NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA216; Bendamustine for the treatment of chronic lymphocytic leukaemia

This guidance was issued in February 2011.

The review date for this guidance is December 2013.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. We should consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost effectiveness of bendamustine within its licensed indication for the first-line treatment of chronic lymphocytic leukaemia.

3. Current guidance

1.1. Bendamustine is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

4. Rationale[1]

The guidance should be transferred to the 'static guidance' list. The new evidence identified for bendamustine is not likely to lead to a change in the recommendations of the original TA216 guidance. The 2 future treatments that may come to market will be assessed for appraisal via the usual topic selection process, if appropriate.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from July 2009 onwards were reviewed. Additional searches of clinical trials registries and other

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The manufacturer of bendamustine has not made any changes to the current marketing authorisations or indicated that they are planning to extend the current marketing authorisations. Literature searches identified 6 new studies which have been published since the original guidance of which 2 were not relevant. 1 study (Fischer 2012) was a single arm phase II study. The other (Knauf 2012) was the published 02CLLIII trial, and this trial was made available to the Committee in an academic in confidence format in TA216. 2 new treatments may come to market in future for the same patient population as TA216. In October 2013 GlaxoSmithKline submitted an application to the European Medicines Agency (EMA) for the use of ofatumumab in combination with an alkylator-based therapy, for first line treatment of chronic lymphocytic leukaemia in patients who are inappropriate for treatment with fludarabine-based therapy. In April 2013 Roche Products submitted an application to the EMA for the use of obinutuzumab in combination with chlorambucil for the first line treatment of chronic lymphocytic leukaemia.

New RCT evidence (n=1)

In TA216 the Committee had evidence from 1RCT (Trial 02CLLIII l) comparing bendamustine with chlorambucil and considered that it had provided sufficient evidence to demonstrate that bendamustine was more clinically effective than chlorambucil. A new RCT (Knauf, 2009) published since the original guidance compared bendamustine with chlorambucil. It also concluded that bendamustine was more clinically effective than chlorambucil.

Systematic reviews (n=2)

A systematic review has been published since the original appraisal (Terasawa 2013). It identified 1 RCT of bendamustine, the Knauf 2009 study.

A Cochrane review (Vidal, 2012) identified 3 RCTs evaluating bendamustine in people with previously untreated chronic lymphocytic leukaemia. Two of the studies did not use comparators identified in the scope for TA216 which were fludarabine combination therapies with or without rituximab and chlorambucil. One study compared bendamustine, vincristine and prednisone (BOP) with cyclophosphamide, vincristine and prednisone (COP) (Herold 2006). One study compared bendamustine plus rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus rituximab (Rummel 2009). The remaining trial was the Knauf, 2009 study.

Cost effectiveness studies (n=1)

A cost effectiveness analysis was identified, which was conducted from a UK NHS perspective comparing bendamustine with chlorambucil (Woods, 2012). Clinical effectiveness data for the economic model was obtained from the Knauf 2009 study. Subgroup analyses in older patients and patients with poor performance status were

carried out. The estimated incremental cost-effectiveness ratio for bendamustine compared with chlorambucil was £11,960 per quality gained. None of the deterministic sensitivity analyses increased the incremental cost-effectiveness ratio by more than £2,000. Subgroup analyses showed that bendamustine remained cost-effective across different patient groups. Probabilistic sensitivity analysis showed that at the £20,000 threshold, bendamustine has a 90% probability of being cost-effective.

On-going RCTs

Two Phase III trials (NCT01886872 and NCT00769522) of bendamustine were identified which are due for completion in 2018. However these trials only evaluate bendamustine in combination with rituximab and do not include bendamustine alone in any arm. One small scale RCT (N=96) was identified (NCT01657955) which evaluated bendamustine compared with chlorambucil in people with previously untreated chronic lymphocytic leukaemia. The primary completion date was October 2013. A Phase II trial was also identified (NCT01109264) evaluating bendamustine compared with chlorambucil people with previously untreated chronic lymphocytic leukaemia. The primary completion date was June 2013.

Conclusion

The new evidence identified is not likely to lead to a change in the recommendations of the original guidance.

8. Implementation

A submission from Implementation is included in Appendix 3. Since the original guidance the published, it appears that NICE guidance is being adhered to and current practice has not significantly changed.

9. Equality issues

No equalities issues were raised in the original guidance

GE paper sign off: Frances Sutcliffe, Associate Director, 5 December 2013

Contributors to this paper:

Information Specialist: Toni Price

Technical Lead: Helen Tucker

Implementation Analyst: Rebecca Braithwaite

Project Manager: Andrew Kenyon

Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Improving outcomes in haematological cancers. NICE cancer service guidance (2003).

Rituximab for the first-line treatment of chronic lymphocytic leukaemia Technology appraisal TA174 (July 2009). Review update October 2012: *"In December 2010, the consideration of a review of TA174 and TA193 was deferred until during 2012 so that the results from the ongoing trial MO20927 could be taken into account. The results of this trial are not likely to be published until early in 2013. Consequently we have decided to defer the consideration of the review, and will consult on our plans for TA174 and TA193 within six months of the publication of MO20927."*

Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukemia. Technology appraisal TA119 (February 2007). Review decision May 2010: move to static.

Fludarabine for the treatment of B-cell chronic lymphocytic leukaemia. Technology appraisal TA29 (September 2001). Review decision (undated): *"The Institute was proposing that the review of NICE Technology Appraisal Guidance No. 29 Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia be deferred to allow the results of the current MRC trial CLL4 to inform the review. During consultation, all of comments received by the Institute agreed with the proposal put forward. The Institute's Guidance Executive has decided to proceed with the proposal. We will therefore contact consultees and commentators during August 2005 for consultation on a draft scope for this review."*
NB TA119 does not replace TA29:
http://www.nice.org.uk/nicemedia/live/11614/48610/48610.pdf

The CLL trial reported in 2012. An RPP is in progress for TA29, with the proposal paper currently suggesting 'move to static' and this was agreed at GE on 8 Oct 13

Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia. Technology appraisal TA193 (July 2010). Review update October 2012*: "In December 2010, the consideration of a review of TA174 and TA193 was deferred until during 2012 so that the results from the ongoing trial MO20927 could be taken into account. The results of this trial are not likely to be published until early in 2013. Consequently we have decided to defer the consideration of the review, and will consult on our plans for TA174 and TA193 within six months of the publication of MO20927."*

Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab. Technology appraisal TA202 (October 2010). Review date: September 2013.

In progress

Bendamustine in combination with rituximab for the first-line treatment of advanced indolent non-Hodgkin's lymphoma. Technology appraisal in progress. Expected date of issue: July 2014.

Leukaemia (chronic lymphocytic, previously untreated) - ofatumumab. Technology appraisal in progress. Expected date of issue: April 2015.

Referred - QSs and CGs

Haematological malignancies (referred QS).

Suspended/terminated

Bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma. Technology appraisal in progress. Expected date of issue: tbc. Suspended Feb 13 (manufacturer unable to provide an evidence submission).

Bendamustine for the treatment of people with indolent (low grade) non-Hodgkin's lymphoma (NHL) who are refractory to rituximab or a rituximab-containing regimen. Technology appraisal TA206 - suspended due to manufacturer non-submission.

Details of changes to the indications of the technology

Indication considered in original appraisal	**Proposed indication (for this appraisal)**
Bendamustine (Levact, Napp Pharmaceuticals) is an alkylating anti-tumour agent. It has a UK marketing authorisation for the 'first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate'.	Unchanged.

Details of new products

Drug (manufacturer)	**Details (phase of development, expected launch date,)**
Obinutuzumab (Roche)	Obinutuzumab for first line chronic lymphocytic leukaemia in combination with chlorambucil. In Phase III development. [redacted] Proposed appraisal.

Registered and unpublished trials

Trial name and registration number	Details
A Randomized Phase III Study of Bendamustine Plus Rituximab Versus Ibrutinib Plus Rituximab Versus Ibrutinib Alone in Untreated Older Patients (≥ 65 Years of Age) With Chronic Lymphocytic Leukemia (CLL). NCT01886872	Phase III RCT, not yet open for recruitment. Estimated enrolment: 523 Primary completion date: March 2018.
Phase III Trial of Combined Immunochemotherapy With Fludarabine, Cyclophosphamide and Rituximab (FCR) Versus Bendamustine and Rituximab (BR) in Patients With Previously Untreated Chronic Lymphocytic Leukaemia. NCT00769522	Phase III RCT, ongoing not recruiting. Estimated enrolment: 564 Primary completion date: July 2011. Estimated study completion date: January 2018.
Study of Bendamustine Hydrochloride Injection in Previously Untreated Chronic Lymphocytic Leukemia Patients. NCT01657955	Phase III RCT, currently recruiting. Estimated enrolment: 96 Primary completion date: October 2013.
Study of Bendamustine Hydrochloride Injection in Previously Untreated Chronic Lymphocytic Leukemia Patients. NCT01109264	Phase II RCT, completed. Estimated enrolment: 147 Primary completion date: June 2013.

Additional information

NHS England says the following about bendamustine on the Cancer Drugs Fund List (30 Sept 13) http://www.england.nhs.uk/wp-content/uploads/2013/09/ncdf-list-sept.pdf

"The treatment of Chronic Lymphocytic Leukaemia where all the following criteria are met:
1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Chronic lymphocytic leukaemia (not licensed in this indication)
3. a) 2nd line indication OR
b) 3rd line indication OR
c) 4th line indication
4. To be used within the treating Trust's governance framework, as Bendamustine is not licensed for this indication"

References

Fischer K, Cramer P, Busch R et al. (Sept. 2012) Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *Journal of Clinical Oncology.* 30 (26): 3209-3216.

Knauf WU, Lissichkov T, Aldaoud A et al. (Sept. 2009) Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *Journal of Clinical Oncology.* 27 (26): 4378-4384.

Knauf WU, Lissitchkov T, Aldaoud A et al. (Oct. 2012) Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial. *British Journal of Haematology.* 159 (1): 67-77.

Terasawa T, Trikalinos NA, Djulbegovic B et al. (June 2013) Comparative efficacy of first-line therapies for advanced-stage chronic lymphocytic leukemia: a multiple-treatment meta-analysis. [Review]. *Cancer Treatment Reviews.* 39 (4): 340-349.

Vidal L, Gafter-Gvili A, Gurion R et al. (2012) Bendamustine for patients with indolent B cell lymphoid malignancies including chronic lymphocytic leukaemia. [Review]. *Cochrane Database of Systematic Reviews.* 9: CD009045-.

Woods B, Hawkins N, Dunlop W et al. (July 2012) Bendamustine versus chlorambucil for the first-line treatment of chronic lymphocytic leukemia in England and Wales: a cost-utility analysis. *Value in Health.* 15 (5): 759-770.

Appendix 3 – Implementation submission

Review of NICE technology appraisal guidance No. 216; Bendamustine for the treatment of chronic lymphocytic leukaemia

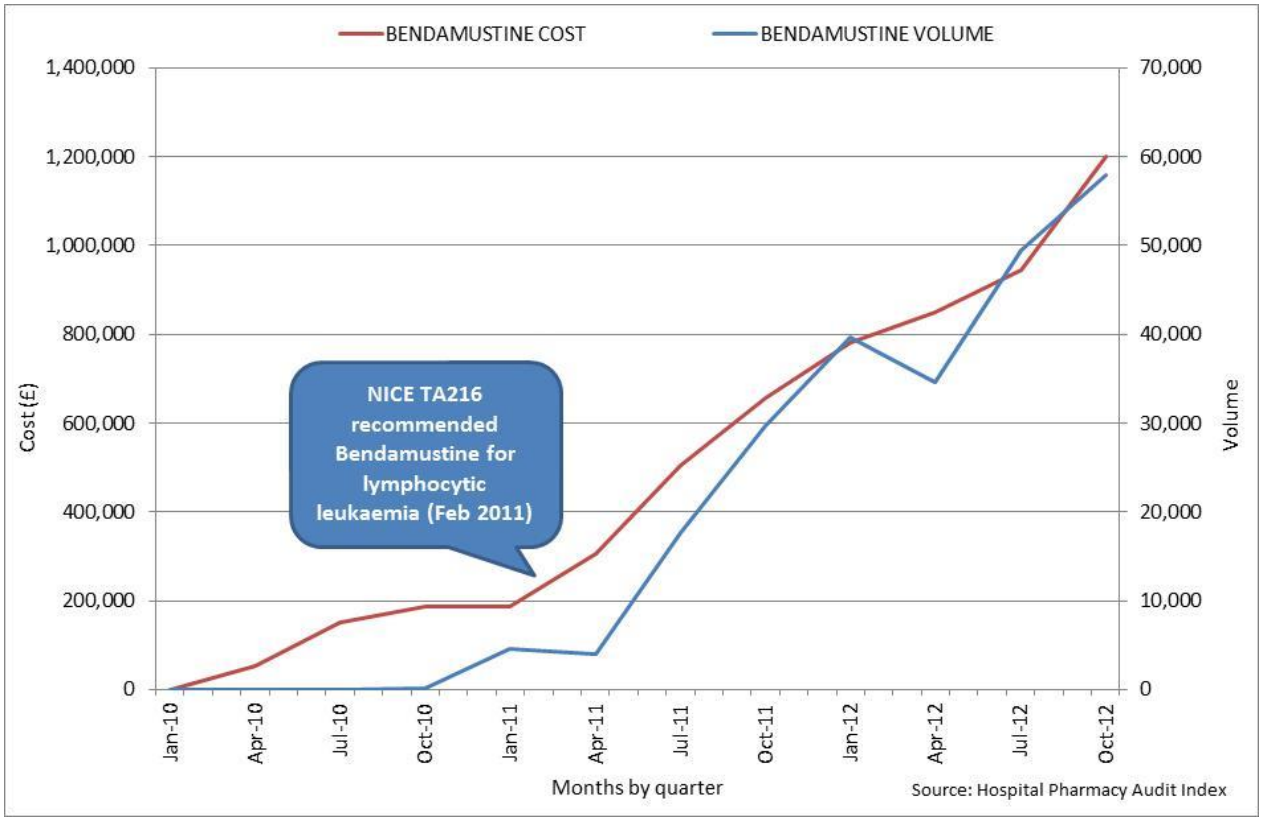
Please contact Rebecca Braithwaite regarding any queries
rebecca.braithwaite@nice.org.uk

1. Routine healthcare activity data

1.1. Hospital Pharmacy Audit Index data

This section presents net ingredient cost (NIC) and volume data for Bendamustine prescribed and dispensed for use in hospitals in England between January 2010 and October 2012.

Figure 1 Cost and volume of Bendamustine prescribed and dispensed for use in hospitals in England



2. Implementation studies from published literature

Information is taken from the uptake database website.

Nothing specific to add.

3. Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing specific to add.

Appendix A: Healthcare activity data definitions

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.