NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487)

Final scope

Final Remit/appraisal objective

To appraise the clinical and cost effectiveness of venetoclax within its marketing authorisation for treating chronic lymphocytic leukaemia.

Background (not updated from TA487)

Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells (lymphocytes). It causes anaemia, swollen lymph nodes, spleen enlargement, unexplained weight loss and increased susceptibility to infection. People with CLL may live with a considerable burden of symptoms impacting on their quality of life whether or not they have received treatment.

CLL is a common form of leukaemia, with an estimated 2,982 new diagnoses in England each year[1]. The risk of developing CLL increases with age and is more common in men[2]. Approximately 5% to 10% of people diagnosed with CLL are considered to have 'high-risk' disease. The British Committee for Standards in Haematology (BCSH) defines people with 'high risk' as those with previously untreated or relapsed CLL associated with a 17p deletion or TP53 mutation (the presence of 17p deletion or TP3 mutation influences the rate of cell growth as well as the resistance of the disease to treatment) and who require treatment, and those whose disease (regardless of biomarkers being present) relapses within 2 years of, or is refractory to purine analogue based chemotherapies (for example fludarabine) [3,4].

This appraisal includes 4 groups of people with CLL:

- People with untreated CLL who have a 17p deletion or TP53 mutation and for whom a B-cell receptor pathway inhibitor is unsuitable**.**
- People with relapsed or refractory CLL who have a 17p deletion or TP53 mutation and for whom a B-cell receptor pathway inhibitor is unsuitable and whose disease has progressed after treatment with chemo-immunotherapy.
- People with relapsed or refractory CLL who have a 17p deletion or TP53 mutation and whose disease has progressed after treatment with a B-cell receptor pathway inhibitor.
- People with relapsed or refractory CLL who have no 17p deletion or TP53 mutation and whose disease has progressed after treatment with both chemo-immunotherapy and a B-cell receptor pathway inhibitor

B-cell receptor pathway inhibitors stop B-cell (lymphocyte) proliferation and promote cell death. Chemo-immunotherapy is a combination of chemotherapy medicines and treatments that stimulate the immune system (monoclonal antibodies) to kill cancer cells.

For untreated CLL

Treatment choice is based on an assessment of fitness to tolerate chemotherapy and/or immunotherapy, and mutational status.

B cell receptor pathway inhibitors or chemotherapy with or without immunotherapy irrespective of 17p deletion or TP53 mutation status:

- NICE technology guidance 119 does not recommend fludarabine monotherapy as a first-line treatment for people with CLL.
- NICE technology appraisal guidance 216 recommends bendamustine as an option for the first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
- The BCSH recommends chlorambucil with or without rituximab[3,4].
- NICE technology appraisal guidance 174 recommends the use of rituximab in combination with fludarabine and cyclophosphamide as a first-line treatment option for people who are able to take fludarabine and cyclophosphamide, and does not recommend rituximab in combination with other chemotherapies.
- NICE technology appraisal guidance 343 recommends obinutuzumab in combination with chlorambucil, as an option for adults with untreated CLL who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if: bendamustine-based therapy is not suitable.
- NICE technology appraisal guidance 344 recommends ofatumumab in combination with chlorambucil as an option for untreated chronic lymphocytic leukaemia only if the person is ineligible for fludarabine-based therapy and bendamustine is not suitable.

B-cell receptor pathway inhibitors for people with 17p deletion or TP53 mutation:

- NICE technology appraisal guidance 359 recommends idelalisib in combination with rituximab for adults with untreated CLL and a 17p deletion or TP53 mutation. Since the publication of NICE technology appraisal guidance 359, the marketing authorisation for idelalisib has been up-dated to state ‘as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies.’

- Ibrutinib has a marketing authorisation in the UK for CLL 'in first-line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy'. Ibrutinib is the subject of an ongoing NICE technology appraisal (ID749). Ibrutinib is not currently funded by the Cancer Drugs Fund for untreated CLL.

There are limited treatment options for **people with untreated CLL associated with 17p deletion or TP53 mutation when a B-cell receptor pathway inhibitor is unsuitable**. This is because chemotherapy (such as fludarabine plus cyclophosphamide, bendamustine, and chlorambucil) is active against sensitive cells but not cells that are resistant to 17p deletion or TP53 mutation and therefore further genetic deletions and mutations occur. Treatment options may include:

- alemtuzumab with or without corticosteroids steroids [3,4]. Alemtuzumab does not have a marketing authorisation for CLL in the European Union because its marketing authorisation for this indication was withdrawn at the request of the company for commercial reasons. However alemtuzumab is currently available in England through a patient access programme agreed by the company and the European Medicines Agency.

- best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support).

Previously treated CLL:

Treatment depends on individual circumstances such as the type and duration of response achieved with previous therapies, fitness to tolerate chemotherapy and/or immunotherapy, and mutational status.

B cell receptor pathway inhibitors or chemotherapy with or without immunotherapy irrespective of 17p deletion or TP53 mutation status:

- NICE technology appraisal guidance 193 recommends rituximab in combination with fludarabine and cyclophosphamide as an option unless their disease is refractory to fludarabine or has been previously treated with rituximab.

- NICE technology appraisal guidance 202 does not recommend ofatumumab for the treatment of CLL that is refractory to fludarabine and alemtuzumab.

- Chlorambucil has a UK marketing authorisation for treating CLL and is used in clinical practice in England with or without rituximab in people with relapsed or refractory CLL for whom rituximab in combination with fludarabine and cyclophosphamide is unsuitable.

B-cell receptor pathway inhibitor for people with or without 17p deletion or TP53 mutation:

- NICE technology appraisal guidance 359 recommends idelalisib, in combination with rituximab for chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed within 24 months.

- Ibrutinib has a marketing authorisation in the UK for 'adult patients with CLL who have received at least one prior therapy'. Ibrutinib is subject to an ongoing NICE appraisal (ID 749) and is used in clinical practice in England through the Cancer Drugs Fund (at the time the final scope was written).

There are no standard treatment options for people with relapsed or refractory CLL[3,4] who have:

- a 17p deletion or TP53 mutation and for whom a B-cell receptor pathway inhibitor is unsuitable and whose disease has progressed after treatment with chemo-immunotherapy.
- a 17p deletion or TP53 mutation and whose disease has progressed after treatment with a B-cell receptor pathway inhibitor.
- no 17p deletion or TP53 mutation and whose disease has progressed after treatment with both chemo-immunotherapy and a B-cell receptor pathway inhibitor

Treatment options for people with relapsed or refractory CLL who have a 17p deletion or TP53 mutation may include enrolment into clinical trials, or best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support)[3,4]. For people with relapsed or refractory CLL who have no 17p deletion or TP53 mutation and whose disease has progressed after treatment with both chemo-immunotherapy and a B-cell receptor inhibitor, treatment options may include enrolment into clinical trials rituximab alone (for refractory disease), corticosteroids (with or without rituximab),or best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support) [3,4].

The technology

Venetoclax (Venclyxto, AbbVie) is an oral inhibitor of the B-cell lymphoma 2 protein that regulates cell death.

Venetoclax has a conditional marketing authorisation for 'the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor' and for 'the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor'.

Table not updated from TA487

Intervention(s)	Venetoclax
Population(s)	• People with untreated CLL who have a 17p deletion or TP53 mutation and for whom a B-cell receptor pathway inhibitor is unsuitable. • People with relapsed or refractory CLL who have a 17p deletion or TP53 mutation and for whom a B-cell receptor pathway inhibitor is unsuitable and whose disease has progressed after treatment with chemo-immunotherapy. • People with relapsed or refractory CLL who have a 17p deletion or TP53 mutation and whose disease has progressed after treatment with a B-cell receptor pathway inhibitor. • People with relapsed or refractory CLL who have no 17p deletion or TP53 mutation and whose disease has progressed after treatment with both chemo-immunotherapy and a B-cell receptor inhibitor.

Comparators	People with untreated CLL with a 17p deletion or TP53 mutation for whom a B-cell receptor pathway inhibitor is unsuitable: • established clinical management without venetoclax such as alemtuzumab (with or without corticosteroids) • best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support) People with relapsed or refractory CLL who have a 17p deletion or TP53 mutation and for whom a B-cell receptor pathway inhibitor is unsuitable and whose disease has progressed after treatment with chemo-immunotherapy: • established clinical practice without venetoclax • best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support) People with relapsed or refractory CLL with a 17p deletion or TP53 mutation whose disease has progressed after treatment with a B-cell receptor pathway inhibitor: • established clinical practice without venetoclax • best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support) People with relapsed or refractory CLL without a 17p deletion or TP53 mutation whose disease has progressed after treatment with both chemo-immunotherapy and a B-cell receptor pathway inhibitor: • established clinical practice without venetoclax • best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support)

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.
Other considerations	If the evidence allows, the economic analysis should model stem cell transplantation further down the treatment pathway. If evidence allows, the appraisal will consider subgroups of people identified as having 'high risk disease'. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia' (2007). NICE technology appraisal guidance 119. Guidance moved to static list 'Rituximab for the first-line treatment of chronic lymphocytic leukaemia' (2009).NICE technology appraisal guidance 174. Guidance on static list 'Rituximab for the treatment of relapsed chronic lymphocytic leukaemia' (2010). NICE technology appraisal guidance 193. Guidance moved to static list.

	‘Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab’ (2010). NICE technology appraisal guidance 202. Review deferred, awaiting results from on-going trials. ‘Bendamustine for the first-line treatment of chronic lymphocytic leukaemia’ (2011). NICE technology appraisal guidance 216. Guidance moved to static list. ‘Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia’ (2015). NICE technology appraisal guidance 343. Review proposal date June 2018 ‘Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia’ (2015). NICE technology appraisal guidance 344. Review proposal date June 2018. ‘Idelalisib for previously treated chronic lymphocytic leukaemia’ (2015). NICE technology appraisal guidance 359. Review proposal date September 2018 Appraisals in development (including suspended appraisals) ‘Ibrutinib for treating chronic lymphocytic leukaemia’ NICE technology appraisal guidance in preparation [ID 749]. Publication expected January 2017. ‘Ibrutinib for treating newly diagnosed chronic lymphocytic leukaemia’ NICE technology appraisal guidance in preparation [ID918]. Suspended. ‘Idelalisib with bendamustine and rituximab for previously treated chronic lymphocytic leukaemia’ NICE technology appraisal guidance in preparation [ID839]. Publication expected November 2017. ‘Ofatumumab for the maintenance treatment of relapsed chronic lymphocytic leukaemia’. NICE technology appraisal [ID732]. Publication date to be confirmed. ‘Idelalisib in combination with ofatumumab for treating previously treated, relapsed chronic lymphocytic leukaemia’. NICE technology appraisal [ID817]. Publication date to be confirmed. ‘Ofatumumab in combination with chemotherapy for treating relapsed chronic lymphocytic leukaemia’. NICE technology appraisal guidance in preparation [ID777]. Publication date to be confirmed. Related Guidelines: ‘Improving outcomes in haematological cancer’ (2003).

	NICE cancer service guidance. Related NICE Pathways: Blood and bone marrow cancers (2015), NICE pathway available at: http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers
Related National Policy	NHS England Manual for prescribed specialised services 2016/2017. Specialist cancer services (adults) [section 105, page 228]: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf NHS England (2016) National Cancer Drugs Fund List v1.0: https://www.england.nhs.uk/ourwork/cancer/cdf/list Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 1–5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

References

1. Cancer Research UK (2013) Chronic lymphocytic leukaemia incidence statistics. Accessed March 2016.

2. Cancer Research UK (2015) Chronic lymphocytic leukaemia risks and causes. Accessed October 2015.

3. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia (2013). British Committee for Standards in Haematology. Accessed March 2016.

4. BCSH CLL guidelines interim statement 2015. Accessed October 2016.