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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Zanubrutinib for treating Waldenström's macroglobulinaemia

Final scope

Final remit/appraisal objective

To appraise the clinical and cost effectiveness of zanubrutinib within its marketing authorisation for treating Waldenström's macroglobulinaemia.

Background

Waldenström's macroglobulinaemia is a type of non-Hodgkin's lymphoma. Lymphomas are cancers of the lymphatic system, which is a part of the immune system. Lymphomas are divided into two types: Hodgkin's lymphoma and non-Hodgkin's lymphoma. Non-Hodgkin's lymphomas can be categorised according to their grade (how fast they grow) or cell type affected (B-cell or T-cell), as well as by their clinical features. Lymphoplasmacytic lymphomas are a group of rare low grade (slow growing or indolent) non-Hodgkin's lymphomas. The most common of these is Waldenström's macroglobulinaemia[1]. Waldenström's macroglobulinaemia is caused by abnormal B cells which produce too much immunoglobulin M (IgM). Overproduction of IgM can reduce red blood cell levels, causing anaemia and fatigue[2]. IgM molecules also cluster together, which can thicken the blood (hyperviscosity). This reduces blood flow through capillaries which can cause headaches, a lack of concentration, breathlessness, poor circulation in the organs and limbs, and an increased risk of stroke[2]. IgM may react against the body, causing inflammatory conditions such as nerve damage (neuropathy)[3]. Cryoglobulinaemia can result when IgM forms immune complexes upon cold exposure, causing kidney damage and ulceration of the skin[4]. In rare cases Waldenström's macroglobulinaemia cells can infiltrate the central nervous system (CNS), resulting in Bing-Neel syndrome[5].

Waldenström's macroglobulinaemia is more common in men and mainly affects people 65 years and older[6]. Waldenström's macroglobulinaemia is incurable and the median life expectancy is 5 years[7]. In 2017, there were 353 newly diagnosed cases of Waldenström's macroglobulinaemia registered in England[8]. In 2018-19, there were a total of 5,384 hospital episodes with a primary diagnosis of Waldenström's macroglobulinaemia in England[9].

There is no established standard of care for Waldenström's macroglobulinaemia in England. The British Committee for Standards in Haematology (BCSH) guidelines recommend treatment with a combination regimen with rituximab and either cladribine, bendamustine, dexamethasone (plus cyclophosphamide) or fludarabine (with or without cyclophosphamide)[7]. Chlorambucil monotherapy is also recommended for those people who cannot tolerate other treatments. Choice of treatment usually depends on a variety of clinical factors including grade of disease, kidney function, co-morbidities and whether a person is able to have stem cell transplantation[7]. Patients treated with existing treatments generally have a partial response which lasts for a time before the disease relapses. More recently, mutations in the MYD88 gene have been found to confer a better prognosis and

greater response to Bruton's tyrosine kinase (BTK) inhibitors. Around 90% of people with Waldenström's macroglobulinaemia have a MYD88 mutation[10].

Ibrutinib monotherapy is recommended for use in the Cancer Drugs Fund as an option for treating Waldenström's macroglobulinaemia in adults who have had at least one prior therapy (NICE technology appraisal 491).

The technology

Zanubrutinib (Brukinsa, BeiGene) is a BTK inhibitor which inhibits B-cell proliferation and promotes cell death. It is administered orally.

Zanubrutinib does not currently have a marketing authorisation in the UK for any indication. It has been studied in a clinical trial in patients with Waldenström's macroglobulinaemia with MYD88 mutation, compared with ibrutinib. Patients with Waldenström's macroglobulinaemia without MYD88 mutation were enrolled in this trial in a separate uncontrolled cohort.

Intervention(s)	Zanubrutinib
Population(s)	Adults with Waldenström's macroglobulinaemia: • who have had at least 1 prior therapy, or • whose disease is untreated, for whom chemo-immunotherapy is unsuitable.
Comparators	For people who have had at least 1 prior therapy: • rituximab and bendamustine • dexamethasone, rituximab and cyclophosphamide • fludarabine and rituximab with or without cyclophosphamide • cladribine and rituximab • autologous stem cell transplantation (SCT), in people for whom autologous SCT is suitable For people for whom chemo-immunotherapy is unsuitable: • chlorambucil • rituximab monotherapy • best supportive care including blood product transfusions, plasma exchange, granulocyte stimulating factors and intravenous immunoglobulin infusions

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Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • time to next treatment • duration of response/remission • 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 of any patient access schemes for the intervention or comparator technologies will be taken into account. The economic modelling should include the costs associated with diagnostic testing for MYD88 in people with Waldenström's macroglobulinaemia who would not otherwise have been tested, if appropriate. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals'.
Other considerations	If the evidence allows the following subgroups will be considered: • people with MYD88 mutation-positive Waldenström's macroglobulinaemia • people with IgM-related conditions (e.g. paraproteinaemic neuropathies, cryoglobulinaemia, secondary cold agglutinin disease and Bing-Neel syndrome). The availability and cost of biosimilars should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic

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	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:** Ibrutinib for treating Waldenstrom's macroglobulinaemia (2017) NICE technology appraisal guidance 491. Review date: when the data collection period has ended (expected to be September 2020) **Terminated appraisals:** Ibrutinib with rituximab for treating Waldenstrom's macroglobulinaemia (2019) NICE technology appraisal 608 **Related Guidelines:** Haematological cancers: improving outcomes (2017). NICE guideline 47 **Related Quality Standards:** Haematological cancers (2017) NICE quality standard 150 **Related NICE pathways:** Non-Hodgkin's lymphoma overview (2018) NICE Pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 and 2. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 NHS England (2018/2019) Manual for prescribed specialised services 2018/19 Chapter 105: Specialist cancer services (adults) NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a NHS England. 2013/2014 NHS Standard Contract for Cancer. Radiotherapy (All Ages). B01/S/a. NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a. Department of Health (2016) NHS outcomes framework 2016 to 2017 Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 Department of Health (2014) The national cancer strategy: 4th annual report NHS England (2018) Specialised Services clinical commissioning policy: Bortezomib for Relapsed/ Refractory Waldenstrom's Macroglobulinaemia. Consultation NHS England (2017) Clinical Commissioning Policy:

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	Haematopoietic Stem Cell Transplantation (HSCT) for lymphoplasmacytic lymphoma (adults). 16067/P

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9. NHS Digital (2019) Hospital Admitted Patient Care Activity 2018-19. Accessed July 2020

10. Baron, M et al. (2019) How Recent Advances in Biology of Waldenström's Macroglobulinemia May Affect Therapy Strategy. Current Oncology Reports, 21:27