

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal**

**Ibrutinib for untreated chronic lymphocytic leukaemia**

**Final scope**

**Remit/appraisal objective**

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

**Background**

Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells (lymphocytes). It causes anaemia, swollen lymph nodes, spleen enlargement, weight loss and increased susceptibility to infection.

In England around 3,000 people were diagnosed with CLL in 2013.<sup>1</sup> The risk of developing CLL increases with age and it is more common in men. Median survival ranges from about 3 to over 10 years depending on the genetic subtype and the stage at which the disease is diagnosed.<sup>2</sup>

Treatment options vary depending on factors such as stage of CLL, performance status and co-morbidities. For people with untreated chronic lymphocytic leukaemia, fludarabine combination therapy is the standard of care when immediate treatment is needed. NICE technology appraisal guidance 193 recommends rituximab only in combination with fludarabine and cyclophosphamide. Fludarabine combination therapy may not be suitable for about half the people needing immediate treatment, for example, people who have comorbidities such as impaired renal function, hypertension or diabetes. NICE technology appraisal 216 recommends bendamustine as a first-line treatment of chronic lymphocytic leukaemia for people who cannot have fludarabine. Obinutuzumab in combination with chlorambucil (NICE Technology appraisal 343), or ofatumumab in combination with chlorambucil (NICE Technology appraisal 344) are recommended as treatment options when bendamustine-based therapy is not suitable. In clinical practice treatment options also include chlorambucil with or without rituximab.

**The technology**

Ibrutinib (Imbruvica, Janssen) is an oral inhibitor of a protein called Bruton's Tyrosine Kinase, which stops B-cell (lymphocyte) proliferation and promotes cell death.

Ibrutinib has been studied in clinical trials compared with chlorambucil in people with one or more comorbidities that may preclude them from treatment with fludarabine, cyclophosphamide and rituximab. On 28 April 2016<sup>3</sup>, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive

opinion recommending a change to the terms of the current marketing authorisation for ibrutinib. The full indications for ibrutinib in CLL will be as follows:

“Imbruvica as a single agent is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Imbruvica is indicated for the treatment of adult patients with CLL who have received at least one prior therapy”.

<b>Intervention(s)</b>	Ibrutinib
<b>Population(s)</b>	People with untreated chronic lymphocytic leukaemia
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• Fludarabine in combination with cyclophosphamide and rituximab</li> </ul> <p>People for whom fludarabine combination therapy is unsuitable:</p> <ul style="list-style-type: none"> <li>• bendamustine, with or without rituximab</li> </ul> <p>People for whom bendamustine-based therapy is unsuitable:</p> <ul style="list-style-type: none"> <li>• chlorambucil, with or without rituximab</li> <li>• obinutuzumab with chlorambucil</li> <li>• ofatumumab with chlorambucil</li> </ul>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• overall survival</li> <li>• progression-free survival</li> <li>• response rates</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>

<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.</p>
<b>Other considerations</b>	<p>Guidance will only be issued in accordance with the marketing authorisation.</p> <p>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.</p>
<b>Related NICE recommendations and NICE Pathways</b>	<p>Related Technology Appraisals:</p> <p>‘Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (2015). NICE Technology Appraisal 343. Review date June 2018.</p> <p>‘Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia’ (2015). NICE Technology Appraisal 344. Review date June 2018.</p> <p>Appraisals in development:</p> <p>‘Ibrutinib for treating chronic lymphocytic leukaemia’ NICE technology appraisals guidance [ID749]. Publication to be confirmed.</p> <p>Related Guidelines:</p> <p>NICE cancer service guidance (2003). Improving outcomes in haematological cancers.</p> <p>Related NICE Pathways:</p> <p>NICE pathway on blood and bone marrow cancers, available at:  <a href="http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers">http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers</a></p>
<b>Related National Policy</b>	<p>National service framework: ‘Improving outcomes: a strategy for cancer’, Jan 2011.</p>

	<p><a href="https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/135516/dh_123394.pdf.pdf">https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/135516/dh_123394.pdf.pdf</a></p> <p>NHS England Manual for prescribed specialised services 2013/2014. Specialist cancer services (adults) [section 105, page 234]: <a href="http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf">http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf</a></p> <p>NHS England 2013/14 NHS standard contract for cancer: chemotherapy (adult). Section B part 1- service specifications: <a href="http://www.england.nhs.uk/wp-content/uploads/2013/06/b15-cancr-chemoth.pdf">http://www.england.nhs.uk/wp-content/uploads/2013/06/b15-cancr-chemoth.pdf</a></p> <p>Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1–5. <a href="https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf">https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf</a></p>
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### References

1. Office for National Statistics (2015). [Cancer registration statistics](#). Accessed November 2015.
2. Cancer Research UK (2015). [Statistics and outlook for chronic lymphocytic leukaemia](#). Accessed November 2015.
3. European Medicines Agency. [Pending EC decisions](#). Accessed May 2016