SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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obinutuzumab, 1,000mg, concentrate for solution for infusion (Gazyvaro®)

SMC No 1286/18

Roche Products Limited

8 December 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 orphan process

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

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's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

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

Obinutuzumab should be administered with chemotherapy 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.[1]

For information on pre-medication please see Summary of Product Characteristics (SPC).[1]

Product availability date

September 2017
Orphan designation for obinutuzumab for the treatment of follicular lymphoma was granted on 19/06/2015, designation EU/3/15/1504.
Obinutuzumab meets SMC orphan criteria.

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 6 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.

The key evidence to support this license extension 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). 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 (MZL), the primary outcome analysis was performed in the pre-specified subgroup of patients with previously untreated advanced follicular lymphoma, known as the FL population, which represents the indication under review.[2, 3]

Induction phase: Patients were randomised equally to the obinutuzumab and rituximab treatment arms, stratified by chemotherapy regimen, follicular lymphoma international prognostic index (FLIPI) score 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 and CVP, and six 28-day cycles with bendamustine.

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.[3]

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 Malignant Lymphoma.[3]

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]

The subgroup analyses were generally consistent with the primary analysis. In the subgroup of patients with FLIPI score 0 to 1 (low risk) (21% [253/1,202] of the FL-ITT population), no difference between the obinutuzumab and rituximab groups was identified: HR 1.17 (95% CI: 0.63 to 2.19). 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 1.

Table 1. 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. Infusion reactions, neutropenia and infections are important adverse events and appear to occur more frequently in the obinutuzumab treated group compared with the rituximab treated group. [5]

In the FL population, during induction, grade ≥3 adverse events were reported in 75% (444/595) versus 68% (405/597), and serious adverse events in 46% versus 40%[5] in the obinutuzumab group and rituximab group respectively. Other important adverse events occurring in >2% of patients in the obinutuzumab and rituximab groups respectively included grade ≥3 serious infusion related reactions 12% versus 6.7%, neutropenia 49% versus 44%, grade ≥3 thrombocytopenia 6.1% versus 2.7%, grade ≥3 infections, 20% versus 16%, and grade ≥3 second malignancies 4.7% versus 2.7%.[5]

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. Follicular lymphoma is a low grade lymphoma that tends to grow relatively slowly and is chemo-sensitive.[6] SMC clinical experts advise that patients with previously untreated advanced, symptomatic follicular lymphoma receive rituximab with

chemotherapy followed by maintenance rituximab. SMC clinical experts state that the majority of rituximab used in NHS Scotland for follicular lymphoma treatment is administered via the subcutaneous route. Obinutuzumab meets SMC orphan criteria.

In the GALLIUM study, the estimated three-year PFS rate was higher in the obinutuzumab group compared with the rituximab group (80% and 73% respectively).[1] The clinical relevance of the difference in three-year PFS rate is unclear, as median PFS and overall survival have not been reached.

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 IRC.

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. They also highlighted concern regarding the higher number of infusion-related reactions, and potential service capacity implications.

The introduction of obinutuzumab offers an alternative to rituximab for the first-line treatment of follicular lymphoma and may offer an advantage in terms of PFS. The obinutuzumab regimen, administered IV, requires two additional doses in the induction phase, necessitating extra cancer centre visits, compared with rituximab, which is administered by subcutaneous (SC) injection over 5 minutes (after an initial first cycle of IV rituximab). A switch to obinutuzumab based treatment will prolong day-case chemotherapy appointments significantly, impacting on both patients and service capacity.

While obinutuzumab meets SMC orphan criteria in this setting, the company did not request a Patient and Clinician Engagement (PACE) meeting to consider the added value of obinutuzumab in the context of treatments currently available in NHS Scotland.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis which compared obinutuzumab-chemotherapy followed by obinutuzumab maintenance (obinutuzumab regimen) against rituximab–chemotherapy followed by rituximab maintenance (rituximab regimen) in the licensed indication. The chemotherapy in both arms consisted of three regimens used in clinical practice: CHOP, CVP, and bendamustine.

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 patients 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.

The sources of the clinical data included the GALLIUM study which provided PFS data for the rituximab regimen. These data were extrapolated using the exponential function in order to generate PFS estimates for the rituximab regimen beyond the pivotal study data**.** Long-term PFS for the obinutuzumab regimen was estimated by applying hazard ratios to the PFS exponential function estimated for the rituximab regimen. The greater treatment effect of the obinutuzumab regimen observed in the GALLIUM study was assumed to remain for up to 9 years, thereafter a hazard ratio of one was applied, equalising the effects of rituximab and obinutuzumab. The probability of death in the PFS health state was determined by the higher of the mortality rate in the GALLIUM study or the UK age-specific all-cause mortality rates. In order to estimate post progression survival (PPS) in the early-PD health state, data from both arms of the pivotal study were pooled and a constant mortality rate was used. 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 the rituximab regimen.[7, 8]

Utility estimates for PFS were taken from the GALLIUM study and differed depending on whether patients were on treatment or treated in the induction or maintenance period. 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 were 0.823 and 0.772, for on and off maintenance treatment in the PFS were 0.831 and 0.818, and for the PD health states was 0.620.

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; the base case analysis did not assume use of biosimilar rituximab but this was considered in sensitivity analysis. The base case analysis did not assume vial sharing however this had a limited impact on the result in a sensitivity analysis.

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 the New Drugs Committee (NDC) by using estimates of the comparator PAS price. The base case results and key sensitivity analyses using an incremental analysis are presented in tables 2 and 3 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.

The base case result indicated that the incremental cost-effectiveness ratio (ICER) for the obinutuzumab regimen versus the rituximab regimen was £47,098 without PAS per quality adjusted life year (QALY) as presented in table 2.

Table 2: Cost-effectiveness results

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Results without PAS							
Obinutuzumab regimen	£82,104	13.33	10.01				
Rituximab regimen	£44,922	12.49	9.23	£37,182	0.84	0.78	£47,425

The submitting company provided one-way deterministic analysis and several scenario analyses. The analysis was most sensitive to the assumption of no difference in overall survival between obinutuzumab and rituximab regimens, decreasing the estimated treatment effect duration for PFS of the obinutuzumab regimen from 9.75 years to 5 years, increasing the discount rate from 3.5% to 6% and using the Gompertz function to model PFS as shown in table 3 below.

Table 3: Selected sensitivity analysis results

Scenario		Results without PAS
1	**Base case**	**£47,425**
2	Discount rate of 6%	£63,609
3	PFS extrapolation – Gompertz (worst case)	£55,644
4	PFS extrapolation – Gamma (best case)	£45,455
5	PFS treatment effect duration (5 years)	£63,160
6	Time on treatment according to SPC	£52,969
7	Pairwise results with individual chemotherapeutic regimens	£42,784-£51,484
8	SC administration costs £50 instead of £253	£48,816
9	Costs of IV rituximab biosimilar medicines	£48,314
10	Alternative set for post-progression utility values (worst case)	£53,019
11	Assuming no overall survival benefit for obinutuzumab regimen	£139,469
12	Assuming a diminishing effect over time for obinutuzumab on PFS	£53,764
13	Composite scenario 11 +12	£165,208

The main issues include:

- The extrapolation of OS appears to be overestimating the expected effect of obinutuzumab. The company modelled the PPS separately for early and late progression on the basis of available evidence indicating that patients who had progressed on treatment within two years after initial therapy had higher probability of dying compared to patients with late progression. Although this can have been the case in GALLIUM, the actual study data did not suggest any statistically significant difference in overall survival. The company applied constant mortality rates to post-progression health states, irrespective of treatment used. Therefore, a revised scenario assuming no difference in overall survival was requested from the company and this resulted in ICERs that were approximately three times those of the base case. The company challenged the validity of the assumption of similar overall survival in both treatment arms which would imply that patients who had been treated with obinutuzumab and had progressed lately would need to be assigned higher probability of death compared with rituximab after

progression so that the same outcomes in overall survival is achieved in both arms. In this context it should be noted that the GALLIUM study did not find a statistical difference in overall survival, neither did the rituximab PRIMA study. This study with a median follow-up of 36 months reported a statistically non-significant difference in overall survival between rituximab maintenance and observation (HR = 0.87, 95% CI: 0.51-1.47), although a significant risk reduction for PFS of rituximab maintenance was observed (HR = 0.55, 95% CI: 0.44-0.68). The updated results with a 6 year follow-up reported a HR for PFS of 0.58 (95% CI: 0.48-0.69) and a 6-year OS estimate of 88.7% for observation arm compared to 87.4% for the rituximab maintenance arm. These results suggest that longer PFS may not necessarily translate into longer OS in patients with early-stage follicular lymphoma. The committee considered that the assumption of the base case gain in overall survival was not appropriate given the lack of data provided to support it and that the analysis which removed this assumption (scenario 11 in table 3) was a more appropriate base case analysis.

- The method applied for extrapolation of progression-free survival tends to overestimate the effect of obinutuzumab as compared to the evidence which is available from the clinical studies. The company extrapolated the observed Kaplan-Meier curves but it appeared that the ends of both curves with less than 10% of patients at risk were ignored. While the Kaplan-Meier curves tended to converge at 5 years, the difference between the extrapolated parametric curves tend to be increasing until 9.75 years. To simulate the course of the whole Kaplan-Meier curves, the company was asked to provide a scenario assuming a diminishing effect of obinutuzumab after the study follow-up which was done by linearly increasing the observed HR until it reached one, equalising the effects of obinutuzumab and rituximab (scenario 12 in table 3). This had little impact on the base case results. The company also provided a scenario assuming that the additional effect of the obinutuzumab regimen compared to rituximab remains for up to 5 years instead of 9 years and applying a HR of one thereafter (scenario 5 in table 3). This latter assumption was considered as more appropriate than the company's base case.
- Health utility values for the post-progression states were taken from published sources other than obinutuzumab and rituximab studies and these were assumed to be too low compared to utility values observed in patients treated with first line treatments (GALLIUM study) and also compared to available evidence for patients treated with second line obinutuzumab (SMC Advice No. 1219/17). It was noted that the GALLIUM utility values may not fully represent the overall quality of life of patients after progression as the post-progression quality of life data were only collected at the first visit when progression was detected and not thereafter. Applying higher utility values taken from the obinutuzumab GALLIUM study (0.776 for early progression state and 0.814 for late progression state) had little impact on the base case results (scenario 10 in table 3).

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

After considering all the available evidence and after application of the appropriate SMC modifiers, the Committee was unable to accept obintuzumab for use in NHS Scotland.

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

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from the Lymphoma Association, which is a registered charity.

- The Lymphoma Association received 5.7% pharmaceutical company funding in its annual organisational income of 2016, including from the submitting company.

- For people with advanced follicular lymphoma, the impact of living with the disease and treatment will depend upon the symptoms they are experiencing. Where symptoms are not troublesome, 'watch and wait' may be adopted and patients report that it is difficult to live with a diagnosis while not receiving any treatment. For those with more severe symptoms such as weight loss and extreme fatigue, day to day life may be disrupted. Many patients have to stop working, either temporarily or permanently. Similarly, the burden of the disease can have a major impact on those caring for someone with a diagnosis.

- Obinutuzumab is important to people with previously untreated advanced follicular lymphoma and their carers and families, as it may offer increased duration of remission compared to current treatment.

- Patients with direct experience of obinutuzumab have reported improvements in relation to their aches and pains and fatigue, along with reductions in enlarged lymph nodes.

- It is recognised that obinutuzumab takes longer to administer compared to current treatment, but patients report that they can accept this as a reasonable trade off as it provides the opportunity for a delay in disease progression.

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.[9] 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.[10]

The British Committee for Standards in Haematology (BCSH) published guidelines on follicular lymphoma in 2011 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.[11]

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.[12]

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 cycle for up to eight cycles[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]	1,100

	Maintenance 375mg/m^2 IV every two months for two years	1,100

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from MIMS online accessed on 6 September 2017. 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]: Eight 21-day cycles when administered in combination with CHOP or CVP and six 28-day cycles when administered in combination with bendamustine. [B]: Rituximab can be given subcutaneous 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 151 patients eligible for treatment with obinutuzumab in all years to which confidential estimates of treatment uptake were applied.

SMC is unable to present the without PAS budget impact estimates due to commercial in confidence issues.

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

References

1. Obinutuzumab Summary of Product Characteristics. Roche Products Ltd. September 2017 [cited 23 November 2017]; Available from: https://www.medicines.org.uk/emc/medicine/29057.

2. Hiddemann W, Barbui A, Canales Albendea MA, Cannell S, Collins G, Duerig J*, et al.*, editors. Immunochemotherapy with obinutuzumab or rituximab in previously untreated follicular lymphoma (FL) in the randomised Phase III GALLIUM study: analysis by chemotherapy regimen. 14th International Conference on Malignant Lymphoma; 2017.

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. Marcus R, Davies A, Pocock C, Ando K, Klapper W, Opat S*, et al.* Obinutuzumab-based induction and maintenance prolongs progression-free survival in patients with previously untreated follicular lymphoma: primary results of the randomised phase 3 GALLIUM study. British journal of haematology Conference: 57th annual scientific meeting of the british society for haematology United kingdom

6. Committee for Medicinal Products for Human Use (CHMP). Assessment Report Gazyvaro. London: European Medicines Agency, 2016.

7. Seymour JF, Feugier P, Offner F, Lopez-Guillermo A, Belada D, Xerri L*, et al.* Updated 6 Year Follow-Up Of The PRIMA Study Confirms The Benefit Of 2-Year Rituximab Maintenance In Follicular Lymphoma Patients Responding To Frontline Immunochemotherapy. Blood. 2013;122:509-.

8. Salles G, Seymour JF, Offner F, Lopez-Guillermo A, Belada D, Xerri L*, et al.* Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet. 2011;377:42-51.

9. The Scottish clinical management group for Follicular NHL. Scottish Consensus Clinical Management Guideline Follicular Non - Hodgkin Lymphoma. 2017.

10. National Institute for Health and Care Excellence. Non-Hodgkin's lymphoma: diagnosis and management National Guideline 52. 2016.

11. 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.

12. Dreyling M. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009;20 Suppl 4:119-20. Epub 07/10.

This assessment is based on data submitted by the applicant company up to and including 13 October 2017.

**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

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.