NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Acalabrutinib for treating chronic lymphocytic leukaemia

Draft scope

Draft remit/appraisal objective

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

Background

Chronic lymphocytic leukaemia (CLL) is one of 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 over the age of 60 and is rare in people under 40. 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 spongy 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.

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. Treatment can also depend on the presence of 17p deletion or TP53 mutation. Tables 1 and 2 below summarise the treatment options which are currently available as routine practice in the NHS in England for previously treated and untreated CLL.

Table 1. Treatment options for untreated CLL in NHS practice

NICE technology appraisal	*Treatment option for untreated CLL*	*Population*
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
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 previously treated CLL in NHS practice

NICE technology appraisal	*Treatment option*	*Population*
TA561	venetoclax with rituximab	for those who have had at least 1 previous therapy
TA193	rituximab with fludarabine and cyclophosphamide	for those not refractory to fludarabine and who have not been previously treated with rituximab**
TA359	idelalisib with rituximab	for those whose disease has been treated but has relapsed within 24 months
TA429	ibrutinib monotherapy	for those who have had at least 1 previous therapy
**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 in people with untreated and previously treated chronic lymphocytic leukaemia.

Intervention(s)	Acalabrutinib
Population(s)	People with chronic lymphocytic leukaemia
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 previously treated CLL, including (but not limited to): • 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 of 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 previously untreated • people previously treated • people for whom fludarabine-based therapy is unsuitable • people for whom bendamustine-based therapy is unsuitable 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 [ID1402] NICE technology appraisal guidance in development [GID-TA10328] Expected publication date to be confirmed Duvelisib for treating relapsed chronic lymphocytic leukaemia NICE technology appraisal guidance in development GID-TA10260. Publication date to be confirmed Leukaemia (chronic lymphocytic, relapsed) - ofatumumab (maintenance) NICE technology appraisal guidance. 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

Questions for consultation

Have all relevant comparators for acalabrutinib been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for treating chronic lymphocytic leukaemia?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom acalabrutinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider acalabrutinib will fit into the existing NICE pathway, blood and bone marrow cancers?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which acalabrutinib will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider acalabrutinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of acalabrutinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?
- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?
- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1. Cancer registration statistics, England: 2017 (2019). Office for National Statistics. Accessed September 2019
2. Chronic lymphocytic leukaemia. NHS Choices, accessed 13 August 2019
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.