NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia

Final scope

Remit/appraisal objective

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

Background

Chronic lymphocytic leukaemia (CLL) is the most common types of chronic leukaemia and is a type of cancer that affects the white blood cells. and tends to progress slowly over many years. It mostly affects people 60 years of age and over and is rare in people 40 years of age and younger. In England there were 3,157 new cases of CLL in 2017. The risk of developing CLL increases with age and is more common in men.[1]

In CLL, the material found inside some bones (bone marrow) produces too many white blood cells called lymphocytes that aren't fully developed and don't work properly. Over time this can cause a range of problems, such as an increased risk of picking up infections, persistent tiredness, swollen glands in the neck, armpits or groin, and unusual bleeding or bruising.[2] People with CLL may live with a considerable burden of symptoms impacting on their quality of life, whether or not they have received treatment. Approximately 5% to 10% of people diagnosed with CLL are considered to have ‘high-risk’ disease, characterised by the presence of cytogenetic mutations or abnormalities (that is, 17p deletion or TP53 mutation).[3] The presence of 17p deletion or TP53 mutation can increase both the rate of cell growth and the resistance of the disease to treatment. The presence of an immunoglobulin heavy chain gene (IgHV) mutation may also affect clinical outcomes.

Treatment for CLL is complex and depends on several factors, including the extent of the disease, whether it has been treated before, and the patient’s age, symptoms and general state of health. Tables 1 and 2 below summarise the treatment options which are currently available as routine practice in the NHS in England for treated and untreated CLL.

Table 1. Treatment options for untreated CLL in NHS practice

NICE technology appraisal	*Treatment option for untreated CLL*	*Population*
People without a 17p deletion (del[17p]) or TP53 mutation		
TA174	rituximab with fludarabine and cyclophosphamide (FCR)	for whom fludarabine in combination with cyclophosphamide is considered appropriate
TA216	bendamustine with or without rituximab (BR)	for those who cannot have fludarabine combination chemotherapy
No TA published*	chlorambucil, with or without rituximab	
TA343	obinutuzumab with chlorambucil	for whom fludarabine-based therapy and bendamustine-based therapy is unsuitable
People with a del(17p) or TP53 mutation		
TA359	idelalisib with rituximab	for those with a 17p deletion or TP53 mutation
TA429	ibrutinib monotherapy	for whom chemo-immunotherapy is unsuitable
*use of chlorambucil, with or without rituximab, is detailed in TA343.		

Table 2. Treatment options for treated CLL in NHS practice

NICE technology appraisal	*Treatment option*	*Population*
TA561	venetoclax with rituximab	for people who have had at least 1 previous therapy
TA193	rituximab with fludarabine and cyclophosphamide	for people not refractory to fludarabine and who have not been previously treated with rituximab**
TA359	idelalisib with rituximab	for people whose disease has been treated but has relapsed within 24 months
TA429	ibrutinib monotherapy	for people who have had at least 1 previous therapy
Not applicable	bendamustine with or without rituximab (BR)	No marketing authorisation for this indication
**unless treated within the context of a clinical trial either at a lower dose than licensed or in combination with chemotherapy other than fludarabine and cyclosphosphamide.		

The technology

Acalabrutinib (ACP-196) is an inhibitor of Bruton's tyrosine kinase (BTK) with potential antineoplastic activity. BTK, a member of the src-related BTK/Tec family of cytoplasmic tyrosine kinases, is overexpressed in B-cell malignancies and plays a role in B-lymphocyte development, activation, signalling, proliferation and survival. It is administered orally.

Acalabrutinib does not currently have a marketing authorisation in the UK for treating chronic lymphocytic leukaemia. It has been studied in clinical trials alone or with obinutuzumab in people with untreated and treated chronic lymphocytic leukaemia.

Intervention(s)	Acalabrutinib alone or with obinutuzumab
Population(s)	People with chronic lymphocytic leukaemia (includes untreated and untreated)
Comparators	For untreated CLL, including (but not limited to): • ibrutinib (17p deletion or TP53 mutation) • idelalisib with rituximab (17p deletion or TP53 mutation) • chlorambucil with or without rituximab • obinutuzumab with chlorambucil • bendamustine with or without rituximab • rituximab with fludarabine and cyclophosphamide • venetoclax with obinutuzumab (subject to NICE appraisal) For treated CLL, including (but not limited to): • bendamustine with or without rituximab • venetoclax with rituximab • ibrutinib • rituximab with fludarabine and cyclophosphamide • idelalisib with rituximab
Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • time to next treatment • 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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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 and cost of biosimilar products should be taken into account. 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 following subgroups will be considered: • people with a 17p deletion or TP 53 mutation • people untreated • people treated • people for whom fludarabine-based therapy is unsuitable • people for whom bendamustine-based therapy is unsuitable • People with IgHV unmutated 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: Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia (2019) NICE technology appraisal guidance 561 Venetoclax for treating chronic lymphocytic leukaemia (2017) NICE technology appraisal guidance 487 Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (2017) NICE technology appraisal guidance 429 Idelalisib for treating chronic lymphocytic leukaemia (2015) NICE technology appraisal guidance 359 Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia. (2015) Technology appraisal guidance 344 Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia. (2015) Technology appraisal guidance 343 Guidance on the use of imatinib for chronic myeloid leukaemia (2003) NICE technology appraisal guidance 70 Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab (2010) NICE technology appraisal guidance 202 Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (2010) NICE technology appraisal guidance 193 **Terminated appraisals** Ofatumumab with chemotherapy for treating chronic lymphocytic leukaemia (terminated appraisal) NICE technology appraisal guidance 470 Idelalisib with ofatumumab for treating chronic lymphocytic leukaemia (terminated appraisal) NICE technology appraisal guidance 469. Ibrutinib with bendamustine and rituximab for treating relapsed or refractory chronic lymphocytic leukaemia

	after systemic therapy (terminated appraisal) (2017) NICE technology appraisal guidance 437 Appraisals in development (including suspended appraisals) Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia NICE technology appraisal guidance in development ID1402. Expected publication date to be confirmed Duvelisib for treating relapsed chronic lymphocytic leukaemia NICE technology appraisal guidance in development ID1083. Publication date to be confirmed Leukaemia (chronic lymphocytic, relapsed) - ofatumumab (maintenance) NICE technology appraisal guidance ID732. Publication date to be confirmed. Suspended February 2017 Idelalisib with bendamustine and rituximab for previously treated chronic lymphocytic leukaemia NICE technology appraisal guidance. Publication date to be confirmed. Suspended May 2018 **Related Guidelines:** Haematological cancers: improving outcomes (2016) NICE guideline NG47. **Related Quality Standards:** Haematological cancers (2017) NICE quality standard 150 **Related NICE Pathways:** Blood and bone marrow cancers (2019) NICE pathway http://pathways.nice.org.uk/
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 105 Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domain 1 https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

References

1. Cancer registration statistics, England: 2017 (2019). Office for National Statistics. Accessed March 2020

2. Chronic lymphocytic leukaemia. NHS Choices, accessed March 2020

3. Eichhorst B, Robak T, Montserrat E et al. on behalf of the European Society for Medical Oncology (ESMO) Guidelines Committee (2015). Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 26 (S5): v78-v84.