NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA359; Idelalisib for previously treated chronic lymphocytic leukaemia

Original publication date:	28 October 2015
Review date	September 2018
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA359, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

No new evidence was identified that suggests a review of this guidance is necessary.

3. Summary of new evidence and implications for review

There are no new published clinical trial data for idelalisib in combination with rituximab. New research focuses on alternative drug combinations of idelalisib with ofatumumab or bendamustine and rituximab. The price of idelalisib has not changed since the original appraisal, the price of rituximab may have reduced due to biosimilar products becoming available but as the original guidance was positive, this is unlikely to lead to a change in recommendations.

Has there been any change to the price of the technologies since the guidance was published?
There has been no change to the list price of £3114.75 for 60 100mg or 60 150mg tablets. (BNF Accessed 25/07/18). There has been no change to the simple discount agreement on this list price for [redacted]. Rituximab now has biosimilar products available that may reduce the overall cost of treatment.

Confidential information has been removed.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
The licence for idelalisib has been extended to include combination with ofatumumab, an alternative anti-CD20 monoclonal antibody in place of rituximab. However, ofatumumab is planned for withdrawal from commercialisation for chronic lymphocytic leukaemia (CLL) in all markets outside the USA, so this licence extension is unlikely to affect existing guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
Most evidence for the appraisal came from a phase III randomised controlled trial which compared idelalisib plus rituximab with rituximab alone and was supported by a phase II trial in a subpopulation of elderly people. No new evidence from published or ongoing trials was identified for idelalisib with rituximab. The phase III trial was stopped early for benefit which may have led to overestimation of treatment effect. A follow-up study of the key trial (Study 117, NCT01539291) has completed but the results are currently unavailable. There was some uncertainty about the comparison with rituximab because it is not approved by NICE as a treatment of CLL. The committee noted that there was no indirect or mixed treatment comparison with NICE approved comparators because a network could not be formed with the current evidence base. A systematic review and evidence synthesis (Quigley et al., 2014) confirmed that idelalisib with rituximab relative to rituximab monotherapy had a low hazard ratio but acknowledged that formal evidence synthesis was not possible to complete a network meta-analysis of CLL treatments. The committee recognised that idelalisib was associated with severe adverse events and noted that treatment discontinuation was a key driver of cost-effectiveness in the economic model. There is published evidence that confirms the committee's conclusions about the role of toxicity during the course of treatment. Lampson et al. (2016) showed that hepatotoxicity was a frequent and often severe adverse event, consistent with an immune-mediated mechanism. Mato et al. (2016) demonstrated that toxicity was the most common cause for kinase inhibitor therapy (of which idelalisib is one) discontinuation. Thompson et al. (2016) showed that permanently stopping therapy because of toxicity was the major determinant of progression free survival.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
None

Confidential information has been removed.

The search strategy from the original ERG report was adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2014 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

No equalities issues were identified in the original guidance.

GE paper sign off: **Helen Knight, 16.08.18**

Contributors to this paper:

Information Specialist: Paul Levay

Technical Analyst: Adam Brooke

Associate Director: Melinda Goodall

Project Manager: Emily Richards

Confidential information has been removed.

Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of idelalisib within its licensed indication for chronic lymphocytic leukaemia.

6. Current guidance

1.1 Idelalisib, in combination with rituximab, is recommended:

- for untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation or
- for chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed within 24 months.

  Idelalisib is recommended only if the company provides the drug with the discount agreed in the simple discount agreement.

1.2 People whose treatment with idelalisib is not recommended in this NICE guidance but was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

Idelalisib is priced at £3114.75 for 60 150‑mg tablets (British National Formulary 2015). The mean list price cost of a 1‑year treatment course for idelalisib is £37,922. The company has a simple discount agreement that provides a discount to the list price of idelalisib. The level of the discount is commercial in confidence.

Confidential information has been removed.

Appendix B – 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. The review will be conducted through the Technology appraisals process.	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 a specific date or trail.	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. The review will be conducted through the MTA process.	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. The review will be conducted through the MTA process.	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 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

Confidential information has been removed.

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going guideline[1].	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
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**
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Confidential information has been removed.

Appendix C – other relevant information

1. Relevant Institute work

Published

Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (2011) NICE technology appraisal guidance 216
Status: static list (March 2014)

Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (2007) NICE technology appraisal guidance 119
Status: static list (May 2010)

Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (2001) NICE technology appraisal guidance 29
Status: static list (December 2013)

Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (2017) NICE technology appraisal guidance 429
Review date: January 2020

Ibrutinib with bendamustine and rituximab for treating relapsed or refractory chronic lymphocytic leukaemia after systemic therapy (terminated appraisal) (2017) NICE technology appraisal guidance 437

Ibrutinib for untreated chronic lymphocytic leukaemia without a 17p deletion or TP53 mutation (terminated appraisal) (2017) NICE technology appraisal guidance 452

Idelalisib with ofatumumab for treating chronic lymphocytic leukaemia (terminated appraisal) (2017) NICE technology appraisal guidance 469

Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (2015) NICE technology appraisal guidance 343
Review date: 3 years after publication

Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab (2010) NICE technology appraisal guidance 202

Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia (2015) NICE technology appraisal guidance 344
Review date: 3 years after publication

Ofatumumab with chemotherapy for treating chronic lymphocytic leukaemia (terminated appraisal) TA470

Rituximab for the first-line treatment of chronic lymphocytic leukaemia (2009) NICE technology appraisal guidance 174
Confidential information has been removed.

Status: static list (March 2014)

Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (2010) NICE technology appraisal guidance 193
Status: static list (March 2014)

Venetoclax for treating chronic lymphocytic leukaemia (2017) NICE technology appraisal guidance 487
Review date: when the CDF data collection ends (expected December 2020)

Blood and bone marrow cancers (2015) NICE pathway

Haematological cancers: improving outcomes (2016) NICE guideline 47

Haematological cancers (2017) NICE quality standard QS150

In progress

Duvelisib for treating relapsed chronic lymphocytic leukaemia [ID1083] NICE technology appraisal guidance. Publication date to be confirmed

Ibrutinib with obinutuzumab for untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma [ID1375] NICE technology appraisal guidance. Publication date to be confirmed

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097] NICE technology appraisal guidance. Publication expected March 2019

Venetoclax with ibrutinib and obinutuzumab for untreated chronic lymphocytic leukaemia [ID1270] NICE technology appraisal guidance. Publication date to be confirmed

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402] NICE technology appraisal guidance. Publication date to be confirmed

Suspended/terminated

Idelalisib with ofatumumab for treating chronic lymphocytic leukaemia [ID817] NICE technology appraisal guidance. Publication date to be confirmed
Status: Currently suspended as the company is not expected to make an evidence submission.

Idelalisib with bendamustine and rituximab for previously treated chronic lymphocytic leukaemia [ID839] NICE technology appraisal guidance. Publication date to be confirmed
Status: Currently suspended as the company is not expected to make an evidence submission.

Confidential information has been removed.

Ofatumumab for the maintenance treatment of relapsed chronic lymphocytic leukaemia following response to induction therapy [ID732] NICE technology appraisal guidance. Publication date to be confirmed
Status: Currently suspended as the company is not expected to make an evidence submission.

2. Details of new products

Drug (company)	**Details (phase of development, expected launch date)** **Source:** Specialist Pharmacy Service	**In topic selection**
Acalabrutinib (AstraZeneca)	Acalabrutinib for untreated chronic lymphocytic leukaemia Phase 2 clinical trials UK launch expected [redacted]	[redacted]
	Acalabrutinib monotherapy for relapsed or refractory chronic lymphocytic leukaemia Phase 3 clinical trials UK launch expected [redacted]	[redacted]

Confidential information has been removed.

Ibrutinib (Janssen)	Ibrutinib with obinutuzumab for untreated chronic lymphocytic leukaemia Phase 3 clinical trials UK launch expected [redacted]	[redacted]
	Ibrutinib with rituximab for untreated chronic lymphocytic leukaemia in younger patients Phase 3 clinical trials UK launch expected [redacted]	[redacted]
	Ibrutinib for Binet Stage A untreated chronic lymphocytic leukaemia with risk of early disease progression Phase 3 clinical trials UK launch expected [redacted]	[redacted]
Idelalisib (Gilead)	Idelalisib with bendamustine and rituximab for untreated chronic lymphocytic leukaemia Phase 3 clinical trials [redacted]	[redacted]

Confidential information has been removed.

	Idelalisib with bendamustine and rituximab for relapsed chronic lymphocytic leukaemia Phase 3 clinical trials [redacted]	[redacted]
MOR208 (MorphoSys)	Chronic lymphocytic leukaemia Phase 2 clinical trials [redacted]	[redacted]
Rituximab biosimilars	Various. Some already available	[redacted]
Ublituximab (TG Therapeutics)	Ublituximab with ibrutinib for high risk chronic lymphocytic leukaemia with 17p deletion, 11q deletion or p53 mutation Phase 3 clinical trials UK launch expected [redacted]	[redacted]
	Ublituximab with with umbralisib for treating chronic lymphocytic leukaemia Phase 3 clinical trials UK launch expected [redacted]	[redacted]

Confidential information has been removed.

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Idelalisib (Zydelig) has a marketing authorisation in the UK for use 'in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia who have received at least 1 prior therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy' (28 October 2015)	Zydelig is indicated in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies. Source: current SPC (June 2018)
Idelalisib is priced at £3114.75 for 60 150-mg tablets (British National Formulary 2015). The mean list price cost of a 1-year treatment course for idelalisib is £37,922. The company has a simple discount agreement that provides a discount to the list price of idelalisib. The level of the discount is commercial in confidence.	No change - £3114.75 for 60 100mg or 60 150mg tablets. Source: BNF (20 June 2018)

4. Registered and unpublished trials

Trial name and registration number	Details
A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) for Previously Treated Chronic Lymphocytic Leukemia GS-US-312-0117 NCT01539291 Phase 3	Purpose: to evaluate the effect of idelalisib on the onset, magnitude, and duration of tumor control Status: completed Enrolment: 160 Start date: March 2012 Completion date: March 2018

Confidential information has been removed.

Trial name and registration number	Details
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Bendamustine and Rituximab for Previously Untreated Chronic Lymphocytic Leukemia GS-US-312-0123 NCT01980888 Phase 3	Purpose: a companion study to Study GS-US-312-0116 to evaluate the progression-free survival in participants with previously untreated CLL Status: terminated Enrolment: 311 Start date: February 2014 Completion date: March 2016
Assessment of the Mechanism of Action of idelalisib (CAL101) in B-cell Receptor Pathway Inhibition in CLL (CALiBRe) ISRCTN52057158	Purpose: assessment of the mechanism of action of idelalisib (CAL101) in B-cell receptor pathway inhibition in CLL: a non-randomised interventional trial Status: no longer recruiting Enrolment: 40 Start date: March 2012 Completion date: May 2017

5. Relevant services covered by NHS England specialised commissioning

NHS England (2017) Manual for prescribed specialised services 2017/18 Chapter 29 – Blood and marrow transplantation services (adults and children)

NHS England (2015) NHS England Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised

NHS England (2013) NHS standard contract for Haematopoietic Stem Cell Transplantation (adult)

NHS England (2013) NHS standard contract for cancer: chemotherapy (adult)

6. Additional information

British Society for Haematology (2012, updated 2015) Investigation and management of chronic lymphocytic leukaemia

British Society for Haematology (2015) Interim statement from the BCSH CLL Guidelines Panel

Confidential information has been removed.

Appendix C

European Society for Medical Oncology (2015) Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up

European Society for Medical Oncology (2016) ESMO consensus conference on malignant lymphoma: general perspectives and recommendations for prognostic tools in mature B-cell lymphomas and chronic lymphocytic leukaemia

Confidential information has been removed.

Appendix D – References

Lampson BL, Kasar SN, Matos TR, Morgan EA, Rassenti L, Davids MS, Fisher DC, Freedman AS, Jacobson CA, Armand P, Abramson JS, Arnason JE, Kipps TJ, Fein J, Fernandes S, Hanna J, Ritz J, Kim HT, Brown JR (2016) Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity. *Blood*. 128 (2): 195-203.

Mato AR, Nabhan C, Barr PM, Ujjani CS, Hill BT, Lamanna N, Skarbnik AP, Howlett C, Pu JJ, Sehgal AR, Strelec LE, Vandegrift A, Fitzpatrick DM, Zent CS, Feldman T, Goy A, Claxton DF, Bachow SH, Kaur G, Svoboda J, Nasta SD, Porter D, Landsburg DJ, Schuster SJ, Cheson BD, Kiselev P, Evens AM (2016) Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience. *Blood*. 128(18): 2199-2205.

Quigley JM, Thompson J, Barcena L, Mealing SJ, Leblond V (2014) A systematic review and evidence synthesis of randomised controlled trials (RCT) for the treatment of relapased or refractory chronic lymphoctyic leukemia (CLL) *Haematologica*. 99: 60

Thompson PA, Stingo F, Keating MJ, Ferrajoli A, Burger JA, Wierda WG, Kadia TM, O'Brien SM (2016) Outcomes of patients with chronic lymphocytic leukemia treated with first-line idelalisib plus rituximab after cessation of treatment for toxicity. *Cancer.* 122 (16): 2505-11

Confidential information has been removed.