NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA343; Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia and TA344; Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia

Original publication date:	TA343, TA344: June 2015
Review date	TA343, TA344: June 2018
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA343 and TA344, see Appendix A.

1. Proposal

We propose that TA343 and TA344 should be transferred to the 'static guidance list'.

2. Rationale

There are no new cost or clinical effectiveness data for obinutuzumab or ofatumumab, which would warrant reconsideration of the existing recommendations.

3. Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?
TA343 (Obinutuzumab in combination with chlorambucil) The details of the patient access scheme (PAS) have changed since the publication of TA343. The discount of the simple scheme has [redacted] (when TA343 was published) to currently [redacted] The simple PAS covers the currently approved indications of Gazyvaro (obinutuzumab) in CLL (TA343) and follicular lymphoma (FL) (TA472, TA513). The company intend to continue the scheme without any further changes. **TA344 (Ofatumumab in combination with chlorambucil or bendamustine)** No change to the price of the technology since the guidance was published. Ofatumumab (Arzerra) is planned for withdrawal from commercialisation for CLL in all markets outside the USA. The timelines for this process in the UK and what specific arrangements will be made for withdrawal, including possible access by

other means, are not yet known. Novartis will update NICE when more details are available.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

TA343 (Obinutuzumab in combination with chlorambucil)

There are currently no plans for an extension of the marketing authorisation for obinutuzumab for the treatment of untreated chronic lymphocytic leukaemia.

TA344 (Ofatumumab in combination with chlorambucil or bendamustine)

There are currently no plans for an extension of the marketing authorisation for ofatumumab for the treatment of untreated chronic lymphocytic leukaemia.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

TA343 (Obinutuzumab in combination with chlorambucil)

The committee was uncertain about the true survival benefits associated with obinutuzumab plus chlorambucil based on the key clinical trial. The committee acknowledged that CLL11 trial [which compared rituximab plus chlorambucil (R-Clb), obinutuzumab plus chlorambucil (G-Clb), and chlorambucil alone] was an open label study, which may have biased the primary outcome of investigator-assessed progression free survival (PFS). The overall survival (OS) data from CLL11 were also immature.

CLL11 also used a lower dose of chlorambucil compared to what is used in UK clinical practice. It is uncertain what effect this had on the results of the trial.

Since the appraisal of obinutuzumab:

- Updated overall survival, progression free survival, and time to next treatment (TTNT) results from the CLL11 pivotal study were published (Follows, G., et al., 2016[1] and Goede, V, et. al., 2015[2])
- A systematic review and Bayesian network meta-analysis (NMA) of treatments for patients with CLL not suitable for fludarabine based therapies has been published (Stadler, N., et al., 2016[3])
- An economic analysis from the NHS perspective that corresponds to the analysis originally submitted for TA343 has been published (Becker, U., et al., 2016[4])
- The CLL Guidelines Panel of the British Society for Haematology has recommended chlorambucil in combination with either ofatumumab or obinutuzumab as initial therapy for previously untreated less fit patients (Follows, G., et al., 2018[5])
- Rituximab biosimilars for treating chronic lymphocytic leukaemia are, or about to, become available

The updated CL11 study results confirmed previously reported results during TA343; treatment with obinutuzumab plus chlorambucil compared with

chlorambucil alone was associated with substantially improved median PFS. Updated progression-free survival and TTNT analyses confirmed previously reported superiority of G-Clb over rituximab plus chlorambucil. Overall survival analysis continued to demonstrate a trend of benefit of G-Clb over R-Clb.

The systematic review and NMA indicated increased PFS with G-Clb compared with R-Clb, ofatumumab plus chlorambucil (O-Clb), fludarabine, and chlorambucil, in line with what was observed during TA343. However, the OS findings were associated with high uncertainty.

Becker, U., et al., 2016 evaluated the cost-effectiveness of treatment with anti-CD20 monoclonal antibody obinutuzumab plus chlorambucil in untreated patients with chronic lymphocytic leukemia unsuitable for full-dose fludarabine-based therapy. This is a summary of the original appraisal and therefore does not provide any new evidence.

The clinical data presented are consistent with the committee's judgement and support the recommendations of TA343.

TA344 (Ofatumumab in combination with chlorambucil or bendamustine)

- Since the appraisal of ofatumumab, the CLL Guidelines Panel of the British Society for Haematology has recommended chlorambucil in combination with either ofatumumab or obinutuzumab as initial therapy for previously untreated less fit patients.
- A systematic review and Bayesian network meta-analysis (NMA) of treatments for patients with CLL not suitable for fludarabine based therapies has been published (Stadler, N., et al., 20163)
- Rituximab biosimilars for treating chronic lymphocytic leukaemia are, or about to become, available

The systematic review and NMA indicated increased PFS with G-Clb compared with R-Clb, ofatumumab plus chlorambucil (O-Clb), fludarabine, and chlorambucil. However, the OS findings were associated with high uncertainty.

Apart from the above, no new findings or new evidence are available for ofatumumab, therefore there are no new data to support changing the conclusions in TA344.

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

The search strategy from the original ERG reports were re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2014 to April 2018 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

TA343 Obinutuzumab – Section 4.19

The Committee considered the potential equality issue raised by a consultee that failure to consider the population who cannot have fludarabine as 2 separate groups (those who can have bendamustine and those who cannot) may be interpreted as discriminatory. This is because people who cannot have bendamustine would not have access to alternative effective treatments if obinutuzumab was not recommended. The Committee decided that this was not an equality issue under the equality legislation. Therefore its recommendations did not lead to discrimination and it did not need to add to, or change, its recommendations.

TA344 Ofatumumab – Section 4.17

The Committee considered the potential equality issue raised by consultees that ofatumumab plus chlorambucil would especially benefit older people with comorbidities, who may be judged as unfit for treatment with other regimens. The Committee concluded that fitness for treatment drives treatment decisions, not age, and therefore there was no need to change its recommendations because of this issue.

GE paper sign off: **Helen Knight, 26 July 2018**

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Appendix A – Information from existing guidance

5. Original remit

TA343
To appraise the clinical and cost effectiveness of obinutuzumab within its licensed indication for previously untreated chronic lymphocytic leukaemia.

TA344
To appraise the clinical and cost effectiveness of ofatumumab within its licensed indication for previously untreated chronic lymphocytic leukaemia.

6. Current guidance

TA343

Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if:

- bendamustine-based therapy is not suitable and
- the company provides obinutuzumab with the discount agreed in the patient access scheme.

People whose treatment with obinutuzumab 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.

TA344

Ofatumumab in combination with chlorambucil is recommended as an option for untreated chronic lymphocytic leukaemia only if:

- the person is ineligible for fludarabine-based therapy and
- bendamustine is not suitable and
- the company provides ofatumumab with the discount agreed in the patient access scheme.

People whose treatment with ofatumumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue ofatumumab 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

TA343

The price of obinutuzumab is £3312 per 1000‑mg vial (excluding VAT; 'British national formulary' [BNF] February 2015). The company stated that a course of treatment costs £26,496 (£9936 for cycle 1 and £3312 for cycles 2–6, excluding VAT). The recommended dosage is 1000 mg administered over days 1 and 2, 1000 mg on day 8 and 1000 mg on day 15 of treatment cycle 1, followed by 1000 mg on day 1 of treatment cycles 2–6. The company has agreed a patient access scheme with the Department of Health that makes obinutuzumab available with a discount. The size of the discount is commercial in confidence.

TA344

The recommended dose and schedule in the summary of product characteristics is 300 mg on day 1 followed by 1000 mg on day 8 (cycle 1), followed by 1000 mg on day 1 of subsequent cycles, for a minimum of 3 cycles, until best response or a maximum of 12 cycles (every 28 days). Best response is defined as a clinical response that did not improve after 3 additional cycles of treatment. Ofatumumab is priced at £182 for a 100‑mg vial and £1820 for a 1000‑mg vial (British national formulary 66, 2014). Assuming 6 cycles and no drug wastage, the mean cost of a treatment course for ofatumumab is £11,466 for 6300 mg. The company has agreed a patient access scheme with the Department of Health that makes ofatumumab available with a discount. The size of the discount is commercial in confidence.

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 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. 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 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

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical 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 to TA343 and TA344
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 untreated chronic lymphocytic leukaemia without a 17p deletion or TP53 mutation (terminated appraisal) (2017) NICE technology appraisal guidance 452

Idelalisib for treating chronic lymphocytic leukaemia (2015) NICE technology appraisal guidance 359
Status: static list (March 2014)

Rituximab for the first-line treatment of chronic lymphocytic leukaemia (2009) NICE technology appraisal guidance 174
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

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

2. Details of new products

Appendix C

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Acalabrutinib (AstraZeneca)	Acalabrutinib for untreated chronic lymphocytic leukaemia Phase 2 clinical trials UK launch expected [redacted]	[redacted]
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]

Confidential information has been removed.

	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 terminated	[redacted]
Rituximab biosimilars	Various. Some are already available	[redacted]
Ublituximab (TG Therapeutics)	Ublituximab with ibrutinib for high risk chronic lymphocytic leukaemia Phase 3 clinical trials UK launch expected [redacted]	[redacted]

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**
Obinutuzumab plus chlorambucil has a UK marketing authorisation for 'the treatment of adult patients with previously untreated chronic lymphocytic leukaemia and with	Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
comorbidities making them unsuitable for full-dose fludarabine based therapy'.	unsuitable for full-dose fludarabine based therapy. Source: current SPC (May 2018) There are currently no plans for an extension of the marketing authorisation for obinutuzumab for the treatment of untreated chronic lymphocytic leukaemia. Source: Roche letter (March 2018)
The price of obinutuzumab is £3312 per 1000-mg vial (excluding VAT; 'British national formulary' [BNF] February 2015).	No change. £3312 per 1000mg/40ml solution for infusion vial. Source: BNF (April 2018)
Ofatumumab in combination with chlorambucil or bendamustine has a marketing authorisation in the UK for treating chronic lymphocytic leukaemia in people who have not had prior therapy and who are not eligible for fludarabine-based therapy.	Arzerra in combination with chlorambucil or bendamustine is indicated for the treatment of adult patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy. Source: current SPC (May 2018)
Ofatumumab is priced at £182 for a 100-mg vial and £1820 for a 1000-mg vial (British national formulary 66, 2014).	£1820 per 1000mg/50ml solution for infusion vial. £546 for x3 100mg/5ml solution for infusion vials. Source: BNF (April 2018) Ofatumumab (Arzerra) is planned for withdrawal from commercialisation for CLL in all markets outside the USA. The timelines for this process in the UK and what specific arrangements will be made for withdrawal, including possible access by other means, are not yet known. Novartis will update NICE when more details are available. Source: Novartis email (March 2018)

No relevant ongoing or unpublished trials identified.

4. Relevant services covered by NHS England specialised commissioning

Confidential information has been removed.

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)

5. 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

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

Appendix D – References

1. Follows, G., et al., *An updated survival analysis from the CLL11 study in patients with chronic lymphocytic leukaemia treated with obinutuzumab or rituximab in combination with chlorambucil versus chlorambucil alone.* British Journal of Haematology, 2016. 173: p. 95.
2. Goede, V., et al., *Updated Survival Analysis from the CLL11 Study: Obinutuzumab Versus Rituximab in Chemoimmunotherapy-Treated Patients with Chronic Lymphocytic Leukemia.* BLOOD, 2015. 126(23).
3. Stadler, N., et al., *A Systematic Review and Network Meta-Analysis to Evaluate the Comparative Efficacy of Interventions for Unfit Patients with Chronic Lymphocytic Leukemia.* Adv Ther, 2016. 33(10): p. 1814-1830.
4. Becker, U., et al., *Cost-Effectiveness Model for Chemoimmunotherapy Options in Patients with Previously Untreated Chronic Lymphocytic Leukemia Unsuitable for Full-Dose Fludarabine-Based Therapy.* Value Health, 2016. 19(4): p. 374-82.
5. Follows, G., et al. *Interim statement from the BCSH CLL Guidelines Panel*. 2017 21/03/2018]; Available from: https://www.b-s-h.org.uk/media/13488/interim-statement-cll-guidelines-version6.pdf.