Scottish Medicines Consortium

Re-Submission

pegylated liposomal doxorubicin, 2mg/ml concentrate for solution for infusion (Caelyx®) No. (503/08)

Schering Plough

05 June 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 re-submission

pegylated liposomal doxorubicin (Caelyx®) is not recommended for use within NHS Scotland in combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.

Results from an interim analysis showed that pegylated liposomal doxorubicin plus bortezomib significantly increased the time to disease progression compared to bortezomib monotherapy. At the time of the interim analysis only 31% of patients in the combination arm had reached the primary endpoint.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Pegylated liposomal doxorubicin in combination with bortezomib is indicated for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.

Dosing information

Pegylated liposomal doxorubicin 30mg/m² as a one hour intravenous (iv) infusion on day 4 plus bortezomib 1.3mg/m² as an iv bolus on days 1, 4, 8, and 11. Regimen repeated every three weeks.

The dose should be repeated as long as patients respond satisfactorily and tolerate treatment. Day four dosing of both medicinal products may be delayed up to 48 hours as medically necessary. Doses of bortezomib should be at least 72 hours apart.

Pegylated liposomal doxorubicin should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic agents

Product availability date

Licence extension approved September 2008

Summary of evidence on comparative efficacy

Doxorubicin, a cytotoxic anthracycline antibiotic, has a number of mechanisms of action, including the formation of covalent topoisomerase-DNA complexes, interference with the function of topoisomerase II, acting as a DNA intercalator and generation of free radical intermediates. Bortezomib is a reversible inhibitor of the 26S proteasome which prevents targeted proteolysis and affects signaling cascades. This inhibition is thought to interfere with the mechanisms malignant cells use to inhibit the effect of chemotherapy, thus helping overcome chemo-resistance. Preclinical studies suggest bortezomib may enhance the activity of doxorubicin.

In a randomised open label study, 646 patients with multiple myeloma, whose disease had progressed after at least one prior therapy or was refractory to initial treatment, were assigned to either combination therapy with bortezomib (1.3mg/m² iv bolus on days 1, 4, 8, and 11) plus pegylated liposomal doxorubicin (30mg/m² iv infusion on day 4) given every three weeks (n=324) or monotherapy with bortezomib (1.3mg/m² on days 1, 4, 8, and 11) every three weeks (n=322). Randomisation was stratified by β_2-microglobulin level (≤2.5 mg/L, >2.5 - ≤5.5mg/L and >5.5mg/L).

The primary endpoint was the time to progression (TTP), defined as the interval between the date of randomisation and the date of disease progression or death due to progression, in the intention to treat (ITT) population. The median TTP was estimated using a Kaplan-Meier plot, and a 95% confidence interval (CI) was computed. Subjects who died without documented disease progression were censored at the date of their last evaluation. Secondary endpoints included overall survival (OS), estimated using the Kaplan-Meier method. An interim analysis and final analysis were planned when 230 and 460 events were observed. The TTP efficacy statistical boundary was set at p=0.003 and p=0.048, for the interim and final analyses, respectively. Patients were treated with permitted supportive therapy as necessary. Treatment continued until disease progression or unacceptable treatment-related toxicity, up to a total of eight cycles. Dose adjustments were permitted.

The interim analysis was performed after 249 events, with a median follow up of 3.9 months, a median of five cycles received and median duration of treatment of approximately 105 days. At the interim analysis, 47% (n=150/322) of patients in the bortezomib group and 31% (n=99/324) of patients in the pegylated liposomal doxorubicin/bortezomib group had progressed or died. The primary outcome, estimated median TTP, was significantly longer with pegylated liposomal doxorubicin/bortezomib treatment (9.3 months) than with bortezomib monotherapy (6.5 months). This represented a 45% reduction in risk of progression in patients treated with the combination. The hazard ratio (HR) for the difference between treatments was 1.82 (95% CI: 1.41 to 2.35). Subgroup analysis showed pegylated liposomal doxorubicin/bortezomib significantly improved TTP compared to bortezomib monotherapy regardless of the patients' baseline characteristics. As the statistical boundary for the primary endpoint was achieved by the interim analysis, a study amendment allowed patients treated with bortezomib alone to crossover to the combination therapy group.

The US Food and Drug Administration (FDA) requested further analyses of TTP and OS. After another six months of follow up and at 407 events (184 (57%) in the pegylated liposomal doxorubicin/bortezomib group and 223 (69%) in the bortezomib group), the median TTP was 8.9 months in the pegylated liposomal doxorubicin/bortezomib group and 6.9 months in the bortezomib group, a significant difference; HR 1.55 (95% CI: 1.27 to 1.89).

At the interim analysis, 28 (9%) patients in the combination therapy and 39 (12%) in the monotherapy group had died, representing a 32% reduction in risk of death for patients treated with pegylated liposomal doxorubicin/bortezomib; HR 1.48 (95% CI: 0.91 to 2.41). At the FDA requested analysis at a median follow up of 11 months, 58 (18%) patients in the pegylated liposomal doxorubicin/bortezomib group and 81 (25%) in the bortezomib group had died, a 29% risk reduction of death; HR 1.41 (95% CI:1.0 to 1.97). Subsequently, the Committee for Medical Products for Human Use (CHMP) requested a further additional analysis of OS. With a median follow up of 18 months, there had been a further 67 deaths, 38 (total = 96 [30%]) in the combination arm and 29 (total = 110 [34%]) in the bortezomib group, giving a 14% reduction in the risk of death.

Summary of evidence on comparative safety

The adverse events observed with the pegylated liposomal doxorubicin/bortezomib combination were consistent with the known safety profiles of both agents. No unexpected safety concerns were observed.

The incidence of serious adverse events was similar in the two treatment groups. However, in the combination group grade 3 or 4 adverse events were more frequent (80% versus 64%). In addition, neutropenia (all grades: 35% versus 20% and grade 3/4: 29% versus 15%) and stomatitis (all grades: 18% versus 3%) were more frequent in the combination group. Hand-foot syndrome only occurred in the combination group (16%) and led to discontinuation of pegylated liposomal doxorubicin in 5% of patients. The incidence of all cardiac adverse events was low and similar between the two treatment groups.

The number of patients who withdrew from the study due to adverse events was 66/322 (20%) in the bortezomib group and 86/234 (27%) in the pegylated liposomal doxorubicin/bortezomib group.

Summary of clinical effectiveness issues

Results from an interim analysis showed that pegylated liposomal doxorubicin/bortezomib combination therapy significantly improved TTP compared with bortezomib monotherapy (HR 1.82) in patients with multiple myeloma who had received at least one prior therapy and who had already undergone or were unsuitable for bone marrow transplant. The study was terminated when only 31% of patients in the combination group had reached the primary endpoint and consequently the FDA requested a further analysis after another six months of follow up. In this analysis, 57% of patients in the combination group had reached the primary endpoint and these results also showed a significant advantage for the combination therapy despite cross-over from the monotherapy group.

The more clinically relevant outcome of OS, a secondary outcome in the study, was estimated using a Kaplan Meier plot. At the interim analysis, only a small percentage of patients had died. The OS results at 18 months follow up were confounded by the termination of the study, the cross-over of patients and the 65% of patients who had progressed and were treated with subsequent therapies. The reduction of risk of death when treated with the combination therapy fell from 32% (HR 1.48) at a median of 3.9 months follow up (interim analysis) to 29% (HR 1.41) at 11 months follow up (FDA analysis) and to 14% at 18 months follow up (CHMP analysis). Only at the time of the FDA analysis did the benefit in mortality approach significance. The CHMP concluded that: "while a benefit on overall survival cannot be considered to have definitively been established, it is strongly suggested, and there is certainly no suggestion of a detrimental effect. The Kaplan-Meier curves show separation of the curves, favouring the combination therapy".

There are a number of issues that might affect the generalisability of the results to the Scottish population. The comparator, bortezomib, used in the study may not reflect Scottish practice for the treatment of multiple myeloma at first relapse due to recent SMC decisions. Current treatments in multiple myeloma are varied, with the use of off-label drugs and combinations, and therefore the place of the pegylated liposomal doxorubicin/bortezomib combination in practice is difficult to assess. The patient population in the study was young for this indication, with the overall median age 61 years. The median age presenting with multiple myeloma is estimated to be 70 years. They were also a fit population with Eastern Cooperative Oncology Group (ECOG) performance status of either 0 (44%) or 1(56%).

The open nature of the study may have biased the reporting of adverse event rates and possibly response rates and although quality of life data was recorded (although not yet reported) due to the open study design its usefulness is expected to be limited.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing pegylated liposomal doxorubicin/bortezomib to treatment with bortezomib monotherapy and treatment with high dose dexamethasone (HDD) in patients with multiple myeloma who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant. Direct comparative study data were available for the comparison with bortezomib monotherapy but an indirect comparison was necessary for the comparison with HDD. An area under the curve approach was used to model the data beyond the end of the clinical study periods over a 10 year time horizon. The cost of managing multiple myeloma patients was estimated to be £470 per month based on a study from the literature and this cost was applied to all treatments. A utility value of 0.81 was used for the period prior to progression

and 0.64 after progression. These values were obtained from a study which measured utility values of patients with multiple myeloma directly using EQ-5D.

In the base case analysis the manufacturer estimated a cost per QALY of £17,303 compared to bortezomib monotherapy based on an increased cost of £11,581 and a QALY gain of 0.67. For the HDD analysis the manufacturer estimated a cost per QALY of £28,329 based on an increased cost of £31,588 and a QALY gain of 1.12.

The main weaknesses of the economic analysis were as follows:

- The comparators used may not be appropriate. Bortezomib monotherapy is not recommended by SMC for 2nd line use, but is used in some patients in combination with dexamethasone in practice. Thalidomide in combination with other therapies, such as cyclophosphamide and dexamethasone, is also used in some patients. HDD does not appear to be widely used, but given the lack of a clear licensed comparator which reflects current practice, it would be difficult to criticise the choice of HDD. However, it should be noted that neither comparator reflects Scottish practice particularly well.
- The difference in overall survival between treatments did not reach statistical significance in the clinical study. The modelling suggested a 10-year survival of around 28% for patients receiving the doxorubicin/bortezomib combination, a figure which seems very high given the likely age of patients in Scotland and the progression of disease in 85% after just 18 months. Additional sensitivity analysis was provided which assumed there was no difference in overall survival between the treatment arms of the model. This increased the ICERs to £127,904 and £52,916 per QALY for the comparisons with bortezomib monotherapy and HDD respectively.
- There was a lack of transparency in relation to the drug administration costs applied in the model. The manufacturer provided clarification which indicated that an administration cost of £100 per cycle of bortezomib had been included in the model in error, instead of £100 per dose. The updated base case analysis results using the correct administration costs were £17,677 and £29,899 per QALY for the bortezomib and HDD comparisons respectively.

Other weaknesses included: using a mean number of cycles of bortezomib of 5.3, when 6 cycles may be more appropriate based on the National Institute for Health and Clinical Excellence bortezomib monotherapy Single Technology Appraisal (sensitivity analysis showed that using 6 cycles increased the ICER versus HDD to £32k); a fairly simple indirect comparison with HDD which had some weaknesses such as the HDD dose used in the study may be lower than used in practice; probabilistic sensitivity analysis which highlighted the considerable uncertainty in the model with only a 35% probability that the combination therapy would be cost-effective compared with bortezomib monotherapy at a willingness-to-pay threshold of £30k.

Due to the weaknesses outlined above and the general uncertainty in the model, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

Patient Interest Group Submission: Myeloma UK.

Additional information: guidelines and protocols

Guidelines on the diagnosis and management of multiple myeloma 2005, published by the British Committee for Standards in Haematology (BCSH). These guidelines recommended that the most appropriate management must be determined on an individual basis depending on age, prior therapy and clinical condition.

Additional information: comparators

There are a variety of treatment options for patients who relapse after initial treatment. Choice of treatment is influenced by the age and performance status of the patient, length of response to previous therapy, relapse after response versus primary refractory disease and initial course of disease management.

Induction of remission with intensive chemotherapy such as CVAD (cyclophosphamide/ vincristine/doxorubicin/dexamethasone) is followed by consolidation with high dose melphalan then bone marrow transplant or less aggressive treatment with regimens such as oral melphalan plus prednisolone or cyclophosphamide.

Bortezomib as monotherapy has been accepted for use by SMC in patients who have received at least two prior therapies but not for patients who have received only one. However, experts advise that bortezomib is often used after a first relapse in an unlicensed combination with dexamethasone.

Thalidomide is frequently used in combination with cyclophosphamide and dexamethasone (CTD) after a first relapse, although this is an unlicensed use.

Cost of relevant comparators

Drug	Dose regimen	Length of cycle	Cost per cycle (£)
Pegylated liposomal doxorubicin **Bortezomib**	**30mg/m^2 iv on day 4** **1.3mg/m^2 iv on days 1, 4, 8, 11**	**21 days**	**4167**
Lenalidomide Dexamethasone	25mg orally on days 1-21 40mg orally on days 1-4, 9-12, 17-20	28 days	4382
Bortezomib Dexamethasone	1.3mg/m^2 iv on days 1,4,8,11 20mg orally on days 1,2,4,5,8,9,11,12	21 days	3054
Bortezomib	1.3mg/m^2 iv on days 1,4,8,11	21 days	3050
Cyclophosphamide[A] Thalidomide Dexamethasone	500mg orally on days 1,8,15,22 200mg orally daily 20mg orally on days 1-4 and 15-18	28 days	1203
Cyclophosphamide[B] Thalidomide Dexamethasone	500mg orally on days 1,8,15 200mg orally daily 40mg orally on days 1-4 and 12-15	21 days	908

Cyclophosphamide[C] Vincristine Doxorubicin Dexamethasone	500mg orally or iv on days 1,8,15 0.4mg iv on days 1-4 9mg/m^2 iv on days 1-4 40mg orally on days 1-4 and 12-15	21 days	206 to 216
Vincristine[D] Doxorubicin Dexamethasone	0.4mg iv on days 1-4 9mg/m^2 iv on days 1-4 40mg orally on days 1-4 and 12-15	21 days	203
Dexamethasone[E]	40mg orally on days 1-4, 9-12, 17-20	28 to 35 days	14
Melphalan Prednisolone	7mg/m^2 orally on days 1-4 40mg orally on days 1-4	28 days	14
Cyclophosphamide	300-500mg/m^2 orally or iv weekly	21 to 28 days	3 to 31

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 25 March 2009 and BNF 57 (March 2009). iv = intravenous; A = attenuated CTD regimen; B = CTD regimen; C = CVAD regimen; D = VAD regimen; E = high dose dexamethasone regimen; costs based on a body surface area of 1.8m^2. Regimens based on Medical Research Council Myeloma IX protocol and advice from Scottish haemato-oncologists.

Additional information: budget impact

The manufacturer estimated a net budget impact of £130k in year 1 rising to £394k in year 5. The manufacturer assumed that the combination therapy would displace HDD and the net budget impact includes resource savings. The number of patients estimated to receive treatment with the combination therapy was 24 in year 1 rising to 69 in year 5, which equates to a market share of 26% in year 1 rising to 73% in year 5. The gross drug budget impact was estimated to be £558k in year 1 rising to £1.4m in year 5.

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 15 May 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.

Orlowski RZ, Nagler A, Sonneveld P et al. Randomised phase lll study of pegylated liposomal doxorubin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma:combination therapy improves time to progression. J Clin Oncol 2007:25;3892-3901

The European Medicines Agency (EMEA) European Public Assessment Report. Pegylated liposomal doxorubicin (Caelyx®). 15/11/2007. EMEA/H/C/000089/II/0045 http://www.emea.europa.eu/