SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND

Resubmission:

obinutuzumab, 1,000mg, concentrate for solution for infusion (Gazyvaro®)

SMC2015

Roche Products Limited

10 August 2018

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 resubmission considered under the orphan medicine process

obinutuzumab (Gazyvaro®) is not recommended for use within NHSScotland.

Indication under review: Obinutuzumab in combination with chemotherapy, followed by obinutuzumab maintenance therapy in patients achieving a response, for the treatment of patients with previously untreated advanced follicular lymphoma.

In a phase III study, obinutuzumab decreased the risk of disease progression compared with another monoclonal antibody in a subgroup of patients with previously untreated advanced follicular lymphoma.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Chairman,
Scottish Medicines Consortium

Published 10 September 2018

Indication

Obinutuzumab in combination with chemotherapy, followed by obinutuzumab maintenance therapy in patients achieving a response, for the treatment of patients with previously untreated advanced follicular lymphoma.[1]

Dosing Information

Induction (in combination with chemotherapy regimen): Obinutuzumab 1,000mg intravenous (IV) infusion on days 1, 8 and 15 of the first chemotherapy cycle, then on day 1 of the remaining chemotherapy cycles.

Obinutuzumab should be administered in addition to chemotherapy regimen as follows:

- Six 28-day cycles in combination with bendamustine or
- Six 21-day cycles in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP), followed by two additional cycles of obinutuzumab alone or,
- Eight 21-day cycles in combination with cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone (CVP).

Maintenance: Patients who achieve a complete or partial response to induction treatment with obinutuzumab in combination with chemotherapy (CHOP or CVP or bendamustine) should continue to receive obinutuzumab 1,000mg 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. For information on pre-medication please see Summary of Product Characteristics (SPC).[1]

Product availability date

September 2017

Obinutuzumab is a designated EMA orphan medicine and meets SMC orphan criteria for this indication.

Summary of evidence on comparative efficacy

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.[1] Obinutuzumab in combination with bendamustine, followed by obinutuzumab maintenance is also 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.[1] SMC accepted obinutuzumab for use in this indication in February 2017. This submission is for the use of obinutuzumab in patients with previously untreated advanced follicular lymphoma and the submitting company has requested that SMC

considers obinutuzumab when positioned for use in patients with intermediate or high (referred to as higher) risk disease, follicular lymphoma international prognostic index (FLIPI) ≥2.

The key evidence to support the indication under review is from GALLIUM, an ongoing, multicentre, phase III, open-label randomised study comparing obinutuzumab plus chemotherapy followed by obinutuzumab maintenance, with rituximab plus chemotherapy followed by rituximab maintenance, in 1,401 adults with previously untreated, histologically documented, advanced indolent non-Hodgkin's lymphoma (NHL). A total of 1,202 of these patients had a diagnosis of follicular lymphoma. Patients had Eastern Co-operative Oncology Group (ECOG) performance status of 0, 1 or 2. Chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone [CHOP], cyclophosphamide, vincristine and prednisone [CVP] or bendamustine) administered to patients with follicular lymphoma was chosen by site prior to study initiation. Only patients achieving a complete or partial response in the induction phase were eligible to commence maintenance treatment. Although the full study population included some patients with marginal zone lymphoma, the primary outcome analysis was performed in the pre-specified subgroup of patients with previously untreated advanced follicular lymphoma, known as the FL population.[2]

Induction phase: Patients were randomised equally to the obinutuzumab and rituximab treatment arms, stratified by chemotherapy regimen, FLIPI score: low (≤1 risk factor), intermediate (2 risk factors), or high (>2 risk factors); and geographic region.[2]

Obinutuzumab 1,000mg IV infusion in combination with chemotherapy (CHOP, CVP or bendamustine) was given on day 1 of each cycle, with additional doses on day 8 and day 15 of cycle 1. Rituximab 375mg/m^2 IV infusion in combination with chemotherapy (CHOP, CVP or bendamustine) was given on day 1 of each cycle. The number of cycles of obinutuzumab and rituximab received depended on the chemotherapy regimen chosen by the patient's clinician; eight 21-day cycles with CHOP (patients received antibody only [obinutuzumab or rituximab] in cycles 7 and 8) and CVP, and six 28-day cycles with bendamustine.[2]

Maintenance phase: Partial or complete responders to treatment in the induction phase continued on treatment with obinutuzumab 1,000mg IV infusion or rituximab 375mg/m^2 IV infusion (as per previous assignment), given every two months for two years or until disease progression. Patients with stable disease or disease progression were observed with no further protocol specified treatment.[2]

The primary outcome was progression free survival (PFS), assessed by investigators, in the follicular lymphoma intention to treat (FL-ITT) population. This was defined as time from randomisation until the first documented day of disease progression or death from any cause, whichever occurred first, on the basis of investigator assessments according to the Revised Response Criteria for Non-Hodgkin's Lymphoma.[2]

There was a pre-specified interim analysis at data cut-off of 31 January 2016 which crossed the pre-specified boundary and became the primary analysis. At this time, after a median follow-up of 35 and 34 months respectively, 17% (101/601) of patients in the obinutuzumab group and 24% (144/601) of patients in the rituximab group had experienced a PFS event as assessed by the investigator. A hazard ratio (HR) of 0.66 (95% confidence interval [CI]: 0.51 to 0.85) and p=0.0012 was reported. The median PFS had not been reached in either group but estimated three-year PFS was 80% and 73% in the obinutuzumab and rituximab groups, respectively.[1]

Almost 80% (949/1,202) of the primary analysis population had higher risk (FLIPI ≥2) disease corresponding to the proposed positioning. In this subgroup PFS events occurred in 17% (79/473) of patients receiving obinutuzumab compared with 26% (126/476) of patients receiving rituximab[2]

Table 1: Results of the primary outcome (investigator assessed PFS) of the GALLIUM study according to FLIPI risk status.[2]

FLIPI risk	Obinutuzumab group		Rituximab group		Unstratified HR (95% CI)
	Patient nos	PFS events (%)	Patient nos	PFS events (%)	
All patients	601	101 (17%)	601	144 (24%)	0.66 (0.51 to 0.85)
Low	128	22 (17%)	125	18 (14%)	1.17 (0.63 to 2.19)
Intermediate	224	31 (14%)	223	49 (22%)	0.59 (0.37 to 0.92)
High	249	48 (19%)	253	77 (30%)	0.58 (0.41 to 0.84)

FLIPI=follicular lymphoma international prognostic index; nos=numbers; PFS=progression free survival; HR=hazard ratio; CI=confidence interval

Other subgroup analyses were generally consistent with the primary analysis. Exploratory analyses across chemotherapy regimens were consistent with the full population although these were not based on randomised comparison.[1] Important secondary outcomes are included in Table 2.

Table 2. Important secondary outcomes.[1]

Secondary Outcome	Obinutuzumab (n=601)	Rituximab (n=601)
PFS IRC; % (n) of patients with an event	15% (93)	21% (125)
	HR 0.71 (95% CI: 0.54 to 0.93), p=0.0138.	
Overall survival; % (n) of patients with an event	5.8% (35)	7.7% (46)
	HR 0.75 (95% CI: 0.49 to 1.17), p=0.21.	
Time to next anti-lymphoma therapy; % (n) of patients commenced at time of primary analysis	13% (80)	18% (111)
	HR 0.68 (95% CI: 0.51 to 0.91), p=0.0094.	

PFS, progression free survival. IRC, independent review committee, HR, hazard ratio.

Patient reported outcomes were recorded using the functional assessment of cancer therapy-lymphoma (FACT-Lym) and euro-quality-of-life-5D (EQ-5D) questionnaires. There were no differences between the treatment groups within the FL-ITT study population that completed all scales of the questionnaires at baseline, during treatment or follow-up.[3] There were similar improvements in health related quality of life (HR-QoL) scores between baseline and follow up in both treatment groups.[4]

Summary of evidence on comparative safety

Obinutuzumab is currently licensed for use in specific patient groups for the treatment of follicular lymphoma and chronic lymphocytic leukaemia. In the GALLIUM study, as obinutuzumab was administered with chemotherapy during the induction phase it is difficult to fully establish the impact of obinutuzumab on the overall adverse event profile. Adverse events have been reported for the full study population only; there are no data available for the proposed positioning higher risk population. Adverse events of special interest (all grades) that occurred at least 3% more

frequently in the obinutuzumab group than the rituximab group included infusion reactions (68% versus 58%), infusion reactions specifically related to the antibody (59% versus 49%), neutropenia (51% versus 45%), thrombocytopenia (11% versus 7.5%), infections (77% versus 70%) and cardiac events (13% versus 9.7%). [2]

Grade ≥3 adverse events were reported in 75% (444/595) versus 68% (405/597), and serious adverse events in 46% versus 40% in the obinutuzumab group and rituximab groups respectively. Important grade ≥3 adverse events in the obinutuzumab and rituximab groups respectively, included infusion related reactions 12% versus 6.7%, neutropenia 46% versus 40%, thrombocytopenia 6.1% versus 2.7%, infections, 20% versus 16%, and second malignancies 4.7% versus 2.7%. Deaths considered to be due to adverse events occurred in 4.0% (24/595) of patients treated with obinutuzumab versus 3.4% (20/597) of patients treated with rituximab.[2]

Summary of clinical effectiveness issues

Follicular lymphoma is a subtype of indolent NHL, which comprises about 70% of indolent NHL and about 20% to 25% of all new NHL. It is a mature B-cell neoplasm and around 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.[5, 6] Follicular lymphoma is a low grade lymphoma that tends to grow relatively slowly and is chemo-sensitive.[6] Clinical experts consulted by SMC advised that patients with previously untreated advanced, symptomatic follicular lymphoma receive rituximab with chemotherapy followed by maintenance rituximab. They noted that the majority of rituximab used in NHS Scotland for follicular lymphoma treatment is administered via the subcutaneous route, but highlighted that not all patients with FLIPI ≥2 score are treated at present; only patients who are symptomatic, in line with current guidelines. Obinutuzumab meets SMC orphan criteria.

The submitting company has requested that SMC considers obinutuzumab when positioned for use in patients with higher risk, (FLIPI ≥2) disease. The SPC for obinutuzumab notes that the efficacy in FLIPI low risk (0 or 1) patients is currently inconclusive and that a therapy choice for these patients should carefully consider the overall safety profile of obinutuzumab plus chemotherapy and the patient-specific situation.[1]

In the GALLIUM study, PFS was higher in the obinutuzumab group compared with the rituximab group.[2] The clinical relevance of the difference is unclear, as median PFS and overall survival have not been reached. Although GALLIUM was not powered to compare outcomes according to FLIPI score, subgroup analysis demonstrated statistically significant benefit for obinutuzumab over rituximab only in patients with higher risk disease. Overall survival data are immature.[2]

The open-label design of the study could limit the assessment of subjective outcomes such as quality-of-life and adverse events. In addition, the primary outcome of PFS was assessed by investigators and the open-label design could have led to potential bias. However, results were consistent with results when assessed by the independent review committee.

Rituximab in combination with CVP is the most commonly used treatment in NHS Scotland for previously untreated, advanced follicular lymphoma, according to SMC clinical experts, but the CVP regimen accounted for only 10% of the chemotherapy regimens in the GALLIUM study. Subgroup analyses indicated that the efficacy of obinutuzumab in combination with chemotherapy for previously untreated follicular lymphoma, in patients with FLIPI scores of 0-1 (low risk) is

inconclusive. In the study, 97% of patients had ECOG performance status score of 0 or 1 at baseline, therefore, there is limited information on the use of obinutuzumab plus chemotherapy in patients with poorer performance status.[1]

Clinical experts consulted by SMC considered that the place in therapy of obinutuzumab plus chemotherapy is as an alternative treatment option to rituximab plus chemotherapy for the first-line treatment of follicular lymphoma and may offer an advantage in terms of PFS. They highlighted concern regarding increased toxicity, including the higher number of infusion-related reactions, and advised caution as many of these patients are relatively frail. They considered that the introduction of obinutuzumab for the indication under review may have potential implications for service capacity and for patients as it is administered IV and requires two additional doses in the induction phase, necessitating extra and significantly longer cancer centre visits, compared with rituximab, which is administered by subcutaneous (SC) injection over 5 minutes (after an initial first cycle of IV rituximab Clinical practice guidelines for follicular lymphoma support the use of FLIPI as a prognostic tool and recommend that FLIPI should be recorded at diagnosis.[1, 7]

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of obinutuzumab, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced follicular lymphoma is considered to be incurable with some patients experiencing troublesome symptoms such as; lumps in lymph nodes, weight loss, drenching night sweats, extreme tiredness, fevers and more frequent or persistent infections than normal.
- These symptoms may reduce or stop everyday activities such as employment, exercising and socialising. This can have a significant impact on family and carers.
- Obinutuzumab plus chemotherapy may delay disease progression and improve the symptoms of follicular lymphoma. These improvements could in turn lead to improvements in quality of life.
- For some older and frail patients with advanced disease, PACE clinicians suggested that obinutuzumab may be a useful treatment option when given with some chemotherapy backbones such as CVP.
- Obinutuzumab administration is via IV infusion and some patients may experience infusion-related reactions which oncology/haematology clinicians are familiar with managing.

Additional Patient and Carer Involvement

We received a patient group submission from Lymphoma Action. Lymphoma Action is a registered charity. Lymphoma Action has received 6.5% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Lymphoma Action participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis which compared obinutuzumab plus chemotherapy followed by obinutuzumab maintenance (obinutuzumab regimen) against rituximab plus chemotherapy followed by rituximab maintenance (rituximab regimen) for patients with higher risk disease (FLIPI ≥2). The chemotherapy in both arms consisted of three regimens used in clinical practice: CHOP, CVP, and bendamustine. In the model, a weighted proportion of bendamustine, CHOP and CVP was assumed and the proportions were 37%, 17% and 46% respectively.

A Markov model was developed which consisted of four health states: PFS, which was further divided into "on treatment" and "off treatment", early progressed disease (early-PD, progression within two years of initial treatment) late progressed disease (late-PD, progression > two years after initial treatment), and death. Patients entered the model in PFS health state and could remain in this health state, or transition to a worse health state. Subsequent therapies were captured in the PD states. Patients who progressed early had higher probability of death. Overall survival was a function of time spent in the PFS and both PD health states.

Within this resubmission, the clinical data were taken from a subgroup analysis of the GALLIUM study. The submitting company pooled clinical data from the intermediate risk and high risk patient groups to estimate the efficacy of obinutuzumab versus rituximab in higher risk patients. Based on this analysis a PFS hazard ratio of 0.62 (0.47 to 0.80) was estimated for obinutuzumab versus rituximab. In order to extrapolate PFS over time and determine the probability of remaining in PFS, the submitting company used a parametric modelling approach whereby independent parametric functions (Log logistic) were fitted to the GALLIUM Kaplan-Meier data for each treatment arm. Within the model, the greater treatment effect associated with obinutuzumab is assumed to remain up to approximately 9 years, thereafter the obinutuzumab treatment effect was capped i.e. no difference in PFS was assumed between treatment arms.

The probability of death in the PFS health state was estimated using treatment specific mortality rates for patients (derived from higher risk subgroup in GALLIUM). Based on this analysis, the monthly mortality rates were estimated to be 0.12% and 0.09% for obinutuzumab and rituximab respectively. These rates were not statistically significantly different. In order to estimate post progression survival (PPS) in the early PD health state, monthly treatment specific mortality rates were also used (derived from the higher risk subgroup within the GALLIUM study). These were 1.26% and 1.51% for obinutuzumab and rituximab respectively; again these rates were not statistically significantly different. No PPS data for the late-PD health states were available from the GALLIUM study, hence data were used from the rituximab PRIMA study to provide longer-term follow up data for both treatment arms (0.56%).

Utility estimates for PFS were taken from the GALLIUM study and differed depending on whether patients were on or off treatment and in the induction or maintenance periods. For PD health states, utility values were taken from a published cross-sectional study which collected EQ-5D data from UK patients. The utility values for on and off induction treatment in the PFS health state were 0.822 and 0.757, for on and off maintenance treatment in the PFS were 0.832 and 0.816. For the early and late progressed PD states, utilities were 0.618 and 0.766 respectively.

Medicines costs were included in the analysis, as were costs associated with administration, adverse events management, supportive care and subsequent therapies. Medicines costs for all treatments in PFS were based on the recommended doses and consistent with the pivotal study.

The analysis accounted for both rituximab formulations (IV and SC) that are used in clinical practice.

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. A PAS is also in place for the comparator SC rituximab and this was included in the results used for decision-making by SMC by using estimates of the comparator PAS price. The base case results and key sensitivity analyses are presented in the tables below. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

Table 3: Base case results (list prices)

Regimen	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY)
obinutuzumab	£81,506	9.64			
rituximab	£42,458	8.96	£39,048	0.67	£57,858

QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio

The submitting company provided one-way deterministic analysis, scenario analyses and probabilistic sensitivity analyses. Selected results are presented below.

Table 4: Key scenario analysis results (list prices)

Scenario		ICER (cost per QALY)
1	Base case	£57,858
2	No OS benefit for obinutuzumab	£188,471
3	Time horizon (reduced to 10 years)	£141,184
4	Time horizon (reduced to 15 years)	£89,177
5	PFS treatment effect capped at 5 years	£62,426
6	Mortality rate for both treatment arms based on pooled data in study (for PFS and PD states)	£55,188
7	Combined analysis incorporating assumptions 2-6 (10 year time horizon)	£379,263
8	Combined analysis incorporating assumptions 2-6 (15 year time horizon)	£303,682

ICER= incremental cost-effectiveness ratio, QALY = quality-adjusted life-year

There were a number of limitations within the analysis, including the following;

- The base case analysis includes an OS gain, despite the primary study data for the subgroup for higher risk patients being too immature to draw conclusions for this outcome. Based on the results of GALLIUM, a hazard ratio of 0.75 (0.49-1.17); p=0.21 was estimated for obinutuzumab compared to rituximab within the higher risk subgroup.

Sensitivity analysis was provided which removed the OS benefit associated with obinutuzumab and this increased the ICER as outlined in table 4.

- The pivotal study was not powered to detect a difference in PFS for these subgroups and there is the potential for an inflated type I error, which may introduce some uncertainty within the analysis. However, on balance it was considered that the pooling of the two risk categories may be appropriate given that obinutuzumab shows similar clinical benefit over rituximab in PFS in the higher risk group compared to the FL-ITT population.
- The revised extrapolation approach does seem to provide more conservative PFS estimates compared to the proportional hazards approach used previously. However, despite the obinutuzumab treatment effect being removed at 9 years, an incremental benefit is accrued throughout the modelled time horizon. Given the lack of long term data supporting the effectiveness of obinutuzumab after follow up, the scenario analyses which reduce the time horizon to 10 years and 15 years address some uncertainty surrounding PFS extrapolation and may provide upper estimates of cost-effectiveness. It is worth noting that the company also provided a one-way sensitivity analysis which capped the effectiveness of obinutuzumab at 5 years (assumes no difference between treatments thereafter). Results were not overly sensitive to this analysis.

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 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 modifiers, the Committee was unable to accept obinutuzumab for use in NHS Scotland.

Additional information: guidelines and protocols

The guidelines below predate the availability of obinutuzumab for use in previously untreated advanced follicular lymphoma.

The Scottish Clinical Management Group for Follicular NHL issued a Scottish consensus clinical management guideline in 2017.[8] It advises that patients with symptomatic stage II to IV follicular lymphoma should be treated initially with rituximab plus chemotherapy for 6 to 8 cycles, with the choice of chemotherapy guided by disease characteristics. It states that the majority of patients will receive rituximab plus CVP.

National Institute for Health and Care Excellence (NICE) national guideline 52, published July 2016, advises on the diagnosis and management of non-Hodgkin's lymphoma. It suggests the use of rituximab in combination with

- CHOP
- CVP
- mitoxantrone, chlorambucil and prednisolone (MCP)
- cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α (CHVPi)
- chlorambucil

for previously untreated, symptomatic, stage III or IV advanced follicular lymphoma. Rituximab monotherapy maintenance is recommended for patients that responded to first-line treatment with rituximab in combination with chemotherapy.[9]

The British Committee for Standards in Haematology (BCSH) published guidelines on follicular lymphoma in 2012 entitled 'guidelines on the investigation and management of follicular lymphoma'. For early stage disease, the BCSH recommend radiotherapy, combined modality treatment and observation alone, where no residual disease is present. For advanced stage asymptomatic follicular lymphoma, the BCSH highlight there is no advantage to immediate treatment, particularly so where patients are over 70 years of age and observation may be the most appropriate approach. For symptomatic patients with newly diagnosed advanced stage follicular lymphoma, rituximab in combination with chemotherapy should be used, and rituximab maintenance in patients responding to first-line rituximab-based chemotherapy. For patients with relapsed disease, a biopsy procedure is recommended.[5]

In 2016, the European Society for Medical Oncology (ESMO) published guidelines for follicular lymphoma entitled 'Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.' For previously untreated, advanced stage III or IV disease, management options for patients with high tumour burden include; rituximab plus chemotherapy (CHOP,CVP or bendamustine), or in selected cases rituximab plus chlorambucil or rituximab monotherapy may be selected with consideration of rituximab maintenance.[7]

Additional information: comparators

Rituximab plus chemotherapy.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
Obinutuzumab	**Induction** **1,000mg IV on days 1, 8 and 15 of cycle 1 then on day 1 only for up to eight cycles[A]** **Maintenance** **1,000mg IV every two months for two years**	**9,936 (cycle 1 only)** **3,312 (cycle 2 onwards)** **3,312**
Rituximab (SC)[B]	Induction 375mg/m^2 IV on day 1 of cycle 1 then 1,400mg SC on day 1 of each subsequent cycle for up to eight cycles in total[A] Maintenance 1,400mg SC every two months for two years	1,100 (cycle 1 only) 1,345 (cycle 2 onwards) 1,345
Rituximab (IV)	Induction 375mg/m^2 IV on day 1 of each cycle for up to eight cycles[A] Maintenance 375mg/m^2 IV every two months for two years	1,100 1,100

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from MIMS online accessed on 25 April 2018. Costs are based on a body surface area of 1.8m^2 and are calculated using the

full cost of vials assuming wastage. SC: subcutaneous, IV intravenous. [A]: Six 21-day cycles when administered in combination with CHOP followed by two additional cycles of obinutuzumab alone; eight 21-day cycles when administered in combination with CVP and six 28-day cycles when administered in combination with bendamustine. [B]: Rituximab can be given subcutaneously if a full dose of IV infusion has been successfully administered. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 120 patients eligible for treatment with obinutuzumab in all years to which confidential uptake rates were applied.

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

References

1. Obinutuzumab concentrate for solution for infusion (Gazyvaro®) Summary of product characteristics. Roche Products Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 16 April 2018. [cited.
2. Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C*, et al.* Obinutuzumab for the First-Line Treatment of Follicular Lymphoma plus supplement. N Engl J Med. 2017;377(14):1331-44.
3. Clinical Trials Gov. A Study of Obinutuzumab (RO5072759) Plus Chemotherapy in Comparison With MabThera/Rituxan (Rituximab) Plus Chemotherapy Followed by GA101 or MabThera/Rituxan Maintenance in Patients With Untreated Advanced Indolent Non-Hodgkin's Lymphoma (GALLIUM). [cited 21 August 2017]; Available from: https://clinicaltrials.gov/ct2/show/NCT01332968?term=21223&rank=1.
4. Davies A TP, Demeter J, Florschütz A, Hänel M, Hong X, Kinoshita T, Pettengell R, Quach H, Robinson S, Sadullah S, Sancho J, Udvardy M, Witzens-Harig M, Rufibach K, Zeuner H, Unterhalt M. Health-related quality of life results from the phase III GALLIUM study of obinutuzumab-based and rituximab-based therapy in patients with previously untreated advanced indolent non-hodgkin lymphoma. Congress of the European Hematology Association 2017; Madrid, Spain.
5. McNamara C, Davies J, Dyer M, Hoskin P, Illidge T, Lyttelton M*, et al.* Guidelines on the investigation and management of follicular lymphoma. Br J Haematol. 2012;156:446-67. Epub 01/04.
6. Committee for Medicinal Products for Human Use (CHMP). Assessment Report Gazyvaro. London: European Medicines Agency, 2016.
7. Dreyling M, Ghielmini M, Rule S, Salles G, Vitolo U, Ladetto M. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v83-v90. Epub 09/25.
8. The Scottish clinical management group for Follicular NHL. Scottish Consensus Clinical Management Guideline Follicular Non - Hodgkin Lymphoma. 2017.
9. National Institute for Health and Care Excellence. Non-Hodgkin's lymphoma: diagnosis and management National Guideline 52. 2016.

This assessment is based on data submitted by the applicant company up to and including 15 June 2018.

**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*

Medicine 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.