NHS England

Clinical Commissioning Policy Proposition: Bortezomib for Relapsed/ Refractory Waldenstrom's Macroglobulinaemia

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1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About Waldenstrom's macroglobulinaemia

Waldenstrom's macroglobulinaemia (WM) is a rare and incurable type of slow-growing, or indolent, non-Hodgkin's lymphoma (NHL) – a cancer of the lymphatic system. The condition is more commonly diagnosed in older adults, however, it can affect people of any age and whilst the condition can affect both males and females, it predominantly affects males.

It develops when a type of white cells, called B cells, become abnormal and grow in an uncontrolled way. The abnormal and growing B cells are primarily found in the bone marrow, spleen and liver and make large amounts of a protein called immunoglobulin M (IgM), which can make the blood thicker than normal (a condition known as hyperviscosity). These underlying changes to the blood can result in a range of symptoms, including tiredness or weakness, a tendency to develop infections and/or a tendency for anaemia and to bleed or bruise easily. However, the disease progresses very slowly and some people with WM will never experience any symptoms.

While WM is incurable, many people will live for several years with the condition and the goal of treatment is to manage symptoms and extend life. It is also a condition that is characterised by extended periods of active surveillance when no treatment is given, episodes of treatment followed by periods of remission, and then commonly by subsequent relapse. Relapse means the return of the disease and its symptoms following a period of treatment and improvement. Sometimes patients do not respond to a particular chemotherapy treatment and when this happens it is called refractory disease.

This policy proposition covers both relapsed and refractory disease, which means that each patient has had at least one prior, or 'first line', treatment.

About current treatments

The treatment of WM is highly-individualised and will depend on a number of factors, including disease biology, each patient's overall level of health and fitness (functional status) and care plan preferences. Chemotherapy is the mainstay treatment for WM with treatment often involving two or more drugs given at the same time – this is called combination chemotherapy. However, stem-cell transplantation is also an option for a small number of patients with relapsed or refractory disease, depending on their fitness and health status.

Because treatment choices are highly individualised there is no single standard of care for the management of WM, either in terms of first or subsequent treatments. There is also a wide range of different chemotherapy medicines currently available, including medicines given on their own and in combination.

In cases of relapsed and refractory WM, further treatment depends on patient choice and is also determined by prior treatment(s) and response to prior treatment(s). Dependent on prior treatment(s), the full range of treatment options available in the first line setting is also generally available in second and subsequent lines.

About the new treatment

Bortezomib belongs to the group of drugs known as proteasome inhibitors, and is a drug that stops cancer cells from growing and causes them to die. It is administered as either a subcutaneous (under the skin) or intravenous (into the vein) injection.

Bortezomib can be used to treat relapsed and refractory WM either on its own or when added to chemotherapy combinations. Most cases of relapsed and refractory WM would be treated with bortezomib for between six and eight cycles of treatment.

What we have decided

NHS England has carefully reviewed the evidence to treat relapsed and refractory WM with bortezomib**.** We have concluded that there is not enough evidence to make the treatment available at this time.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission bortezomib for relapsed and refractory Waldenstrom's macroglobulinaemia (WM).

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether bortezomib for relapsed and refractory Waldenstrom's macroglobulinaemia will be routinely commissioned is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Clinical Indication

Waldenstrom's macroglobulinaemia (WM) is a rare, incurable, slowly growing (indolent) form of non-Hodgkin's lymphoma. WM affects B lymphocyte cells in their development into plasma cells. The cancer cells in WM share features with the cancer cells seen in both myeloma (a cancer of plasma cells) and non-Hodgkin lymphoma (a cancer of lymphocytes) and this is why the disease is known as being lymphoplasmacytoid in nature.

WM is a condition that is characterised by episodes of treatment followed by periods of remission, and then commonly by subsequent relapse. Relapse means the return of the disease and its symptoms following a period of treatment and improvement. Sometimes patients do not respond to a particular chemotherapy treatment and when this happens it is called refractory disease. However, some people with WM may remain asymptomatic for a significant period of time and generally the treatment recommended for this group will be active surveillance.

Where symptoms do develop, the most common include fatigue, weight loss, anaemia, bruising or bleeding and symptoms associated with hyperviscosity

including headaches and changes in vision. Treatment is generally recommended when symptoms are present.

For patients with relapsed disease, the most recent United Kingdom (UK) guidelines for the management of WM recommend that treatment should be reserved until symptoms develop. The exception is cases with a history of hyperviscosity syndrome, where treatment may be commenced based on previous symptom threshold (Owen et al, 2014).

The treatment of WM is highly-individualised and will depend on a number of factors, including disease biology, each patient's overall level of health and fitness (functional status) and care plan preferences. For relapsed and refractory disease both the prior treatment(s) and response to prior treatment(s) are also important factors.

Chemotherapy is the mainstay treatment for WM, though stem-cell transplantation is available to some patients with relapsed disease or primary resistant disease responsive to salvage chemotherapy, and an ability to tolerate the treatment. Where chemotherapy is chosen, there is a wide range of options available which is important because WM is mainly a disease of older age and often patients have significant comorbidities. It is therefore important that treatments are convenient and tolerable, especially as such therapies are administered over long periods of time.

Chemotherapy medicines that are currently available include chlorambucil, rituximab, chlorambucil plus rituximab, cladribine plus rituximab, fludarabine with cyclophosphamide and rituximab and the combination of dexamethasone, rituximab and cyclophosphamide. As such, there is no single standard of care for the management of WM, either in the first or subsequent (i.e., relapsed and refractory disease) treatment settings.

<u>Proposed Intervention</u>

Bortezomib is a biological therapy which acts to prevent the breakdown of protein in cells by proteasomes, leading to protein build up in cells and eventual cell death. It

can be given on its own or as part of combination chemotherapy and is able to be administered either subcutaneously or intravenously. Bortezomib is usually given over a three week cycle and in cases of relapsed and refractory disease each patient will usually receive between six and eight cycles of treatment if they respond to bortezomib therapy. It is not currently licensed for the treatment of relapsed and refractory WM.

4 Definitions

Bortezomib - a form of biological therapy called a proteasome inhibitor which allows proteins to build up in cells which then die.

Complete Response (CR) – No detectable disease following a course of treatment.

Overall survival (OS) - the length of time from either diagnosis or start of treatment that the patient is still alive.

Partial Response (PR) - a decrease in tumour size or the amount of cancer detected in the body following treatment.

Progression-free survival (PFS) - the length of time from either diagnosis or start of treatment to disease progression or patient death from any cause.

Progressive disease – is where the disease is progressing and therefore worsening. In the context of WM, this generally relates to the amount of IgM present in the blood and increasing symptoms of disease.

Relapsed disease – describes when a condition has recurred following response to previous treatment, this may occur at any time following completion of treatment.

Refractory disease – means that there has been no response to the immediately preceding treatment, patients have either progressed during treatment or have stable disease whenever treatment has been stopped.

Rituximab - a form of biological therapy which works by targeting the protein CD20, which is found on the surface of B cells. It is used in the treatment of non-Hodgkin lymphomas, chronic lymphocytic leukaemia and a wide range of autoimmune diseases.

Stable disease – is where a cancer is neither growing nor shrinking following a course of treatment. In the context of WM, this is generally related to the amount of IgM present in the blood.

Waldenstrom's macroglobulinaemia (WM) - an indolent (low grade) form of non-Hodgkin's lymphoma affecting B lymphocytes. It may also be known as lymphoplasmacytic lymphoma (LL).

White cells – these are cells in the lymph nodes and blood that fight infection. The abnormal white blood cells in WM grow in an uncontrolled way and manufacture excessive amounts of immunoglobulin M.

5 Aims and Objectives

This policy proposition considered bortezomib as a treatment for patients with relapsed and refractory WM.

The objectives were to establish, via an evidence review, the following:

- Is bortezomib, either alone or as combination therapy, clinically effective in patients with relapsed/refractory Waldenstrom's macroglobulinaemia following ≥1 first-line treatment?
- Is bortezomib more effective than comparison therapies in patients with relapsed/refractory Waldenstrom's macroglobulinaemia following ≥1 first-line treatment?
- Is bortezomib safe to use in patients with relapsed/refractory Waldenstrom's macroglobulinaemia following ≥1 first-line treatment?
- Is bortezomib more cost-effective then comparison therapies in patients with relapsed/refractory Waldenstrom's macroglobulinaemia following ≥1 first-line treatment?

6 Epidemiology and Needs Assessment

Waldenstrom's macroglobulinaemia (WM) is a relatively rare disease with an age standardised incidence rate of 0.55 cases per 100,000 per year in the UK (Owen et al, 2014). Based on current estimates of the population in England, this leads to an overall estimate of 304 new cases per year.

It is typically a disease of older adults with a median age at presentation of over 70 years, with a male predominance and higher incidence in Caucasians (Owen et al, 2014). The overall median survival is approximately 8 years.

Emerging epidemiology of the condition demonstrates an increased risk of WM for those with a personal or family history of a wide range of autoimmune, inflammatory and infective disorders including Sjogren's syndrome and autoimmune haemolytic anaemia. However, the absolute level of risk for first-degree relatives remains low (Owen et al, 2014).

Clinical features of WM include hepatosplenomegaly, lymphadenopathy, oronasal bleeding and hyperviscosity syndrome. Fatigue due to anaemia is the commonest presenting symptom. Complications include bone marrow failure, immune complex vasculitis and infections. However, the disease may remain stable or progress very slowly, without symptoms, for many years and patients in the asymptomatic stage are monitored, with treatment reserved for those who develop symptoms of disease.

7 Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of bortezomib for relapsed and refractory WM.

Although bortezomib does appear to be active in the treatment of relapsed WM, the number of published trials for bortezomib in relapsed WM is small, they are of variable quality and provide limited data on important outcomes, such as overall survival and progression-free survival, meaning the degree of effectiveness, or effectiveness compared to other regimens, cannot be estimated.

1. Is bortezomib, either alone or as combination therapy, clinically effective in patients with relapsed/refractory Waldenstrom's macroglobulinaemia following ≥1 first-line treatment?

Five clinical trials of bortezomib in people with relapsed and refractory Waldenstrom's macroglobulinaemia (WM), either alone or in combination with rituximab or bendamustine, were reviewed. The most commonly reported outcomes were assessments of treatment response, such as complete response, partial response, or stable disease.

Two trials treated patients with bortezomib alone. Treon et al (2007) recruited patients who had failed treatment with at least one first-line therapy (n=27), while Chen et al (2007) recruited both relapsed and treatment-naïve patients (n=27). A total of 15/27 patients (56%) had relapsed disease in this latter trial; this cohort should be considered a post-hoc subgroup.

No participants in either trial achieved a complete response. Treon et al defined a major response as ≥50% reduction in serum IgM, which was achieved by 13 patients (48%). Chen et al reported a similar endpoint of partial response, which had a stricter definition of ≥50% reduction in serum IgM, plus confirmation of the reduction 6 weeks later and reduced lesion size. Only 4 patients (27%) with relapsed disease met this more stringent definition.

The remaining patients in these trials had a minor response (≥25% reduction in serum IgM) or stable disease. Again, Chen et al had a stricter definition of stable disease, requiring ≤50% change in serum IgM, plus no new lesions or sites of disease. This led to a greater proportion of patients in this trial being classified as stable (70% vs. 0) but these data are confounded by the inclusion of treatment-naïve patients.

Chen et al reported a median progression-free survival of 16.3 months, while Treon et al reported a median time to progression of 6.6 months. Time to progression is similar to progression-free survival, but does not capture instances where a patient

has died. Treon et al did not report any deaths, so in this case the two outcomes are likely to be similar. The difference may reflect the uncertainty that is inevitable with such small sample sizes, or the confounding influence of the inclusion of treatment-naïve patients in the study by Chen et al. Chen et al also found the median duration of response was 10 months and median duration of stable disease was 14.3 months. As before, these data may be confounded.

Ghobrial et al (2010) assessed the effectiveness of bortezomib plus rituximab in patients with relapsed and refractory WM (n=37). The primary endpoint was the proportion of patients with at least a minor response to treatment (as defined by the Third International Workshop on Waldenstrom's Macroglobulinaemia) (Kimby et al., 2006). After a median follow-up of 16 months, this outcome was achieved by 30 patients (81%, 95% CI 65% to 92%), including one patient (3%) with complete remission and one with near complete remission. The remainder of patients meeting the primary endpoint had partial remission (n=17, 46%) or a minor response (n=11, 30%). Four patients (11%) maintained stable disease and one had disease progression.

Median progression-free survival was 15.6 months (95% CI 11.2 to 21.1) and median time to progression was 16.4 months. Median time to next therapy was reported to account in view of the fact that guidance recommends patients with relapsed disease should not be treated until they become symptomatic, despite clinical evidence of relapsed disease. The median time to next therapy was 17.6 months (range 1 to 25 months). Progression-free survival was 58% and 45% at 12 and 18 months respectively. Median overall survival was not reached during the follow-up period, but the estimated 12 month survival was 94% (95% CI 86% to 100%).

One trial (n=49) with a combined phase 1/2 design compared the effectiveness of weekly bortezomib plus rituximab to twice-weekly bortezomib (Agathocleous et al., 2010). Enrolled patients had follicular lymphoma, of whom 1 of 7 in the phase 1 stage and 10 of 42 in the phase 2 stage had WM. Patients in the phase 2 stage of the trial were randomised to receive bortezomib 1.3 mg/m^2 twice weekly in 21 day

cycles (Arm A), or bortezomib 1.6 mg/m^2 once weekly (Arm B) in 35-day cycles. Patients in both arms received rituximab 375 mg/m^2 which was administered on the same days as bortezomib in both treatment arms, but only during cycles 1 and 4.

The primary outcome was safety. Efficacy outcomes were secondary endpoints. Whilst results were reported for WM patients as a subgroup, the study did not confirm which arm the WM patients were treated in. Nine of the ten patients treated with bortezomib achieved at least a partial response, but the doses these patients were receiving were not specified. The remaining patient had stable disease. Four of the 10 WM patients had no disease progression 2-2.5 years following treatment, while five had progressive disease. The remaining patient was not accounted for.

One trial assessed the effectiveness of bortezomib plus bendamustine for treatment of relapsed WM (Moosmann et al., 2010). However, this study enrolled patients with several types of indolent non-Hodgkin's lymphoma and only one participant had a diagnosis of WM. The study should therefore be considered a case report for purposes of assessing efficacy in WM treatment and extreme caution should be used when extrapolating the results to other patients.

The WM patient in this trial was a 59-year old male with refractory stage IV disease who had failed treatment with seven prior therapies, including several rituximab-containing regimens. The patient achieved partial remission of disease, but no definition of partial remission was supplied. The only safety event reported was bendamustine dose-limiting thrombocytopenia. The authors of this study highlight that it is beyond the scope of the data to determine the efficacy of this combination.

There are several problems with the trials discussed above which limit how useful they are in making decisions about treating WM:

- The trials were all very small; the largest trial enrolled 27 people. This means it is difficult to know if the results would also apply more widely to people with WM. The most commonly reported efficacy outcome was treatment response, but use of slightly different definitions of response by each trial confound efforts to make a pooled estimate of the treatment effect. These differences,

together with the diversity of endpoints used, mean that many outcomes reported only have evidence from a single trial.

- The trials used slightly different definitions of treatment response, which makes it difficult to compare the trials to see if bortezomib has a consistent effect.
- None of the trials compared bortezomib to any other drugs or treatments for WM. This means that it is not clear whether any benefits to the patient were due to bortezomib, or whether they were due to the normal course of the disease or to chance.

2. Is bortezomib more effective than comparison therapies in patients with relapsed/refractory Waldenstrom's macroglobulinaemia following ≥1 first-line treatment?

As stated, there are no published studies comparing bortezomib with other treatments or standard care in patients with relapsed Waldenstrom's macroglobulinaemia. It is not possible, therefore, to establish whether bortezomib, either alone or in combination with other therapies, is more effective than other therapies available for patients with relapsed/refractory disease.

3. Is bortezomib safe to use in patients with relapsed/refractory Waldenstrom's macroglobulinaemia following ≥1 first-line treatment?

The 5 reviewed trials found that adverse events were common and were in line with what is already known about the safety of bortezomib. Side effects such as fatigue, sensory neuropathy, reduced blood cell counts and reduced platelet counts were common.

In the two studies which assessed bortezomib alone for treatment of Waldenstrom's macroglobulinaemia, grade III (moderate) or IV (severe) toxicities were reported frequently. Neuropathy is a particular concern with bortezomib, and was reported by 11-22% of patients. Other commonly reported adverse drug reactions (ADRs) were fatigue, myalgia, leukopenia, neutropenia, thrombocytopenia, neuropathic pain, dizziness, diarrhoea and dyspnoea.

Ghobrial et al (2010) reported grade III or IV toxicities including lymphopenia (24%), neutropenia (16%), leukopenia (14%), thrombocytopenia (13%), anaemia (11%) and peripheral neuropathy (5%). One patient died of viral pneumonia.

Agathocleous et al. (2010) compared weekly bortezomib plus rituximab to twice-weekly bortezomib. The primary outcome was saftety, however events were not reported for the subgroups of patients with different diagnoses. It is therefore, not known how many events occurred in patients with WM. Overall, grade III or IV events were relatively common in both treatment arms. The most common were lymphopenia (24-38%), thrombocytopenia (10-29%) and neutropenia (14-24%). Neuropathy of grade III or IV was reported in 14% of patients in arm A and 19% in arm B.

Because bortezomib was not compared to any other treatments, or to standard care, it is not possible to tell whether bortezomib is any more or less safe than other drugs for Waldenstrom's macroglobulinaemia.

4. Is bortezomib more cost-effective then comparison therapies in patients with relapsed/refractory Waldenstrom's macroglobulinaemia following ≥1 first-line treatment?

As stated, there are no published studies comparing bortezomib with other treatments or standard care in patients with relapsed Waldenstrom's macroglobulinaemia. It is not possible, therefore, to establish whether bortezomib, either alone or in combination with other therapies, is more cost-effective than other therapies available for patients with relapsed/refractory disease.

Conclusion

In summary, the published evidence suggests that bortezomib produces a clinical response in the treatment of relapsed or refractory WM. However, its use is associated with major adverse effects. The paucity of data given the variable rigour in assessment of response, the modest durations of follow-up and the small size of the clinical studies means that it is difficult to assess the value of bortezomib in

relapsed or refractory WM.

8 Proposed Criteria for Commissioning

This is proposed not to be funded.

9 Proposed Patient Pathway

This is proposed not to be funded.

10 Proposed Governance Arrangements

This is proposed not to be funded.

11 Proposed Mechanism for Funding

This is proposed not to be funded.

12 Proposed Audit Requirements

This is proposed not to be funded

13 Documents That Have Informed This Policy Proposition

- PICO 1601 NHS England
- Preliminary Policy Proposal 1601, NHS England
- Evidence Review 1601, NHS England

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

15 References

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