

## obinutuzumab 1,000mg concentrate for solution for infusion (Gazyvaro®) SMC No. (1219/17)

### Roche Products Ltd

10 February 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission considered under the ultra-orphan-medicine process.

**obinutuzumab (Gazyvaro®)** is accepted for use within NHS Scotland.

**Indication under review:** obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance is indicated for the treatment of patients with follicular lymphoma who did not respond or who progressed during or up to six months after treatment with rituximab or a rituximab-containing regimen.

Obinutuzumab plus bendamustine induction therapy followed by obinutuzumab maintenance significantly increased progression free survival compared with bendamustine monotherapy induction without any maintenance treatment, in patients with rituximab-refractory follicular lymphoma.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of obinutuzumab. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

**Chairman Designate,  
Scottish Medicines Consortium**

## Indication

Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to six months after treatment with rituximab or a rituximab-containing regimen.<sup>1</sup>

## Dosing Information

**Induction (in combination with bendamustine):** obinutuzumab 1,000mg intravenous (IV) infusion, in combination with bendamustine, on days 1, 8 and 15 of the first 28-day treatment cycle, then on day 1 of the next five 28-day cycles.

### Maintenance

Patients who respond to induction treatment (i.e. the initial 6 treatment cycles) or have stable disease should continue to receive obinutuzumab 1,000 mg IV infusion as single agent maintenance therapy once every two months for two years or until disease progression (whichever occurs first).

Obinutuzumab should be administered under the close supervision of an experienced physician and in an environment where full resuscitation facilities are immediately available.

The dose of bendamustine used in combination with obinutuzumab is detailed in the summary of product characteristics.<sup>1</sup>

## Product availability date

13 June 2016

Obinutuzumab meets SMC ultra-orphan criteria for this indication.

## Background

Obinutuzumab is a recombinant humanised and glycoengineered type II monoclonal antibody that targets CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes. It induces direct cell death, mediates antibody-dependent cellular cytotoxicity and phagocytosis through immune effector cells and produces some complement-dependent cytotoxicity. It is licensed for patients with follicular lymphoma who are refractory to the anti-CD20 monoclonal antibody, rituximab.<sup>1,2</sup> It has been designated as an orphan medicinal product by the European Medicines Agency (EMA) for this indication and fulfils SMC ultra-orphan criteria.<sup>3</sup>

Obinutuzumab for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

## Nature of condition

Follicular lymphoma is a subtype of indolent non-Hodgkin's lymphoma (iNHL), which comprises about 70% of iNHL and about 20% to 25% of all new non-Hodgkin's lymphoma (NHL). It is a mature B-cell neoplasm and about 85% of patients have the t(14;18)(q32;q21) translocation that leads to over expression of the BCL-2 protein, which blocks programmed cell death and apoptosis. The median age at diagnosis is 59 years and median survival is eight to ten years. Follicular lymphoma is a low grade

lymphoma that tends to grow relatively slowly and is chemo-sensitive. Systemic therapy is recommended for patients with symptomatic advanced disease. Remission may be induced with initial treatment (typically rituximab plus chemotherapy) and the quality and duration of this appears to be related to overall survival. However, patients relapse and as the disease progresses to the resistant and refractory stages treatment options are limited. Treatment choice depends upon the patient's symptoms, fitness and response to previous therapy. Options include chemotherapy alone or for some patients in combination with rituximab, <sup>90</sup>Y-ibritumomab, transplant for some younger patients who are suitable, and idelalisib for double-refractory patients (e.g. refractory to two lines of therapy).<sup>2,4,5</sup>

A patient and clinician engagement (PACE) meeting was held to consider the added value of obinutuzumab in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the unmet need for effective treatment options in patients with very poor prognosis and a narrow range of treatment options, which can be associated with significant adverse events and/or limited benefits.

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely for effective therapies for certain rituximab-refractory patients with limited treatment options.

## Impact of new technology

### Summary of evidence on comparative efficacy

An ongoing open-label phase III study (GADOLIN) recruited 413 adults with CD20-positive iNHL who had no response to or had progressed within six months of rituximab as monotherapy or within a regimen, an Eastern Co-operative Oncology Group (ECOG) performance status of 0 to 2 and life expectancy of at least five years. Randomisation was stratified by iNHL subtype (follicular or other), refractory regimen (rituximab monotherapy or rituximab plus chemotherapy), prior therapies ( $\leq 2$  or  $> 2$ ) and geographic region. Patients were equally assigned to obinutuzumab (1,000mg IV on days 1, 8 and 15 of the first 28-day cycle then on day 1 of the next five 28-day cycles) plus bendamustine (90mg/m<sup>2</sup> IV on days 1 and 2 of six 28-day cycles) or to bendamustine monotherapy (120mg/m<sup>2</sup> IV on days 1 and 2 of six 28-day cycles). Patients in the obinutuzumab-bendamustine group who had no evidence of disease progression after this six-cycle induction regimen could receive obinutuzumab maintenance at a dose of 1,000mg IV every two months for two years or until disease progression. Crossover was not permitted before the primary analysis. The primary outcome was progression free survival (PFS), defined as the time from randomisation to progression or relapse according to the modified response criteria for NHL and assessed by a blinded independent review committee (IRC) or death from any cause. This was assessed in the intention-to-treat population, which comprised all randomised patients.<sup>2,6</sup>

Obinutuzumab-bendamustine significantly increased PFS compared with bendamustine, with a hazard ratio (HR) of 0.55 (95% confidence interval [CI]: 0.40 to 0.74),  $p=0.0001$  at the primary PFS analysis (cut-off 1<sup>st</sup> September 2014) and within the subgroup of 335 (81%) patients who had follicular lymphoma (with data shown from the updated 1<sup>st</sup> May 2015 cut-off): HR of 0.47 (95% CI: 0.34 to 0.64),  $p<0.0001$ . In the primary analysis, median PFS was not reached in the obinutuzumab-bendamustine group and was 14.9 months in the bendamustine group. Within the follicular lymphoma subgroup, at the updated analysis, median PFS was 29.2 and 13.8 months in the respective groups.<sup>2,6</sup>

At time of the primary analysis 18% (34/194) and 20% (41/202) patients in the obinutuzumab-bendamustine and bendamustine groups had died. In the subgroup with follicular lymphoma at data cut-off on 1<sup>st</sup> April 2016 the respective figures were 24% (39/164) and 37% (64/171). Median overall

survival could not be estimated in the obinutuzumab group and was 53.9 months in the bendamustine group. The HR was 0.58 (95% CI: 0.39 to 0.86),  $p=0.0061$ .<sup>2,6,7</sup>

At the time of the primary analysis there was no significant difference between the obinutuzumab-bendamustine and bendamustine groups in IRC-confirmed overall response rate (ORR), defined as complete or partial response according to the modified response criteria for NHL, achieved at end-of-induction (within the population who reached end-of-induction response assessment or withdrew prematurely): 69% (130/188) versus 63% (119/189). Similar results were observed in the subgroup with follicular lymphoma in the updated analyses, 68% (111/164) versus 65% (111/170) at end-of-induction and 76% (125/164) versus 79% (135/171) overall.<sup>2,6,8,9</sup>

Duration of ORR was significantly longer in the obinutuzumab-bendamustine group, compared with bendamustine, with a HR of 0.42 (95% CI: 0.29 to 0.61) at the primary analysis. In the follicular lymphoma subgroup at the updated analysis, the HR was 0.39 (95% CI: 0.27 to 0.55), with median duration of response not possible to estimate in the obinutuzumab-bendamustine group and 11.6 months in the bendamustine group.<sup>2,6</sup>

There were no differences between the treatment groups within the whole study population during treatment or follow-up for the patient reported outcomes of functional assessment of cancer therapy-lymphoma (FACT-Lym) and euro-quality-of-life-5D (EQ-5D) questionnaire. Time to deterioration in FACT-Lym, defined as deterioration from baseline of at least 6 points, was greater in the obinutuzumab-bendamustine group, compared with bendamustine, with a HR of 0.74 (95% CI: 0.56 to 0.98) and median of 8.0 versus 4.6 months in the respective groups. There were no quality of life analyses in the follicular lymphoma subgroup.<sup>2</sup>

*Other data were also assessed but remain commercially confidential.\**

### **Summary of evidence on comparative safety**

The adverse event profile of obinutuzumab is characterised within its existing indication in chronic lymphocytic leukaemia (CLL) and the European Medicines Agency (EMA) review concluded that overall there were no unexpected safety findings or new important risks identified. The safety profile of obinutuzumab-bendamustine was considered similar to that of bendamustine alone and consistent with that seen in the pivotal study of obinutuzumab plus chlorambucil in CLL. The safety profile of obinutuzumab-bendamustine in follicular lymphoma subgroup was considered to be similar to the total study population in the GADOLIN study.<sup>2</sup>

During the induction phase of the GADOLIN study 97% of patients in both the obinutuzumab-bendamustine group and bendamustine monotherapy group reported adverse events, which were  $\geq$  grade 3 in severity for 55% (113/204) and 52% (107/205), serious for 28% (58/204) and 22% (44/205) and led to the withdrawal of any study medication in 14% (29/204) and 17% (34/205) in the respective groups. The imbalance in serious adverse events was mainly due to serious neutropenia and infusion related reactions. During the induction phase neutropenia occurred in 31% of patients in both groups and in 12% of patients receiving obinutuzumab during the maintenance phase. In the obinutuzumab-bendamustine group, compared with the bendamustine group, infusion-related reactions were reported by more patients over the whole study period, 69% versus 63%, respectively. In the respective groups corticosteroid prophylaxis for infusion-related reactions was given to, 78% and 37% of patients. The incidence of thrombocytopenia was lower in the obinutuzumab-bendamustine group (where bendamustine dose was  $90\text{mg}/\text{m}^2$ ) compared with the bendamustine monotherapy group (where bendamustine dose was  $120\text{mg}/\text{m}^2$ ) over the whole study period: 15% versus 24%. The incidence of haemorrhagic events was similar 11% and 10% in the respective treatment groups over the whole study period. Cardiac adverse events were reported more frequently in the obinutuzumab-

bendamustine group, compared with the bendamustine group, 11% versus 5.6%, with the difference partly due to symptoms of infusion-related reactions.<sup>2,6</sup>

During the obinutuzumab maintenance phase 77% (118/154) of patients reported an adverse event, which were  $\geq$  grade 3 in severity for 30% (46/154), serious for 13% (20/154) and led to discontinuation of study medication for 3.2% (11/154).<sup>2</sup>

### **Summary of clinical effectiveness issues**

Obinutuzumab is the second anti-CD20 monoclonal antibody (after rituximab) for treatment of follicular lymphoma and it is licensed for use in patients who are refractory to rituximab alone or as part of a regimen. In follicular lymphoma, rituximab is licensed for use in combination with chemotherapy for treatment of previously untreated patients with stage III to IV follicular lymphoma; as maintenance therapy for treatment of follicular lymphoma patients responding to induction therapy; and as monotherapy for treatment of patients with stage III to IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.<sup>10</sup> SMC has accepted the first two indications for restricted use within NHS Scotland (advice numbers 135/04, 330/06 and 675/11 for IV preparation and 975/14 for the subcutaneous preparation). Obinutuzumab has been designated as an orphan medicinal product by the EMA for treatment of follicular lymphoma and fulfils SMC ultra-orphan criteria.<sup>3</sup>

In the pivotal study obinutuzumab-bendamustine induction plus obinutuzumab maintenance, compared with bendamustine induction, significantly improved PFS by about 15 months in rituximab-refractory patients with follicular lymphoma, with divergence of the PFS Kaplan-Meier curve from about nine months onwards. ORRs were similar across the groups, but duration of ORR was longer in the obinutuzumab group. Overall survival data were immature and long-term safety data were limited.<sup>2,6</sup>

The study compared an induction plus maintenance regimen (obinutuzumab-bendamustine then obinutuzumab) with an induction regimen (bendamustine). The design of the study did not allow differentiation of the contribution of the induction regimen and the maintenance regimen to the overall treatment effect. The open-label design of the study could limit assessment of subjective outcomes such as quality-of-life and adverse events. Also, safety data from the study should be interpreted with reference to the longer treatment duration of up to 2.5 years in the group that received obinutuzumab-bendamustine induction then obinutuzumab maintenance, compared with the group that received bendamustine induction only for six months. Additionally a lower dose of bendamustine was administered when combined with obinutuzumab, compared to the monotherapy dose: 90mg/m<sup>2</sup> versus 120mg/m<sup>2</sup>.<sup>2,6</sup>

In the ITT population at 1<sup>st</sup> September 2014 cut-off, small proportions of the study population had received three or more prior therapies (21% [84/396]) or had ECOG performance status of 2 (4.5% [18/396]). This may limit the application of results to these patient groups. Conclusions on efficacy in these patients cannot be drawn from the small subgroup analyses.<sup>2</sup>

At 1<sup>st</sup> May 2015 cut-off in the obinutuzumab-bendamustine and bendamustine groups, 19% (38/204) and 23% (48/209), respectively, were refractory to rituximab monotherapy. Rituximab monotherapy is generally not used to treat follicular lymphoma in Scottish practice. In the patients who were refractory to rituximab plus chemotherapy (81% [166/204] and 77% [161/209], respectively), for 82 and 70 patients respectively, refractory status was on the basis of progressive disease during or within six months of rituximab maintenance therapy. There were 33 and 60 patients (16% and 29% of the total study population) respectively who had progressive disease within six months of rituximab plus chemotherapy induction, with only 5 and 2 patients having progressive disease during rituximab plus chemotherapy induction.<sup>2</sup>

Subgroup analyses (in the ITT population at 1<sup>st</sup> September 2014 cut-off) indicated that the HR (95% CI) for PFS was 0.55 (0.28 to 1.08) with obinutuzumab-bendamustine versus bendamustine in patients refractory to rituximab monotherapy (n=83), was 0.57 (0.35 to 0.93) in patients refractory to rituximab maintenance after chemotherapy induction (n=146) and was 0.59 (0.36 to 0.95) in patients refractory to rituximab plus chemotherapy induction, defined as no complete or partial response or progressive disease during or within six months, (n=162).<sup>2</sup>

In the ITT population at 1<sup>st</sup> September 2014 cut-off within the obinutuzumab-bendamustine and bendamustine groups, respectively, 76% (147/194) and 81% (164/202) were double-refractory (i.e. refractory to both rituximab and an alkylating agent). Subgroup analysis indicated that the HR (95% CI) for PFS was 0.56 (0.40 to 0.78) with obinutuzumab-bendamustine versus bendamustine in those who were double-refractory and 0.55 (0.28 to 1.10) in those who were not.<sup>2</sup>

To support the economic analysis, an indirect comparison of the licensed obinutuzumab-bendamustine induction and maintenance regimen versus rituximab-chemotherapy induction in patients with rituximab-refractory follicular lymphoma was presented. Patient level data from the GADOLIN study were matched and adjusted using propensity scoring methods with that from a US prospective observational cohort of patients diagnosed with follicular lymphoma between 2004 and 2007 within the Lymphocare database. It suggested PFS benefit for obinutuzumab-bendamustine, compared with rituximab-chemotherapy. The indirect comparison was limited by uncertainty around the potential heterogeneity of the regimens received by patients in the Lymphocare cohort versus Scottish practice. Characteristic of this type of analysis is potential bias due to unobserved confounders and there was insufficient information on demographic and disease characteristics within the rituximab-chemotherapy group to assess heterogeneity relative to the obinutuzumab-bendamustine group and to assess external validity. There was heterogeneity across the studies in design, settings, follow-up and assessment of primary outcome. Finally, the indirect comparison did not assess overall survival, quality-of-life or safety outcomes.

Clinical experts consulted by SMC considered that obinutuzumab is a therapeutic advancement due to its clinical effects. They considered that the place in therapy of obinutuzumab may be for certain rituximab-refractory patients. Clinical experts consulted by SMC considered that the introduction of this medicine may impact on patients and service delivery through the requirement during the maintenance phase for additional visits to the day ward for IV administration of obinutuzumab, which can be associated with infusion reactions.

## **Patient and clinician engagement (PACE)**

A PACE meeting with patient group and clinical specialist representation was held to consider the added value of obinutuzumab, as an ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by this group were:

- This regimen may address an unmet need for effective treatment options in patients with very poor prognosis and a narrow range of treatment options. The available options can be associated with significant adverse events and/or limited benefits.
- Relative to the alternative treatment option of intensive chemotherapy, the regimen of obinutuzumab-bendamustine is easier for the service to administer and may be easier for the

patient to receive in terms of treatment schedule and severity and management of adverse events.

- The obinutuzumab-bendamustine regimen may produce a remission of about 2.5 years and may offer improvements in progression-free and overall survival relative to bendamustine induction. This may be achieved without a decrease in quality of life and with a manageable adverse event profile, that the service has experience of dealing with.
- As patients are generally well in remission, the obinutuzumab-bendamustine regimen may benefit the patient, their carers and family by allowing the patient to lead a relatively normal life, to contribute to the family and spare them from the burden of receiving an intensive chemotherapy regimen.

### **Additional Patient and Carer Involvement**

We received a patient group submission from the Lymphoma Association, which is a registered charity. The Lymphoma Association has received 5.7% pharmaceutical company funding in the annual organisational income of 2016, including from the submitting company. A representative from the Lymphoma Association also participated in the PACE meeting. The key points of the submission have been included in the full PACE statement.

## **Value for money**

The submitting company presented a cost-utility analysis which compared obinutuzumab-bendamustine against rituximab-chemotherapy (R-chemo) in the licensed indication. The cost of R-chemo reflected rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) in the base case analysis.

A three-state Markov model was developed which consisted of a PFS health state, a progressed disease health state (PD) and death. Patients entered the model in PFS health state and patients could remain in this health state, or transition to a worse health state. The PFS health state was subdivided into on and off treatment with subsequent therapies captured in the PD state. Overall survival was a function of time spent in the PFS and PD health states.

The sources of the clinical data included the GADOLIN study which provided PFS data for obinutuzumab-bendamustine. These data were extrapolated using the Weibull function in order to generate PFS estimates for obinutuzumab-bendamustine beyond the pivotal study period. PFS for R-chemo was estimated by applying a hazard ratio from an indirect comparison to the PFS Weibull function estimated for obinutuzumab-bendamustine. The probability of death for obinutuzumab-bendamustine in the PFS health state was taken from the mortality rate in the GADOLIN study. For R-chemo the probability of death in PFS was estimated by taking an average of the mortality rate from the obinutuzumab-bendamustine and bendamustine arms of the pivotal study. In order to estimate post progression survival (PPS) in the PD health state for both obinutuzumab-bendamustine and R-chemo, data from both arms of the pivotal study were pooled and extrapolated using the Weibull function.<sup>6</sup>

Utilities estimates were taken from a cross-sectional study which collected EQ-5D data from UK patients.<sup>11</sup> The utility values in the PFS and PD health states were 0.81 and 0.62 respectively.

Medicines costs were included in the analysis as were costs associated with administration, adverse events management, supportive care and subsequent therapies. Medicine costs for obinutuzumab-

bendamustine were based on the observed duration of treatment in the pivotal study. The base case analysis assumed vial sharing but removing this assumption had a limited impact on the result.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a simple discount was offered on the price of the medicine. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

The base case result indicated that the incremental cost-effectiveness ratio (ICER) for obinutuzumab-bendamustine versus R-chemo was £27,988 per quality adjusted life year (QALY). This result was based on an incremental cost of £42,775 and 1.53 QALYs and an incremental life year gain of 1.84 in favour of obinutuzumab-bendamustine.

The analysis was most sensitive to increasing the PFS hazard ratio for obinutuzumab-bendamustine versus R-chemo from the mean estimate to the upper limit of the confidence interval (ICER increased to £37,840), assuming that all patients in PFS received treatment as per protocol instead of as observed in the pivotal study (£35,673), using the Gamma function to model PPS (£33,419), increasing the health benefit discount rate to 6% (£32,443), and using utility values from an alternative published study (£31,374).<sup>12</sup>

The company also presented an analysis which compared obinutuzumab-bendamustine versus bendamustine. This analysis generated an ICER of £34,245 and the result was based on an incremental cost of £45,041 and 1.32 QALYs. The economic model also estimated an incremental life year gain of 1.54 in favour of obinutuzumab-bendamustine.

The main weaknesses were:

- The company considered that R-chemo was the appropriate comparator for the base case analysis and a sensitivity analysis was also provided against bendamustine monotherapy. However, it was unclear whether a patient who has become rituximab refractory would be re-treated with a rituximab regimen such as R-chemo. While it was considered appropriate to use a rituximab regimen as a comparator in the analysis, rituximab-bendamustine followed by rituximab maintenance was identified as potentially the most relevant comparator for the economic case. Therefore, the company was requested to provide a sensitivity analysis versus rituximab-bendamustine followed by rituximab maintenance. The company was unable to provide this comparison due to a lack of clinical data but did note that a proportion of patients in the Lymphocare database (which was used to estimate the efficacy of R-chemo in the indirect comparison) received rituximab maintenance treatment.
- The company confirmed that the R-chemo comparator represented a general weighted average R-chemo mix based on the treatments included in the indirect comparison as opposed to R-CHOP, which informed the medicines costs and adverse events for the comparator. As a result, the company provided an analysis which used medicines costs based on the range of medicines included in the indirect comparison and the ICER reduced to £27,849. However, it is uncertain whether the modelled efficacy of R-chemo would generalise to the potential range of treatments available in Scottish clinical practice, and as noted above rituximab-bendamustine followed by rituximab maintenance was identified as the relevant comparator.
- No direct or indirect OS data were presented versus R-chemo. The company also considered the OS data for obinutuzumab-bendamustine from the GADOLIN study too immature to be extrapolated and used in the economic model, which may reflect the nature of the condition and the relatively long median OS. Despite these weaknesses with the data, the economic model still produced a material increase in OS of 1.84 discounted life years in favour of obinutuzumab-

bendamustine versus R-chemo. The result was generated as the economic model estimated OS as the sum of time spent in the PFS and PD health states, and as there was a significant difference between the medicines in terms of PFS this was assumed to result in an OS advantage with approximately 89% of the PFS gain assumed to result in an OS gain. The analysis may also lack face validity as the estimated life years for R-chemo were less than for bendamustine and it may be that R-chemo would be more effective than bendamustine in clinical practice. The company has subsequently provided additional analyses and clarification regarding the modelling of OS as well as a hazard ratio demonstrating a difference in OS between obinutuzumab-bendamustine and R-chemo. Additional sensitivity analysis which reduced the proportion of the PFS gain assumed to result in an OS gain to 75%, 50% and 25% increased the ICER to £32k, £41k and £59k respectively.

## **Impact beyond direct health benefits and on specialist services**

At the PACE meeting it was highlighted that by the time patients become refractory to rituximab-containing therapy, they may be affected by the cumulative psychological impact of repeated relapses and may suffer significant physical symptoms of relapsed lymphoma. This may impact their quality of life, ability to work and/or provide care to any dependents.

Obinutuzumab-bendamustine may be associated with an improved adverse event profile relative to intensive chemotherapy, with less frequent visits to hospital for administration of treatment or to manage adverse events. This may be associated with overall improved quality of life and ability to continue to work and care for any dependents. As many patients are adults of working age this can be an important issue.

When the patient is in remission and leading a relatively normal life for a significant period, the patient's carers and family may benefit emotionally from having them well. In addition they may benefit in terms of family routine and financial contributions to the household. They would also be spared from the impact of helping the patient deal with symptoms of lymphoma or with receiving an intensive chemotherapy regimen.

## **Costs to NHS and Personal Social Services**

The submitting company estimated there would be 74 patients eligible for treatment with obinutuzumab-bendamustine in all years. The estimated uptake rate was 10% in year 1 (7 patients) rising to 50% in year 5 (37 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

## **Conclusion**

The Committee also considered the benefits of obinutuzumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as obinutuzumab is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifier, the Committee accepted obinutuzumab for use in NHS Scotland.

### **Additional information: guidelines and protocols**

In July 2016 the National Institute for Health and Care Excellence (NICE) published guideline number 52, non-Hodgkin's lymphoma: diagnosis and management. This noted that it was not possible to develop recommendations on treating advanced stage relapsed or refractory follicular lymphoma due to published technology appraisals or those in development and provided direction to technology assessment number 137: rituximab for treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma.<sup>13</sup>

In 2011 the British Committee for Standards in Haematology (BCSH) published guidelines on the investigation and management of follicular lymphoma. These recommend that relapsed patients have a biopsy to exclude transformation to a more aggressive lymphoma. Treatment of relapsed disease is influenced by the patient's symptoms, fitness and response to previous treatment. Rituximab plus chemotherapy is recommended for rituximab-naive patients and those who have previously responded to rituximab, with the choice of chemotherapy dependent on individual patient characteristics. <sup>90</sup>Y-ibritumomab tiuxetan is recommended as an option for older patients and those that are refractory or intolerant rituximab and chemotherapy. It is noted that benefits of high dose therapy with ASCT should be balanced against long-term risks of the procedure and considered in the setting of emerging therapies. Palliative radiotherapy should be considered for patients with localised symptomatic disease.<sup>4</sup>

In 2016 the European Society for Medical Oncology (ESMO) published guidelines for newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. These recommend that a biopsy be obtained at relapse to exclude transformation to an aggressive lymphoma. They note that observation is an accepted approach in asymptomatic patients with low tumour burden. For patients requiring treatment the choice is dependent on efficacy of prior regimens. In patients with early relapse (within 12 to 24 months) a non-cross resistant regimen is recommended (i.e. bendamustine after CHOP or vice versa). If a previous anti-body (i.e. rituximab) containing regimen achieved remission for more than 6 to 12 months, then rituximab should be added also. In symptomatic patients with low tumour burden rituximab monotherapy may be considered. <sup>90</sup>Y-ibritumomab tiuxetan is noted to be a potential effective approach in elderly patients with comorbidities, who are not suitable for chemotherapy. High dose therapy with ASCT should be considered especially in patients who experience short first remissions (less than two to three years) after rituximab-containing regimens, who usually have a much worse long-term outcome, but its role has to be redefined. In later relapses it is noted that palliative monotherapy is an established option and idelalisib has been approved for patients refractory to two prior lines of therapy. Selected younger patients with later relapses, high-risk profile or relapse after ASCT may be considered for allogenic stem cell transplant, especially for those with early relapse or refractory disease.<sup>5</sup>

### **Additional information: comparators**

There is no standard regimen for rituximab-refractory patients and identification of the relevant comparator that it might replace in Scottish practice is challenging. Clinical experts consulted by SMC identified a variety of treatments that it might replace, including chemotherapy ± rituximab.

## Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)
<b>Obinutuzumab</b>	<b>1,000mg IV on days 1,8,15 of first 28-day cycle, then on day 1 of next five 28-day cycles</b>	<b>10,805<sup>A</sup></b>
<b>Bendamustine (induction)</b>	<b>90mg/m<sup>2</sup> IV on days 1 and 2 of six 28-day cycles</b>	<b>4,181<sup>A</sup></b>
<b>Obinutuzumab (maintenance)</b>	<b>1,000mg IV every two months for up to two years</b>	<b>3,312<sup>B</sup></b>
Rituximab Bendamustine*	375mg/m <sup>2</sup> IV on day1 of 21-day cycle 90mg/m <sup>2</sup> on days 1 and 2 of 21-day cycles	<b>2,091<sup>C</sup></b>
Rituximab Cyclophosphamide Doxorubicin Vincristine Prednisolone	375mg/m <sup>2</sup> IV on day1 of 21-day cycle 750mg/m <sup>2</sup> IV on day 1 of 21-day cycle 50mg/m <sup>2</sup> IV on day 1 of 21-day cycle 1.4mg/m <sup>2</sup> (max 2mg) IV on day 1 of 21-day cycle 100mg orally daily on days 1 to 5 of 21-day cycle	<b>1,430<sup>C</sup></b>
Idelalisib	150mg orally twice daily	2,907 <sup>A</sup>
Bendamustine**	120mg/m <sup>2</sup> IV on days 1 and 2 of 21-day cycles	1,117 <sup>C</sup>
Cyclophosphamide Doxorubicin Vincristine Prednisolone	750mg/m <sup>2</sup> IV on day 1 of 21-day cycle 50mg/m <sup>2</sup> IV on day 1 of 21-day cycle 1.4mg/m <sup>2</sup> (max 2mg) IV on day 1 of 21-day cycle 100mg orally daily on days 1 to 5 of 21-day cycle	208 <sup>C</sup>

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis on 3 October 2016 and BNF online accessed on 2 November 2016. Costs are based on a body surface area of 1.8m<sup>2</sup>. A = 28-day cycle; B = 56 day cycle; C = 21-day cycle. Costs do not take any patient access schemes into consideration. \* off-label; \*\* not accepted for use in Scotland by SMC.

## References

The undernoted references were supplied with the submission.

1. Roche Products Ltd. Summary of product characteristics for Gazyvaro<sup>®</sup>, last updated 22 June 2016.
2. European Medicines Agency. European public assessment report for Gazyvaro<sup>®</sup>, Committee for Medicinal Products for Human Use (CHMP), EMA/CHMP/345935/2016, 28 April 2016.
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8. Commercial In Confidence\*
9. Commercial In Confidence\*
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11. Wild D, Walker M, Pettengell R, Lewis G. Utility elicitation in patients with follicular lymphoma. Value in Health 2006; 9(6): A294
12. Bec M, Cagnet M, Taieb V, et al. French utility elicitation in previously treated European patients with indolent non-Hodgkin Lymphoma. Value in Health 2014; 17(7): A646.
13. National Institute for Health and Care Excellence. NICE guideline number 52, non-Hodgkin's lymphoma: diagnosis and management, July 2016.

This assessment is based on data submitted by the applicant company up to and including 14 December 2016.

\*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: [http://www.scottishmedicines.org.uk/About\\_SMC/Policy\\_statements/Policy\\_Statements](http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements)

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*