

The probabilities of patients undergoing subsequent/other treatments of allogeneic transplant, BMH and standard chemotherapy are all reported to be based on company-sought expert opinion[2].

The probability of dying due to transplant procedures is assumed to be 1.4% for all patients, based on retrospective analysis of records of MM patients who had undergone initial mobilisation with G-CSF plus chemotherapy[23]. Length of overall and event-free survival for modelled MM patients who have achieved a successful transplant or failed transplant are derived from the high-dose chemotherapy plus autologous stem cell transplant arm and the standard chemotherapy arm of a randomised controlled trial (RCT), respectively[23]. This trial compared these two treatment approaches as first-line treatments for MM, and 92% of patients who received transplant did so with peripheral blood stem cells[23]. For modelled NHL patients, the respective lengths of overall and event-free survival are derived from a RCT that compared high-dose chemotherapy plus autologous bone marrow transplant against standard chemotherapy in patients who had experienced relapse following/during chemotherapy[24]. Both trials were terminated early due to poor patient accrual[23,24], and the trial in NHL patients appears not to have concealed allocation[9], which may potentially lead to overestimation of treatment effects. It is unclear how reliable the estimates of overall and event-free survival derived from these trials are. The same survival times have been assigned to patients who successfully underwent transplant, irrespective of actual CD34+ cell counts that were obtained[2].

A range of historical cohort studies and clinical studies have been cited to provide estimates of the incidence of febrile neutropenia for patients receiving chemotherapy, either as remobilisation or as part of standard treatment[2]. Adverse events such as severe diarrhoea have been reported (see section 5.2), however, the model does not consider any other adverse events in addition to febrile neutropenia.

Utility values for weighting life years were reportedly obtained from published sources relating to NHL and MM identified via structured literature reviews. It is assumed that transplantation returns patients to the same quality of life as those in remission but the process of transplantation results in a temporary disutility. A temporary disutility is applied also for the duration of apheresis (magnitude of disutility based on assumption), and for the duration of the adverse event of febrile neutropenia[2]. The durations of these disutilities are based on the average number of bed days associated with relevant inpatient Healthcare Resource Groups (HRG) obtained from 2007-8 NHS reference cost data[25].

Drug regimens and doses are based on company-sought expert opinion and costed using British National formulary (BNF) list prices[26], with the exception of plerixafor which is based on reported use in a CUP[10]. G-CSF is assumed to be provided as Neupogen®[2]. No prophylactic anti-infective agents are considered in the model. Administration costs are guided by expert opinion and costed using published unit costs[2].

The costs of transplant procedures and febrile neutropenia are derived from inpatient HRGs in the 2007-8 NHS reference costs[25], using a weighted average approach. The costs of apheresis are based on an audit conducted in the UK[27]. In addition, all patients, irrespective of remobilisation treatment received and outcome, are assumed to receive routine care to include four visits with consultant per year throughout their lifetime[2].

7.3 Results

The model outputs suggest that plerixafor increases the probability of patients achieving successful remobilisation and subsequent transplant. The estimated incremental costs per QALY gained are presented in Table 1. Tables 2A and 2B, Appendix 2 provide additional model outputs, including the costs per successful mobilisation and the cost effectiveness of G-CSF plus cyclophosphamide compared against G-CSF alone. The company considers the comparison of G-CSF plus plerixafor against G-CSF plus cyclophosphamide to be the most relevant for this submission, as G-CSF alone is used infrequently in Wales[2].

Table 1. Base case analyses – G-CSF + Plerixafor versus G-CSF alone and G-CSF + cyclophosphamide[2]

	G-CSF + Plerixafor	G-CSF alone	G-CSF + cyclophosphamide
MM patients			
Total costs	£46,846	£29,248	£32,872
Total LYG	4.06	3.54	3.61
Total QALYs	2.32	1.88	1.94
ICER (£/QALY gained) for G-CSF + plerixafor		**£40,342**	**£36,794**
NHL patients			
Total costs	£52,425	£27,970	£32,425
Total LYG	4.35	2.41	2.65
Total QALYs	2.41	1.29	1.43
ICER (£/QALY gained) for G-CSF + plerixafor		**£21,823**	**£20,391**

Multiple one-way sensitivity analyses have been presented. In MM patients, the ICERs presented for G-CSF plus plerixafor versus G-CSF plus cyclophosphamide were in the range £21,068 to £47,746 per QALY gained, although the vast majority remained well above £30,000 per QALY gained. In NHL patients, the range was £14,665 to £30,094 per QALY gained[2]. For the key areas of uncertainty outlined above, the one-way sensitivity analyses reveal the following:

- For the probability of successful remobilisation with plerixafor: ICERs in MM patients ranged £41,714 to £34,436 per QALY gained when the probability of success ranged from 71.4% to 95%. ICERs in NHL patients ranged £24,944 to £19,485 when the probability of success ranged from 60.3% to 95%.
- For the mean number of days of apheresis with plerixafor: ICERs in MM patients ranged £22,044 to £45,292 per QALY gained and ICERs in NHL patients ranged £14,665 to £23,699 when the mean number of days ranged from one to 2.5

The company has provided additional sensitivity analyses to explore the combined impact of the uncertainty in these parameter values. Assuming the lowest successful remobilisation rates (71.4% for MM and 60.3% for NHL) and highest duration of apheresis (2.5 days), the ICER for MM increased to £52,806 per QALY gained and for NHL increased to £30,680 per QALY gained.

Other parameters to which the model is most sensitive include the costs of autologous transplants and the costs of treating the adverse event of febrile neutropenia.

Probabilistic sensitivity analyses (PSAs) have been conducted using distributions constructed around the central estimates of parameter values in the base case analysis, with results generated from 1,000 simulations. Visual inspection of the cost-effectiveness acceptability curves suggests the probability of G-CSF plus plerixafor being cost effective compared with G-CSF plus cyclophosphamide at a willingness to pay (WTP) threshold of £20,000/QALY is around 0% in patients with MM and around 55% in patients with NHL. At a WTP threshold of £30,000 per QALY, the probabilities are around 11% and 94%, respectively.

As the distributions used in the original PSAs did not capture the worst case scenarios of remobilisation rates and durations of apheresis noted in the CUPs, the company has provided additional analyses. Visual inspection of the new cost-effectiveness acceptability curves suggests the probability of G-CSF plus plerixafor being cost effective compared with G-CSF plus cyclophosphamide at a willingness to pay (WTP) threshold of £20,000/QALY is around 6% in patients with MM and around 55% in patients with NHL. At a WTP threshold of £30,000 per QALY, the probabilities are around 33% and 92%, respectively. The company notes that the median and range of ICERs for G-CSF plus plerixafor are lower than for G-CSF plus cyclophosphamide when each are compared with G-CSF alone. However, G-CSF alone is infrequently used for remobilisation of stem cells, and the source of the input data and the approach to adjusting the distributions for the PSAs limit the interpretation of these findings.

7.4 WMP critique of the company's economic evidence

It is not clear that the base case analyses presented in the company submission provide the most plausible point estimates of the cost effectiveness of plerixafor. The model is driven by efficacy data derived from small patient numbers, and small variations due to the play of chance could dramatically change the modelled outputs. Sensitivity analyses demonstrate that the use of alternative estimates of the key efficacy parameter values result in higher ICERs.

7.4.1 Strengths of the economic evidence provided in the company submission

These include:

- The modelled clinical pathway and comparators appear adequately representative of the decision problem
- In the absence of direct comparative evidence, extensive literature searches and reviews have been conducted to inform parameter value estimates
- Multiple one-way sensitivity and scenario analyses have been conducted to explore the impact of parameter value assumptions. These have been supplemented with additional multi-way and probabilistic sensitivity analyses.

7.4.2 Limitations of the economic evidence provided in the company submission

These include:

- The lack of robust, direct comparative efficacy data for plerixafor and the comparators to inform key parameter values
- The base case analyses employ efficacy data derived from small numbers of patients. A small change in the number of successful remobilisations due to chance could have a dramatic impact on the reported success rates and the mean duration of apheresis, and consequently the modelled outputs.
- CUP study reports[11,14] indicate a possible differential response to plerixafor treatment in patients with MM and NHL (successful remobilisation rates numerically greater in patients with MM compared with NHL), but the base case analyses assume equal efficacy across the two conditions. This may serve to favour NHL patients more than MM patients, and it is of note that the ICERs appear more favourable in patients with NHL compared with MM.
- The PSAs retain favourable central estimates for rates of successful remobilisation and duration of apheresis with plerixafor. Additional analyses have been provided to capture less favourable but plausible estimates of these parameter values, but the approach used limits the interpretation of the findings.
- The model only considers achievement of the minimum CD34+ cell counts required for autologous transplant. There is a lack of data with which to model the impact of actual CD34+ cell counts achieved with remobilisation treatment, and previous treatment histories[2].

7.5 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published evidence on the cost effectiveness of plerixafor.

8.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

8.1 Methods

The company submission reports that, based on BSBMT Registry data, 51 patients in Wales with MM (32 patients) and NHL (19 patients) received autologous transplants in 2008, and there has been relatively little variation over the previous four years[2]. Based on a retrospective analysis of US patient records[15], it is estimated that 19% of patients will have previously failed to mobilise sufficient stem cells on their first attempt, which would potentially increase the population for initial first stem cell mobilisation. The resultant number of patients estimated to be failed mobilisers each year in Wales is, therefore, 12 (51 x 1.19 x 0.19). This is assumed to remain constant each year[2].

The net budget impact estimates provided by the company relate only to the drug acquisition costs and the costs of autologous transplants. The direct drug costs for G-CSF, cyclophosphamide and plerixafor are based on the same assumptions as used in economic model for the base case analyses (see section 7). Current remobilisation practice in Wales is assumed to be undertaken with G-CSF plus cyclophosphamide in 95% of cases and G-CSF alone in 5% of cases. It is further assumed that, of the 12 patients estimated to undergo remobilisation therapy each year, only three would progress to autologous transplant and all of these would have received G-CSF plus cyclophosphamide (in line with the rates of successful remobilisation and subsequent transplantation assumed for these regimens in the economic model).

It is assumed that uptake of plerixafor would be 100%, i.e. all 12 eligible patients would undergo remobilisation therapy with G-CSF plus plerixafor. It is further assumed that 10 of these 12 patients would proceed to autologous transplant (in line with the economic model, which assumed that 85% of recipients achieve successful remobilisation and all of these proceed to transplant)[2]. The costs of transplant are as included in the economic model.

8.2 Results

The annual budget impact estimate included in the company submission is summarised in Table 2. This relates to 100% uptake of plerixafor in the relevant population and is assumed to be the same in each of the next five years. No further scenario or sensitivity analyses have been provided.

Table 2. Annual budget impact estimate for each of the next 5 years

	Current practice — 95% G-CSF + cyclophosphamide, 5% G-CSF alone	Plerixafor — 100% G-CSF + plerixafor	Net additional cost per year
Number of eligible patients	12		
Drug costs	£17,550	£131,963	£114,414
Transplant costs	£50,064	£166,880	£116,816
Total costs	£67,614	£298,843	**£231,230**

8.3 Critique

The budget impact estimates rely on a range of assumptions that warrant caution in their interpretation.

Strengths of the analysis include its use of up-to-date estimates of the annual incidence of autologous transplants in the relevant population. However, the uncertainties as outlined for the economic model discussed in section 7 regarding the assumed plerixafor efficacy and treatment duration (and hence costs), and transplant procedural costs, feed through to the budget impact analysis. Other limitations include the lack of consideration of administration costs and the costs of adverse events, which in the economic model are lower with G-CSF plus plerixafor than with G-CSF plus cyclophosphamide.

8.4 Comparative unit costs

Table 3 provides example costs for the plerixafor and comparator regimens. These are based on the assumptions employed in the company's economic analysis[2]. In practice, drug doses and treatment durations would be based on patients' characteristics and their response to their remobilisation regimens.

Table 3. Example comparator costs

Regimen	Example doses*	Approximate cost[2]
G-CSF + plerixafor	G-CSF at 10micrograms/kg/day for 4 days prior to apheresis and for 2 days during apheresis plus Plerixafor 240micrograms/kg.day for 2 days during apheresis	£10,997 (of which £9,766 is plerixafor)
G-CSF + cyclophosphamide	G-CSF at 10micrograms/kg/day for 5 days prior to apheresis and for 2 days during apheresis plus cyclophosphamide at a total dose of 2.88g/m^2	£1,465
G-CSF alone	G-CSF at 10micrograms/kg/day for 4 days prior to apheresis and for 3 days during apheresis	£1,437

This table does not imply therapeutic equivalence of the regimens and doses
*Based on patient weighing 70kg with body surface area 1.7m^2
G-CSF assumed to be Neupogen®

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements

- 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 monitoring of haematopoietic progenitor cells can be correctly performed[1].
- Plerixafor (Mozobil®▼) should be initiated and supervised by specialists and would not be deemed suitable for shared care.

9.2 Previous NICE advice

- National Institute for Clinical Excellence (NICE) Guidance on Cancer Services - Improving Outcomes in Haematological Cancers - The Manual. 2006[4]. See section 3.3.

9.3 Ongoing studies

- Additional information was provided by the company which remains confidential.

9.4 Other information

- CHMP have requested that tumour cell mobilisation specifically in poor mobilisers will be addressed by the company by evaluation of progression free survival (as well as other long-term outcomes) by use of a registry[10]. The proposed plan is therefore to demonstrate the safety of Mobozil®▼ to mobilise stem cells in poor mobilisers with lymphoma or MM.
- Three patient organisation submissions were made by Leukaemia Care, Lymphoma Association, and Myeloma UK.
- Medical expert views were provided.

GLOSSARY

Apheresis[28]: removal, to take away

R-ICE comprises[2]:

- Rituxan (MabThera) = 500mg per pack, daily dose of 375mg/m^2 given for 1 day per cycle
- Ifosfamide (Mitoxana) = 2000mg per pack, daily dose of 5000mg/m^2 given IV for 1 day per cycle
- MESNA (Uromitexan) = 1000mg per pack, daily dose of 5000mg/m^2 given IV for 1 day per cycle and 1000/m2 given IV for 4 days
- Carboplatin = 600mg per pack, daily dose of 800mg given for 1 day per cycle
- Etoposide = 500mg per pack, daily dose of 100mg/m2 given IV for 3 days per cycle
- Neupogen = 300µg/mL per 1mL vial, daily dose of 5µg/kg given for 6 days per cycle

Bortezomib: 3.5 mg per vial with no fractional doses allowed

- Daily dose of 1.3mg/m^2 given IV twice weekly for 2 weeks (Days 1, 4, 8 and 11) followed by a 10-day rest period (Days 12 -21)
- In combination with Oral Dexamethasone - 20mg/day given for 8 times over 21 days

National Comprehensive Cancer Network (NCCN) Evidence and Consensus (Category 1)[4]:
The recommendation is based on high-level evidence (e.g. randomised controlled trials) and there is uniform NCCN consensus.

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Appendix 1. Additional Clinical Information

Table 1. Compassionate Use Programme (CUP) studies supporting the use of plerixafor (Mozobil®▼)

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
Fowler CJ et al. [12]	Multi-centre, open-label study USA	20 NB: A total of **16** patients had either MM or NHL.	**Inclusion criteria:** Identified as benefiting from auto-SCT but had failed to collect enough CD34+ cells with conventional mobilisation or, in the opinion of the physician, would not collect enough PBSCs on the basis of peripheral CD34+ cell measurements after standard mobilisation. Target was for patients to proceed to mobilisation on the CUP no sooner than two weeks and no later than four weeks after the determination that they would not collect sufficient PBSCs.	Multiple myeloma: n=6 Non-Hodgkin's lymphoma: n=10. AILD: n=1 Hodgkin's disease: n=2 Amyloidosis: n=1 Female: n=5 Male: n=15 Median age : 58 yrs (range:35 to 71yrs) Median prior mobilisation regimens: 2 (range 0 to 8)	G-CSF 10 mcg/kg (SC) for 4 days plus plerixafor 240 mcg/kg (SC) on the fourth day (10-11 hours prior to apheresis). G-CSF 10 mcg/kg (SC) was administered on day 5; followed by apheresis. This regimen of G-CSF, plerixafor and apheresis was continued on a daily basis until the patient collected ≥ 2.0 X 10^6 CD34+ cells/kg.	**Results (n=20): Primary end point?** Patients achieving ≥2.0 x 10^6 CD34+ cells/kg: 85% (17/20) **Other Outcomes:** **Median CD34+ cells collected (n=20):** Previous chemotherapy-mobilized patients: 4.0 (range 2.5-6.2) x 10^6 /kg in 2 (range 1-3) days Previous G-CSF only mobilised patients: 3.7 (range 2.0-7.9) x 10^6/kg in 2 (range 2-3) days. **Transplant achieved:** 13/16 patients (9/10 NHL and 4/6 MM) **Median time to neutrophil engraftment:** 14 days (range 10-21) **Median time to PLT engraftment:** 25 days (range 13-38)
Calandra et al. [11]	Multi-centre, open-label study USA, Canada	115 NB: A total of **98** patients had either MM or NHL.	**Inclusion criteria:** ▪ Aged 18 to 70 yrs* ▪ Ability to undergo transplant ▪ WBC count >3.0 x 10^9 per litre* ▪ ANC >1.5 x 10^9 per litre* ▪ PLT count >100 x 10^9 per litre* ▪ Serum creatinine ≤1.5mg/dL* ▪ LFT within 2 x ULN ▪ ECOG performance status = 0 or 1 ▪ Negative HIV test ▪ FEV >60% of predicted; CO diffusing capacity ≥45%; LVEF >45% *later broadened to allow additional patients onto the study **Exclusion criteria:** ▪ Brain metastases ▪ Acute infection, or Hepatitis B or C ▪ Hypercalcaemia (>1mg/dL above ULN) ▪ Pregnancy	Multiple myeloma: n=35 Female:14,Male:21 Median age = 61yrs Non-Hodgkin's lymphoma n=63 Female:25,Male:38 Median age = 601yrs Hodgkin's disease n=17 Female:8, Male:9 Median age = 40yrs Median prior mobilisation regimens: 2	The same treatment regimen was used as above. The G-CSF dose administered was 10mcg/kg for the majority of patients with a range of 5-16 mcg/kg and a median dose of 10.2 mcg/kg.	**Primary endpoint (n=98):** Patients achieving ≥2.0 x 10^6 CD34+ cells/kg: NHL: 60.3% (38/63); MM: 71.4% (25/35) **Other Outcomes:** **Success rates (≥2.0 X10^6 CD34+ cells/kg):** Patients previously failed chemotherapy mobilisation: NHL (65.5%): MM (75%) Patients previously failed chemokine mobilisation: NHL (55.9%): MM (63.6%) **Transplant achieved:** 73.5% (72/98 patients) (45/63 NHL and 27/35 MM) **Number receiving cells mobilised with only plerixafor plus G-CSF who proceeded to transplant:** 40 (21 NHL; 19 MM). Remaining 32 (24 NHL; 8 MM) received cells mobilised by plerixafor plus G-CSF but pooled from other mobilisations. **Median time to neutrophil engraftment:** NHL: 11 days; MM 11 days **Median time to PLT engraftment:** NHL: 18 days; MM: 21 days **Graft durability up to 12 months** (n=36 [23 NHL and 6 MM]): 34/36 met the definition of graft durability i.e. ANC >1.0 x10^9 /litre and PLTs >20 x10^9/litre.

Table 1 Continued.

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
Gordon et al.[13] (Poster)	Open-label Scotland	20	All had at least one previous attempt at PBSC mobilisation which failed or resulted in an insufficient cell dose for transplant. Two patients had two attempts.	Multiple Myeloma: n=12 Lymphoma: n=8 Median age 59 yrs; (range 34 yrs to 67 yrs) Six patients had a pre-existing dose of CD34+ cells from previous collections (range: 0.98-2.32 x 10^6/kg; median 1.38).	G-CSF 10 mcg/kg sc for 4 days plus plerixafor 240 mcg/kg (SC) on the fourth day (11 hours prior to apheresis). G-CSF 10mcg/kg was administered (SC) on day 5; followed by apheresis. All patients were administered this regimen apart from one patient with dialysis dependent renal failure who received a reduced dose of 160 mcg/kg plerixafor. This regimen of G-CSF, plerixafor and apheresis was continued until the patients collected ≥ 2.0 x 10^6 CD34+ cells /kg.	**Primary endpoint:** Patients who mobilised a transplantable PBSC dose of >2.5 x 10^6 CD34+ cells/kg after a median of two apheresis procedures: 95% (19/20) **Other Outcomes:** **Total number of apheresis procedures undergone to achieve a transplantable dose:** 1 (= 5); 2 (n=8); 3 (n=3); 4 (n=3) **Transplant achieved:** 10 patients had under gone transplant at the time of the poster presentation **Median time to neutrophil engraftment:** 13.5 days (>0.5 x 10^6/L); 15 days (>1.0 x 10^6/L) **Median time to PLT engraftment**: 24 days (>50 x 10^6/L) but not yet reached by one patient; 26.5 days (>100 x 10^6/L) but not yet reached by two patients
Shaunessy et al.[14] (Abstract)	Open-label USA	286 NB: A total of **251** patients had either MM or NHL.	Patients had documented failure to harvest adequate CD34+ cells (≥2.0 x 10^6/kg) with prior chemomobilisation or inability to achieve ≥10 CD34+ cells/ microlitre without having undergone apheresis.	Multiple myeloma: n=87 Non-Hodgkin's lymphoma: n=164 Hodgkin's disease: n=35 Median age: 54.9± 13.4 yrs	G-CSF 10 mcg/kg (SC) for 4 days plus plerixafor 240 mcg/kg (SC) on the evening of day 4. G-CSF 10mcg/kg was administered (SC) on day 5; followed by apheresis. This regimen of G-CSF, plerixafor and apheresis was continued until the patients collected ≥ 2.0 x 10^6 CD34+ cells /kg.	**Primary endpoint:** Patients achieving ≥2.0 X10^6 CD34+ cells/kg: NHL: 67.1%; MM: 81.0% **Other Outcomes:** **Proceeded to transplant:** NHL: 65.2% MM: 65.5% **Median time to neutrophil engraftment:** NHL: 11 days; MM: 12 days **Median time to PLT engraftment**: NHL: 21 days; MM: 21 days

AILD: Angioimmunoblastic lymphadenopathy with dysproteinaemia; ASCT: Autologous stem cell transplantation; CUP: Compassionate-Use protocol; ECOG: Eastern Cooperative Oncology Group; FEV: Forced Expiratory Volume; kg: kilogram; G-CSF: Granulocyte colony stimulating factor; LVEF: Left Ventricle Ejection Fraction; mcg: micrograms; mcg: micrograms; MM: Multiple Myeloma; NHL: Non-Hodgkin's Disease; PBSC: Peripheral Blood Stem Cells; SC: subcutaneously; SCT: Stem Cell Transplant; ULN: upper limit of normal; WBC: white blood cell; ANC: Absolute Neutrophil Count; PLT: platelet

Appendix 2. Additional Health Economic Model Information

Table 2A. Health economic model detail[2]

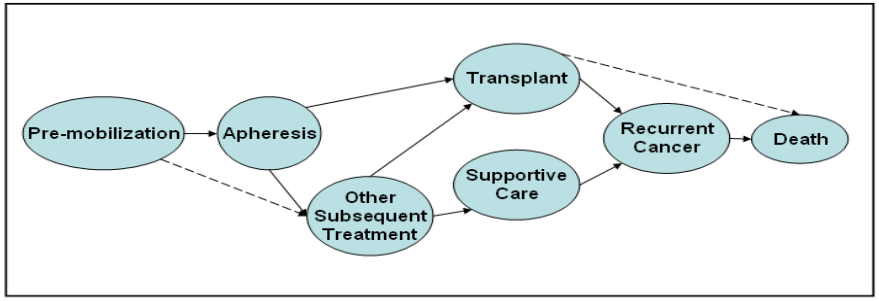
Base Case Model		Appropriate?
Comparator(s)	G-CSF plus plerixafor compared against: G-CSF alone and G-CSF plus cyclophosphamide chemotherapy	Yes – as requested by WMP
Population	Simulated cohort of patients with MM or NHL, eligible for stem cell transplant and previously failed haematopoietic stem cell mobilisation. Assumed body surface area 1.7m^2 and mass 70kg.	Yes – population meets licensed indication
Model type and description	State transition model, summarised as:  	Yes, but the model only permits one attempt at apheresis and autologous peripheral blood stem cell transplant. Once a patient leaves a health state it is not possible to return to that health state.
Perspective	Considers direct medical costs only, from perspective of NHS Wales	Yes
Time Horizon	Lifetime	Yes
Discount rate	3.5% per annum (rates of 0% and 6% explored in sensitivity analyses)	Yes
Efficacy	Retrospective data from compassionate use programmes and chart reviews, supplemented by expert opinion. No relevant clinical trial data available.	Yes - but the data used in the base case analysis based on small patient numbers and so prone to effects of chance (see sections 8.2 and 8.4)
Adverse effects	Only rates of febrile neutropenia associated with chemotherapy included in model.	Model does not consider diarrhoea, which may be severe and occurs very commonly with plerixafor treatment
Utility values	Obtained from structured literature review.	Yes in the absence of other sources
Resource use	Based on assumptions and expert opinion.	Yes in the absence of trial derived resource use
Costs	Based mainly on published unit costs and BNF	Yes
Model Provided?	Yes	Yes
Other considerations	Plerixafor has orphan drug status and the number of patients estimated by the company to meet the sub-section of the licensed indication each year is 12. On this basis, plerixafor appears to meet the AWMSG criteria for ultra-orphan drug status.	

Table 2B. Model outputs as presented in the company submission for MM patients[2]

	Results for each Mobilisation Treatment Regimen			Incremental Results		
	G Alone	G + C	G + P	G+P vs. G Alone	G+P vs. G+C	G+C vs. G Alone
Mobilisation						
Cost	£4,331	£6,846	£12,834	£8,503	£5,988	£2,516
No. of successful mobilisations	**0.18**	**0.27**	**0.85**	**0.67**	**0.59**	**0.08**
Average cost per successful mobilisation	**£23,536**	**£25,835**	**£15,099**	-----		
Lifetime						
Cost	£29,248	£32,872	£46,864	£17,616	£13,992	£3,624
LY	3.54	3.61	4.06	0.51	0.44	0.07
QALY	1.88	1.94	2.32	0.44	0.38	0.06
Cost-effectiveness results						
Cost per successful mobilisation gained				**£12,768**	**£10,235**	**£31,058**
Cost per LY gained				£34,364	£31,475	£53,231
Cost per QALY gained				£40,342	**£36,794**	£64,277

Table 2C. Model outputs as presented in the company submission for NHL patients[2]

	Results for each Mobilisation Treatment Regimen			Incremental Results		
	G Alone	G + C	G + P	G+P vs. G Alone	G+P vs. G+C	G+C vs. G Alone
Mobilisation						
Cost	£4,331	£6,846	£12,834	£8,503	£5988	£2,516
No. of successful mobilisations	**0.18**	**0.27**	**0.85**	**0.67**	**0.59**	**0.08**
Average cost per successful mobilisation	**£23,536**	**£25,835**	**£15,099**	-----		
Lifetime						
Cost	£27,970	£32,425	£52,425	£24,455	£19,999	£4,455
LY	2.41	2.65	4.35	1.94	1.70	0.24
QALY	1.29	1.43	2.41	1.12	0.98	0.14
Cost-effectiveness results						
Cost per successful mobilisation gained				**£12,768**	**£10,235**	**£31,058**
Cost per LY gained				£12,611	£11,781	£18,444
Cost per QALY gained				£21,823	**£20,391**	£31,872