Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

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

SMC No. (1008/14)

Roche Products Limited

07 November 2014

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

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

Indication under review: In combination with chlorambucil, obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy.

The combination of obinutuzumab plus chlorambucil produced a statistically and clinically significant increase in progression free survival compared with an alkylating agent alone or an alkylating agent/antibody combination, in older patients with previously untreated CLL who had substantial comorbidities.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In combination with chlorambucil, obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia and with comorbidities making them unsuitable for full-dose fludarabine based therapy.

Dosing Information

Cycle 1: The recommended dose of obinutuzumab is 1,000mg administered by intravenous infusion over days 1 and 2, and on days 8 and 15 of the first 28 day treatment cycle. Two infusion bags should be prepared for the infusion on days 1 and 2 (100mg for day 1 and 900mg for day 2). If the first bag is completed without modifications of the infusion rate or interruptions, the second bag may be administered on the same day (no dose delay necessary, no repetition of premedication), provided that appropriate time, conditions and medical supervision are available throughout the infusion. If there are any modifications of the infusion rate or interruptions during the first 100mg the second bag must be administered the following day.

Cycles 2 to 6: The recommended dose of obinutuzumab is 1,000mg administered on day 1.

The Summary of Product Characteristics (SPC) for obinutuzumab includes details of infusion rates, and medications to be administered for prophylaxis of tumour lysis syndrome and infusion related reactions.

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

Product availability date

31 July 2014. Obinutuzumab meets SMC orphan criteria. [1]

Summary of evidence on comparative efficacy

Chronic lymphocytic leukaemia (CLL) is a malignant lymphoproliferative disease with an estimated prevalence in the European Union of 2.91 per 10,000 population.[1] Obinutuzumab is the first in a new class of recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibodies.[2] The mechanism of action of anti-CD20 monoclonal antibodies involves a combination of antibody-dependent cell-mediated cytotoxicity, direct cell death and complement-dependent cytotoxicity. Compared with Type I antibodies (e.g rituximab), obinutuzumab is a more potent inducer of direct cell death while complement-dependent cytotoxicity is strongly reduced.[1]

The evidence supporting the marketing authorisation is from a phase III open label, two-stage randomised controlled study, CLL11, which recruited a total of 781 adult patients with previously untreated, documented CD20-positive CLL who required treatment with: a total Cumulative Illness Rating Scale (CIRS) score >6 and/or creatinine clearance <70mL/min; absolute neutrophil count ≥1.5 × 10^9/L and platelets ≥75 × 10^9/L (unless caused by the underlying disease); and life expectancy >6 months.[1,3]

In Stage 1 (comparison of all three treatment arms), 589 patients were randomised in parallel, stratified according to geographic region and Binet stage, in a 2:2:1 ratio to receive obinutuzumab+chlorambucil (n=238), rituximab+chlorambucil (n=233) or chlorambucil alone (n=118). If disease progression occurred in patients receiving chlorambucil monotherapy during or within six months of finishing treatment, they could cross over to the obinutuzumab+chlorambucil group.[3] In Stage 2 (comparison of the two antibody+chlorambucil combination treatments), an additional 192 patients were randomised in a 1:1 ratio between these two groups resulting in a total of 333 patients in the obinutuzumab+chlorambucil group and 330 patients in the rituximab+chlorambucil group.[1,3] Treatment was administered for six 28-day cycles: obinutuzumab 1,000mg by intravenous infusion (the first dose over two days) on days 1, 8 and 15 of cycle 1 and on day 1 of subsequent cycles; rituximab 375mg/m^2 body surface area by intravenous infusion on day 1 of cycle 1 and 500mg/m^2 on day 1 of subsequent cycles; and chlorambucil 0.5mg/kg orally on days 1 and 15 of each cycle. Allopurinol, paracetamol, antihistamines, corticosteroids and antibiotics were used if required prophylactically for tumour lysis syndrome, infusion-related reactions (IRRs) and infection.[3]

The primary end point was progression free survival (PFS) defined as the time from randomisation to the first occurrence of progression, relapse, or death from any cause, as assessed by the investigator. The primary analysis was in the intention to treat (ITT) population (all randomised patients) with data censored for patients without disease progression or death by the data cut.[1-3] The results of the primary outcome were supported by an Independent Review Committee assessment. A total of 25% (30/118) of patients crossed over from chlorambucil monotherapy to obinutuzumab+chlorambucil. See Table 1 for the primary end point results.

Secondary outcomes included overall survival and end of treatment response, defined as the response occurring at the first assessment >56 days after the end of treatment, and before the start of new anti−leukaemia treatment are also presented in Table 1.[1]

Table 1: CLL11 study outcomes; (9th May 2013 data cut)[2]

	Stage 1		Stage 2*	
	Obinutuzumab + chlorambucil	Chlorambucil	Obinutuzumab + chlorambucil	Rituximab + chlorambucil
	n=238	n=118	n=333	N=330
Median duration of observation (months)	22.8 months		18.7 months	
Progression free survival (investigator assessed)				
Patients with PFS event n (%)	93 (39%)	96 (81%)	104 (31%)	199 (60%)
Median duration of PFS	26.7 months	11.1 months	26.7 months	15.2 months
HR (95% CI) p value (Log-Rank test, stratified)	0.18 (0.13 to 0.24) p<0.0001		0.39 (0.31 to 0.49) p<0.0001	
Overall survival**				
Number (%) deaths	22 (9.2%)	24 (20%)	28 (8.4%)	41 (12%)
Median time to event (months)	NR	NR	NR	NR
HR (95% CI) p value (Log-Rank	0.41 (0.23 to 0.74]) p=0.0022		0.66 (0.41 to 1.06) p=0.0849	

test, stratified)				
Response rates (end of treatment)				
Overall response rate	77%	31%	78%	65%
p value	p<0.0001		p<0.0001	
Complete response rate	22%	0	21%	7.0%

n=number; PFS=progression free survival; HR=hazard ratio; CI=confidence interval NR=not reached; *pre-planned interim analysis **immature data;

The submitting company also presented updated, unpublished results which are confidential.

The risk of disease progression or death was reduced in the obinutuzumab+chlorambucil group, compared with the rituximab+chlorambucil group or the chlorambucil monotherapy group, in all subgroups except in the subgroup of patients with deletion 17p where there was no significant difference between the obinutuzumab+chlorambucil group and either of the other two groups. For subgroups, reduction of the risk of disease progression or death ranged from 92% to 58% for obinutuzumab+chlorambucil versus chlorambucil and 72% to 29% for obinutuzumab+chlorambucil versus rituximab+chlorambucil.[2]

The addition of obinutuzumab to chlorambucil therapy did not result in a significant reduction in quality of life. Assessment of health related quality of life, measured using the QLQC30 and QLQ-CLL-16 questionnaires, found no significant difference among the three treatment groups.[2]

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

Summary of evidence on comparative safety

In the CLL11 study, 81% of patients in the obinutuzumab+chlorambucil group received six treatment cycles, compared with 89% of patients in the rituximab+chlorambucil group and 67% of patients in the chlorambucil monotherapy group.[3] Adverse events occurred in 85% (286/336), 98% (315/321) and 83% (96/116) of patients in the obinutuzumab+chlorambucil, rituximab+chlorambucil and chlorambucil groups, respectively. Serious adverse events were reported in 39% (131/336), 32% (102/321) and 38% (44/116) of the respective groups.[3] Adverse events were the main reason for withdrawal in all three groups: 13% in the obinutuzumab+chlorambucil group; 7.6% in the rituximab+chlorambucil group and 14% in the chlorambucil monotherapy group.[3]

In Stage 1, the incidence of Grade 3 to 5 adverse events was higher in the obinutuzumab+chlorambucil group (73%) than in the chlorambucil group (50%). These were mainly neutropenia (35% versus 16%), IRR (21% versus 0%), infections (11% versus 14%), thrombocytopenia (11% versus 4%), anaemia (5% versus 4%) and leucopenia (5% versus 0%).[3] Anti-infective medications and granulocyte-colony stimulating factors (G-CSF) were administered to a higher proportion of patients in the obinutuzumab+chlorambucil group compared with the chlorambucil monotherapy group, both for prophylaxis prior to the study and treatment during the study: prophylaxis 21% (51/240) versus 11% (13/116) and treatment: 74% (178/240) versus 56% (65/116), respectively.[1]

In Stage 2, the incidence of Grade 3 to 5 adverse events was higher in the obinutuzumab+chlorambucil group (70%) than in the rituximab+chlorambucil group (55%). They

included neutropenia (33% versus 28%), IRR (20% versus 4%), infections (12% versus 14%) and thrombocytopenia (10% versus 3%).[3]

During the first cycle, IRRs occurred in 65% of patients receiving obinutuzumab although in subsequent cycles they occurred in fewer than 3% of patients. The most frequently reported symptoms associated with an IRR were nausea, chills, hypotension, pyrexia, vomiting, dyspnoea, flushing, hypertension, headache, tachycardia, and diarrhoea.[1]

Six deaths were considered (by the investigator) to be related to treatment: two in the obinutuzumab+chlorambucil group (haemorrhagic stroke and plasma cell myeloma); one in the rituximab+chlorambucil group (cardiac arrest) and three in the chlorambucil group (intracranial haemorrhage, respiratory failure and respiratory tract infection).[3]

Prophylaxis is required to prevent tumour lysis syndrome, IRRs and hypersensitivity reactions. Other severe and life-threatening adverse reactions associated with obinutuzumab include neutropenia, thrombocytopenia, hepatitis B reactivation and progressive multifocal leucoencephalopathy.[2]

Summary of clinical effectiveness issues

The clinical course of CLL varies substantially among patients. Treatment decisions depend on disease stage, previous treatment and individual patient factors including age, symptoms and general health.[1] Patients who are sufficiently fit should receive fludarabine-based treatment as initial therapy; however, many elderly patients with comorbidities cannot tolerate this treatment.[6] Although obinutuzumab has orphan designation for the treatment of CLL, the submitting company has chosen to submit under the standard SMC process.

Clinical guidelines suggest that in patients not fit enough to receive high-dose fludarabine-based chemotherapy, chlorambucil or bendamustine are recommended treatment options.[4,5] SMC has previously accepted bendamustine for the first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. Ofatumumab is accepted by SMC for use in CLL that is refractory to fludarabine and alemtuzumab. In August 2014, the marketing authorisation for ofatumumab was extended to include use in patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy,[6] this licence extension is currently undergoing SMC assessment.

The pivotal study was robust, well designed and conducted in an appropriate patient population. The results convincingly demonstrated that the combination of obinutuzumab+chlorambucil produced a statistically and clinically significant increase in PFS compared with rituximab+chlorambucil and with chlorambucil alone in older (median age 73 years) patients with previously untreated CLL and substantial comorbidities. The addition of obinutuzumab to chlorambucil resulted in an increase in overall survival compared with chlorambucil alone although as event numbers were still relatively low and the data are immature, it is too early to draw conclusions. The overall survival estimates do not account for crossover from the chlorambucil monotherapy arm to the obinutuzumab+chlorambucil arm.[3]

A limitation of the pivotal study is its open-label design; however, PFS outcomes from an Independent Review Committee were similar to the investigator-assessed outcome. The dose of chlorambucil in the pivotal study (0.5mg/kg body weight on days 1 and 15 of each cycle) was

based on the median dose from the German CLL Study Group (GCLLSG) CLL5 study which demonstrated that fludarabine monotherapy is not superior to chlorambucil for PFS in elderly (and in the subgroup of medically unfit) CLL patients. It is lower than in some studies and differs from the licensed dose regimen.[6]

The company also presented a Bayesian mixed treatment comparison (MTC) comprising a network of 16 studies of adults with untreated CLL. The network included 14 different interventions including the comparators relevant to the economic case: obinutuzumab+chlorambucil, chlorambucil monotherapy, bendamustine, and rituximab+bendamustine. The outcome compared in the analysis was PFS. Some results from the MTC have been highlighted as confidential in the company submission.

The MTC results were presented in terms of the probability of being the best treatment and treatments were ranked. The results of the MTC suggest that obinutuzumab+chlorambucil was likely to be the most effective treatment. The original NMA results did not include a hazard ratio for the comparison of obinutuzumab+chlorambucil versus rituximab+bendamustine. The submitting company has since advised that the PFS hazard ratio between rituximab+bendamustine and obinutuzumab+chlorambucil estimated by the MTC is 0.52 (fixed effects model), 0.59 (random effects model) and 0.37 (fixed effects model with age as a covariate). However the company also highlighted the uncertainty of these estimates.

There were a number of limitations with the analyses. The study selection process was unclear, with the systematic literature search identifying 42 studies but only 16 were included in the network. Checks for consistency between direct and indirect comparisons were not presented. The company identified a potential source of bias in the MTC due to differences in age among the study populations. This was addressed through meta-regression. However, other potential sources of bias were not explored (e.g. variations in co-morbidity, performance status and dose of intervention such as chlorambucil used). Missing information prevented a thorough appraisal of the analyses. The external validity of the MTC results is limited by the fact that most of the studies included patients who were fit enough to receive full-dose fludarabine-based chemotherapy and many of the treatment arms included fludarabine.

Expert statistical advice confirmed these weaknesses.

The combination of obinutuzumab+chlorambucil is associated with more toxicity than chlorambucil alone. Obinutuzumab is administered by intravenous infusion whereas chlorambucil is given orally; therefore, there are implications for patient choice and for the service.[3]

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

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing obinutuzumab+chlorambucil with four comparators: chlorambucil monotherapy, rituximab+chlorambucil, bendamustine monotherapy and rituximab+bendamustine. The range of comparators included is appropriate and expert feedback indicates chlorambucil and rituximab+chlorambucil may be the key comparators.

A Markov model was used with three health states: PFS, progression and death. In the PFS health state, patients were either PFS on-treatment or PFS off-treatment. A 20-year time horizon and weekly cycle length were used. A 10-year time horizon was explored in the sensitivity analysis and the results were not overly sensitive to the shorter time horizon. The model structure is appropriate.

The source of clinical data for the comparisons with chlorambucil and rituximab+chlorambucil is the CLL11 study. PFS data were used in the model and extrapolated using parametric functions based on goodness of fit. In the base case, the Kaplan-Meier (KM) PFS data were used for as long as possible and a gamma distribution was fitted to the tail. In terms of overall survival, the CLL11 overall survival data were not used in the model on the basis that the data are immature and had not reached the median in any arm. Instead, data from another study (CLL5 comparing fludarabine with chlorambucil) were used as the basis for estimating overall survival in the model. Using these data, a single post-progression survival rate was estimated and applied to each treatment arm with some adjustment made to account for patients progressing at different ages. For the comparison with bendamustine, data from the MTC were used to derive estimates of PFS, and for the comparison with rituximab+bendamustine, a number of assumptions were used. Overall survival was estimated using the CLL5 study as described above.

The utility values were derived from a utility elicitation study conducted by the company. The study involved 100 members of the UK public and used the time trade off technique to derive utility values. The utility values for the PFS health state were 0.71 for patients receiving oral treatment (chlorambucil) and 0.67 for patients receiving intravenous treatment (obinutuzumab, rituximab and bendamustine). A lower utility value of 0.55 was also included for patients receiving their first dose of obinutuzumab to account for increased hospital visits.

Drug acquisition, administration and pharmacy costs were included. No vial sharing was assumed. Adverse event treatment costs were also included. When patients are on treatment it was assumed a 30 minute consultation with a haematologist per cycle would be required. Post-progression treatment costs were also included and the company noted that while the treatment received will depend on a number of factors, an assumption was made that all patients would receive a course of chlorambucil treatment second-line. Health state best supportive care costs were also included. For the PFS health state, patients were assumed to require one follow-up attendance with a haematologist every 3 months. For patients in the progressed health state, this increased to one visit every month. Resource use estimates were based on a combination of European Society for Medical Oncology (ESMO) guidelines and expert opinion.

In the base case analysis, the submitting company estimated the following results:

Table 4: Base case cost-effectiveness results

Comparator	Incremental cost (obinutuzumab vs comparator)	Incremental quality-adjusted life-years	Incremental cost-effectiveness ratio (ICER)
chlorambucil	£26,868	1.06	£25,347
rituximab + chlorambucil	£14,886	0.65	£22,901
bendamustine	£19,331	0.68	£28,428
rituximab + bendamustine	£7,673	0.34	£22,568

The following limitations were noted:

- Overall survival data from the pivotal CLL11 study were not used in the model. The company argued that the data were too immature to use as the basis for extrapolation in the model. The SMC statistical advisor suggested it would be possible to use the CLL11 overall survival data despite the data being immature. The company subsequently provided an alternative analysis using the CLL11 data and, while it was highlighted these results are uncertain, the analysis provided some reassurance that the company's base case cost-effectiveness estimates for the comparisons with chlorambucil and rituximab+ chlorambucil were reasonable.
- In order to model overall survival, the company used data from a separate study (CLL5) which compared fludarabine with chlorambucil. As the licence for obinutuzumab specifically excludes patients who are able to tolerate fludarabine, the use of data from a study where patients received fludarabine is not appropriate and is likely to overestimate survival. However, additional sensitivity analysis provided by the company showed that when a higher mortality rate was applied the ICERs reduced slightly.
- For the comparisons with bendamustine and rituximab+bendamustine, indirect comparisons were required. There are a number of limitations with the MTC and, in addition, the comparison with rituximab+bendamustine is based on a number of assumptions. The economic results based on the MTC are particularly uncertain.
- Disease-specific quality of life data were collected in the pivotal study but were not used in the model. The company subsequently clarified that these data were not used initially as there is no established algorithm to map from the disease specific QLQ-C30 data to EQ-5D in CLL patients, but this analysis has now been conducted and indicated the PFS utility value used in the model may be lower than the quality of life data collected in the study. However, the utility values derived from the disease specific data are perhaps higher than would be considered plausible in patients with CLL.

The Committee considered the benefits of obinutuzumab in the context of SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and where there is increased uncertainty due to the orphan status of the medicine. Despite the limitations in the economic analysis, after application of the appropriate modifiers, the Committee accepted obinutuzumab for use in NHS Scotland.

Summary of patient and public involvement

The following information reflects the views of the specific patient group.

- A submission was received from Leukaemia CARE, which is a registered charity.
- Leukaemia CARE has received funding from several pharmaceutical companies in the past two years, including from the submitting company.
- Chronic lymphocytic leukaemia (CLL) is condition that often results in levels of fatigue that significantly affect sufferers and thus their quality of life and that of their families and carers. This can lead to frustration and depression. Patients may also experience recurring infections - persistent colds and chest infections leading them to avoid others with these complaints. Sufferers report uncomfortable abdominal cramps and weight loss, reducing body weight below normal levels.
- All the above effects interfere with the course of daily life, and work or the enjoyment of retirement.
- Current treatments include other medicines, which some sufferers of CLL are unable to take due to co-morbidities. Obinutuzumab has the advantage of offering patients the choice of an alternative medication for this illness with a good side effect profile.
- Leukaemia CARE supports the introduction of obinutuzumab.

Additional information: guidelines and protocols

The British Committee for Standards in Haematology (BCSH) issued Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia in 2012.[4] They recommend that treatment of early stage disease is not indicated. Fludarabine+cyclophosphamide+rituximab (FCR) is recommended as initial therapy for previously untreated fit patients outside clinical trials. Options for patients unfit for fludarabine+cyclophosphamide+rituximab (FCR) include chlorambucil or bendamustine.

- entry of patients into trials of chlorambucil or bendamustine in combination with anti CD20 antibodies is strongly encouraged.
- further studies are required to determine the efficacy of dose-reduced fludarabine+cyclophosphamide (FC) or FCR.

The BCSH guidelines note that although the outcome of patients over the age of 65 to 70 years entered into clinical trials of FC and FCR may be was comparable to that of younger patients, the data should not be extrapolated to elderly patients with co-morbidities, as these patients have a higher incidence of myelosuppression, often fail to tolerate a full course of treatment and generally have a poorer outcome with therapy.[4]

The European Society for Medical Oncology issued: Chronic lymphocytic leukemia - ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up in 2011.[5] They note that in patients with relevant comorbidity, chlorambucil seems to be the standard therapy. Alternatives

are dose reduced purine analogue-based therapies (FC, pentostatin+ cyclophosphamide+ rituximab or bendamustine).

Additional information: comparators

Chorambucil monotherapy; rituximab+chlorambucil; bendamustine monotherapy; rituximab+bendamustine.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per 6 cycle course (£)
Obinutuzumab plus Chlorambucil (dose in pivotal CLL11 study)	**28 day cycle Obinutuzumab: by i.v. infusion Cycle 1: 1,000mg on days 1,[a] 8 and 15 Cycles 2 to 6: 1,000mg on day 1 plus chlorambucil: Orally 0.5mg/kg[b] on days 1 and 15 of each cycle**	**Cycle 1: 9,985 to 10,001 Subsequent cycles: 3,361 to 3,377**	**26,790 to 26,886**
Ofatumumab[c] plus Bendamustine	28 day cycle Ofatumumab: by i.v. infusion Cycle 1: 300mg on day 1 and 1,000mg on day 8 Subsequent cycles: 1,000mg on day 1 for a minimum of 3 cycles, until best response or a maximum of 12 cycles Bendamustine: by i.v. infusion 90mg/m^2 on days 1 and 2 of each cycle [d,e]	Cycle 1: 3,334 Cycles 2 to 6: 2,788	17,274
Rituximab plus Bendamustine	28 day cycle Rituximab: by i.v. infusion Cycle 1: 375mg/m^2 on day 0 Cycles 2 to 6: 500mg/m^2 on day 1[d] Plus 28 day cycle By i.v. infusion 100mg/m^2 bendamustine hydrochloride on days 1 and 2 of each cycle[d]	Cycle 1: 2,325 Cycles 2 to 6: 2,675	15,698

Ofatumumab[c] plus Chlorambucil	28 day cycle Ofatumumab: by i.v. infusion Cycle 1: 300mg on day 1 and 1,000mg on day 8 Subsequent cycles: 1,000mg on day 1 for a minimum of 3 cycles, until best response or a maximum of 12 cycles Chlorambucil: Orally:10mg/m^2 orally on days 1 to 7 of each cycle [d,f]	Cycle 1: 2,468 Cycles 2 to 6: 1,922	12,078
Rituximab plus Chlorambucil (dose in pivotal CLL11 study)	28 day cycle Rituximab: by i.v. infusion Cycle 1: 375mg/m^2 on day 0 Cycles 2 to 6: 500mg/m^2 on day 1[d] plus chlorambucil: see CLL11 dose above	Cycle 1: 1,271 to 1,287 Cycles 2 to 6: 1,621 to 1,637	9,376 to 9,472
Bendamustine (licensed dose)	28 day cycle By i.v. infusion 100mg/m² bendamustine hydrochloride on days 1 and 2 of each cycle[d]	1,103	6,619
Chlorambucil monotherapy (licensed dose)	Orally 0.15mg/kg/day until the total leucocyte count has fallen to 10,000 per microlitre. Treatment may be resumed 4 weeks after the end of the first course and continued at a dosage of 0.1mg/kg/day [b,g]	136 to 181	817 to 1,089
Chlorambucil monotherapy (dose in pivotal CLL11 study)	See CLL11 dose above	49 to 65	294 to 390

Doses are for general comparison and do not imply therapeutic equivalence. Costs on 05.09.14 from eVadis for chlorambucil; costs of rituximab, bendamustine and ofatumumab from MIMS online; cost of obinutuzumab from company submission

(a) initial infusion over 2 days; (b) doses based on weight of 60 to 80kg; c) ofatumumab has not yet been reviewed by SMC; (d) based on 1.8m^2 body surface area; (e) bendamustine dose from OMB115991 study (f) chlorambucil dose from OMB110911 study; (g) chlorambucil licensed dose: cost calculated at a dose of 0.1mg/kg/day

Additional information: budget impact

The submitting company estimated the population eligible for treatment with obinutuzumab to be 93 patients in each year, with an estimated uptake rate of 40% (37 patients) in year 1 and 80% (74 patients) in year 5.

The gross impact on the medicines budget was estimated to be £989k in year 1 and £1.98m in year 5. No medicines were assumed to be displaced as obinutuzumab would be used in addition to current treatments.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. European Medicines Agency Committee for Medicinal Products for Human Use assessment report for obinutuzumab (Gazyvaro®) EMEA/H/C/002799/0000. 22 May 2014

2. Obinutuzumab concentrate for solution for infusion (Gazyvaro®) Summary of product characteristics. Roche Products. Electronic Medicines Compendium Last updated 30 July 2014

3. Goede V, Fischer K, Busch R et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014; 370:1101-10 plus supplement

4. Oscier D, Dearden C, Erem E et al. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia British Journal of Haematology, 2012; 159: 541-64

5. Eichhorst BF, Dreyling M, Robak T et al. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011; 22 Suppl 6: vi50-vi54.

6. Ofatumumab concentrate for solution for infusion (Arzerra®) Summary of product characteristics. GlaxoSmithKline UK. Electronic Medicines Compendium Last updated 11 August 2014

This assessment is based on data submitted by the applicant company up to and including 17 October 2014.

**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

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.

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.