Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

bendamustine hydrochloride 25mg, 100mg powder for solution for infusion (Levact®) SMC No. (694/11)

Napp Pharmaceuticals Limited

04 March 2011

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

bendamustine hydrochloride (Levact®) is accepted for use within NHS Scotland.

Indication under review: first-line treatment of chronic lymphocytic leukaemia (CLL) (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

Bendamustine showed significantly improved response rates and progression free survival when compared with another alkylating agent in patients with previously untreated advanced CLL, although the patients studied may have been younger and fitter than those eligible to receive bendamustine in Scottish clinical practice.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

Dosing Information

Bendamustine hydrochloride 100mg/m² body surface area as an intravenous (iv) infusion over 30 to 60 minutes on days 1 and 2; every 4 weeks.

Infusions must be administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.

Product availability date

1 September 2010

Summary of evidence on comparative efficacy

Chronic lymphocytic leukaemia (CLL) is incurable and treatment aims to improve progression-free survival (PFS), by inducing as deep a remission as possible, and to improve quality of life. Bendamustine hydrochloride (hereafter referred to as bendamustine) is an alkylating agent that has demonstrated different anti-tumour activity in vitro from other alkylating drugs.

Evidence supporting the licence is from a phase III randomised, open-label study in treatment-naïve patients with advanced symptomatic CLL (Binet stage B [≥ 3 lymph node regions involved including hepatomegaly and splenomegaly] or stage C [anaemia and/or thrombocytopenia regardless of the number of lymph node regions]). Patients were aged less than 75 years, had World Health Organisation (WHO) performance status (PS) 0 to 2 and a life expectancy ≥ 3 months. Need to treat criteria included haematopoietic insufficiency with non-haemolysis-induced haemoglobin < 10 g/dL and/or thrombocytopenia <100 x 10^9/L and/or B symptoms defined as: unexplained > 20% weight loss in the last 6 months; persistent or recurrent fever of unknown origin > 38°C; night sweats and/or rapidly progressive disease and/or risk of organ complications from bulky lymphomas.

A total of 319 patients were randomised in a 1:1 ratio, stratified by centre and Binet stage, to receive bendamustine or chlorambucil in 4-week cycles for a maximum of six cycles. Bendamustine 100mg/m^2 was infused intravenously over 30 minutes on days 1 and 2. Chlorambucil was administered orally, 0.8mg/kg using Broca's normal weight in kg (body weight calculated as patient height in cm minus 100) on days 1 and 15 (or as divided doses on days 1 to 2 and 15 to 16 in some individual patients for patient comfort). Dose modification was permitted according to National Cancer Institute Working Group (NCIWG) guidelines for haematologic toxicity or according to investigator judgement for non-haematologic toxicity. Hyperuricaemia prophylaxis was recommended to prevent uric acid-induced nephropathy. No other anti-cancer drugs were permitted. The drop out rate was higher in those receiving bendamustine compared with chlorambucil, 25% versus 19%, respectively.

There were two primary outcomes, reported at 35 months (median observation time): overall response rate (ORR) and PFS that were evaluated in the intention to treat (ITT) population.

Response was assessed after three cycles according to NCIWG guidelines for CLL and had to be maintained for at least 8 weeks. Patients with complete response (CR) or partial response (PR) could have two or three additional cycles of treatment. Patients with no change could have additional cycles of treatment at the investigator's discretion. Patients whose disease had progressed were withdrawn from the study. After treatment ended, follow-up occurred every 3 months for response and survival outcomes. The final assessment of best response was carried out by a blinded independent committee. Patients were classified as non-responders if PR or CR was not confirmed or if their tumour response was not evaluable. Patients who were alive without progression at the time of the final analysis were right censored and entered into the analysis with time from randomisation to the last date at which occurrence of progressive disease or relapse could be excluded by tumour evaluation.

Significantly more patients receiving bendamustine compared with chlorambucil responded, 68% (110/162) versus 31% (48/157), respectively, relative risk 2.22, (95% confidence interval [CI] 1.76 to 2.81). Patients in the bendamustine group achieved higher rates than chlorambucil of CR (31% versus 1.9%) and nodular PR (nPR) (11% versus 2.6%) whereas PR was similar between groups, (27% versus 26%), respectively. Median PFS was significantly longer in the bendamustine group (21.6 months) than in the chlorambucil group (8.3 months), hazard ratio (HR) 4.37, (95% CI 3.14 to 6.07) and this difference was demonstrated in patients with Binet stage B disease (21.4 versus 9.0 months, respectively) and stage C disease (25.4 versus 6.3 months, respectively).

Median time to progression was significantly longer for bendamustine (23.9 months) compared with chlorambucil (8.3 months). Median duration of CR was 29.3 and 8.0 months in bendamustine and chlorambucil groups, respectively. Median duration of PR was 17.4 months with bendamustine and 8.0 months with chlorambucil.

Overall survival data were not mature at the primary analysis (35 months follow up) and there was no significant difference between treatment groups. There were 72 deaths in total, 31 in the bendamustine group and 41 in the chlorambucil group (HR 1.45, (95% CI 0.91 to 2.31). Thirteen deaths in the bendamustine group and 21 deaths in the chlorambucil group were reported as being due to CLL.

Patients were followed up to a median observation time of 54 months and unpublished results show that the improvement in median PFS was maintained; 21.2 months with bendamustine and 8.8 months with chlorambucil. Significantly more patients in the bendamustine group than in the chlorambucil group had not received any second line therapy; (63 versus 35, respectively). The median time to next treatment in the ITT population was 31 months with bendamustine and 10 months with chlorambucil. There was no significant difference in overall survival in the ITT population (HR 1.3 in favour of bendamustine), however the data were still not mature. In comparison with chlorambucil, the additional efficacy of bendamustine was achieved without compromising quality of life. There was no significant difference between treatment groups in change from baseline of quality of life evaluated using the European Organisation for Research and Treatment of Cancer questionnaires QLQ C30 and QLQ-CLL25.

Summary of evidence on comparative safety

Adverse events (AEs) were reported in 89% (143/161) patients in the bendamustine group and 81% (122/151) in the chlorambucil group. Eighteen patients who received bendamustine and five who received chlorambucil discontinued the study due to AEs, most commonly because of hypersensitivity reactions.

The most frequent AEs were haematologic and were more common in patients receiving bendamustine than chlorambucil, (all grades): thrombocytopenia 25% versus 21%, anaemia 22% versus 14%, neutropenia 27% versus 14%, and neutropenia (grade 3 or 4) 23% versus 11%, respectively.

Bendamustine was associated with more gastrointestinal AEs (all grades) than chlorambucil: nausea 19% versus 14%, vomiting 16% versus 7%, and diarrhoea 10% versus 4%.

Severe infections (grade 3 or 4) were reported in 8% and 3% of patients in the bendamustine and chlorambucil groups, respectively. Tumour lysis syndrome was reported in two patients after receiving their first cycle of bendamustine however both patients were able to continue treatment.

Summary of clinical effectiveness issues

The company has positioned bendamustine as an alternative to first-line chlorambucil in patients who are considered unfit for fludarabine-based regimens. The submission to the Scottish Medicines Consortium (SMC) focuses on patients without the rare cytogenic abnormality 17p-deletion (17p-deletion was not investigated in the pivotal study). Whilst alemtuzumab is also licensed for use in patients with B-CLL for whom fludarabine combination chemotherapy is not appropriate, SMC has previously published advice which restricts use to patients with the 17p-deletion. Chlorambucil is therefore the relevant comparator treatment to bendamustine in the Scottish setting.

The pivotal study demonstrated a substantial benefit for bendamustine over chlorambucil in patients with previously untreated CLL. However, unlike the licensed indication for bendamustine, fludarabine-eligible patients were not excluded from the study. As study patients had a mean age of 63 years, over 70% were Binet stage B and 97% had PS 0 or 1, they may be younger and fitter than those expected to receive bendamustine in practice. The European Society for Medical Oncology describes two categories of patients with appropriate Binet staging eligible for first line treatment: a) physically fit patients i.e. physically active, no major health problems, normal renal function or b) having relevant co-morbidity. The physically fit patients in the former category would generally be eligible for treatment with fludarabine. Only the latter category would be eligible for treatment with bendamustine according to its licence and it is unclear if this patient group would gain as much benefit as those patients recruited to the pivotal study.

Limitations of the study include the open-label design which is a potential cause of bias. The ORR for chlorambucil in the pivotal study was substantially lower than in other CLL studies (ranging from 31% (pivotal study) to 72%). The company noted in their submission to SMC that

CR rates are similar between the studies and that the disparity in rates of overall response for chlorambucil is due to differences in PR rates. They offer a possible explanation that there tends to be more scope for subjective judgement in the assessment of a PR than in the assessment of a CR. The dose of chlorambucil differs from the licensed dose for CLL though it was broadly similar to that used in other CLL studies.

Bendamustine has been used for many years in Germany and more recently in the rest of Europe.

Bendamustine is administered intravenously compared to chlorambucil which is administered orally. This may have implications for the patient and service delivery.

Even when mature survival data are available, interpretation may be problematic due to confounding by treatments received after patients have progressed.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing bendamustine with chlorambucil as first-line treatment of CLL in patients for whom fludarabine combination therapy is not appropriate. Chlorambucil is an appropriate comparator. A lifetime Markov model was used and the main source of clinical data was the bendamustine pivotal study. The economic model was relatively complex in its structure as it included the different levels of response to treatment (CR, PR, nPR and stable disease) in order to make full use of the study data. The clinical data were extrapolated over the model time horizon using appropriate parametric survival models which were selected based on goodness-of-fit statistics and visual inspection of the data. Different functional forms were tested in the sensitivity analysis.

The utility value for patients at baseline was estimated using QLQ-C30 data from the pivotal trial which were then mapped to EQ-5D using a published mapping algorithm. The baseline utility value was used as the reference value to which increments and decrements were applied for the various health states using a study commissioned by the manufacturer. Resource use included in the model relating to the different health states was based on clinical opinion only.

In the base case the manufacturer estimated a cost per quality-adjusted life year (QALY) of £10,621 (incremental cost of £12,915 and QALY gain of 1.216). The life years gained was estimated as 1.99 years.

The following weaknesses were noted:

- The difference in overall survival observed in the pivotal study was not statistically significant but the numerical difference was applied in the model base case. However, sensitivity analysis was provided which removed the treatment effect on overall survival and this resulted in the cost per QALY increasing to around £17k.
- The model structure assumed that patients who fail first-line treatment with chlorambucil or bendamustine subsequently received fludarabine-based therapy. This seems counterintuitive given the licensed indication for bendamustine specifies use in patients who are not suitable for fludarabine therapy. SMC clinical experts were asked to comment on this assumption and responses received were mixed. However, as the assumption applied to both arms of the model it is unlikely to bias the analysis.

- Additional sensitivity analysis was provided to further test the chlorambucil response rate in light of the lower response rate observed in the pivotal study in comparison with other CLL studies. This analysis indicated the results were relatively robust to changes in the chlorambucil response rate.
- The patients in the clinical trial are likely to be younger and fitter than the patients who will receive bendamustine in practice. However, subgroup analyses indicated the cost-effectiveness of bendamustine would be similar in older patients with a poorer performance status.
- Some of the resource use assumptions used in the model are questionable, such as the frequency of blood transfusions. However, sensitivity analysis indicated that changing these assumptions did not have a major impact on the results.

Despite these weaknesses the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group submission was received from the Chronic Lymphocytic Leukaemia Support Association.

Additional information: guidelines and protocols

Chronic lymphocytic leukemia: ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up were updated in 2010.

For treatment of advanced disease (Binet stages A and B with symptoms, Binet stage C) the guideline recommends:

First-line treatment

- Fludarabine in combination with cyclophosphamide plus rituximab
- In patients with relevant comorbidity; chlorambucil
- Alternatives are dose-reduced purine analogue-based therapies: fludarabine plus cyclophosphamide or pentostatin plus cyclophosphamide plus rituximab or bendamustine.

Second line treatment:

- If relapse occurs >12 months after the initial therapy: the initial regimen may be repeated as a second line treatment.
- If relapse occurs < 12 months after the initial therapy or 24 months after immunochemotherapy, or if the disease does not respond to first-line monotherapy, the therapeutic regimen needs to be changed to one of the following options:
    - Alemtuzumab-containing regimen followed by allogeneic stem cell transplantation in physically fit patients.
    - Fludarabine plus cyclophosphamide plus rituximab for patients relapsed or refractory to first-line therapy with an alkylating agent.
    - Alemtuzumab- or bendamustine-containing regimen in physically non-fit patients without deletion (17p). In these patients an attempt with high-dose ofatumomab or rituximab with high-dose steroids can be made.
    - Alemtuzumab in physically non-fit patients with deletion (17p).

Guidelines on the *diagnosis and management of chronic lymphocytic leukaemia* were published by the Guidelines Working Group of the UK CLL Forum on behalf of the British Committee for Standards in Haematology (BCSH) in 2004. These guidelines are now outdated.

Additional information: comparators

Chlorambucil is the relevant comparator. Although alemtuzumab is licensed for the treatment of patients with B-cell CLL for whom fludarabine combination chemotherapy is not appropriate, SMC has restricted its use to patients with previously untreated B-CLL, with the cytogenetic abnormality 17p-deletion. Vincristine sulphate, as monotherapy or in conjunction with other oncolytic drugs, is licensed for the treatment of CLL. However it is not mentioned in current guidance.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per 6 month course (£)
Bendamustine	**100mg/m^2 intravenously over 30 minutes on days 1 and 2 of a 28-day treatment cycle.** [1]	**966**	**5,796**
Chlorambucil (dose in pivotal study)	Chlorambucil 0.8mg/kg (Broca's normalised weight) orally on days 1 and 15 or, if necessary, given as divided doses on day 1/2 and day 15/16 of a 28-day treatment cycle. [2]	19	114
Chlorambucil (licensed dose)	0.15mg/kg/day orally until the total leucocyte count has fallen to 10,000 per microlitre. Treatment may be resumed 4 weeks after the end of the first course and continued at a dosage of 0.1mg/kg/day. [3]	-	183 to 243

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 15 December 2010. Median treatment duration in pivotal bendamustine study was 6 months and therefore cost for a 6 month course cited.

[1] Cost of bendamustine based on body surface area of 1.8m^2 and dose rounded down to 175mg.

[2] Cost of chlorambucil based on height of 170cm and the following formula; Broca's weight in kg = height in cm minus 100.

[3] Cost of chlorambucil based on weight of 60 to 80kg and calculated at a dose of 0.1mg/kg/day.

Additional information: budget impact

The manufacturer estimated the net budget impact would be £80k in year 1 rising to £407k in year 5. These estimates included drug acquisition and administration costs. Based on drug acquisition costs alone the net budget impact was estimated to be £63k in year 1 rising to £321k in year 5. The manufacturer estimated that the uptake rate would be 70% by year 5 and assumed a linear growth of 14% per year. This resulted in 14 patients estimated to receive bendamustine in year 1 rising to 69 in year 5. SMC clinical experts have indicated that the uptake rate may be higher in practice.

References

The undernoted references were supplied with the submission.

Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia. J Clin Oncol 2009 27:4378-84.

This assessment is based on data submitted by the applicant company up to and including 10 February 2011.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.