

## ibrutinib 140mg hard capsules (Imbruvica®)

SMC No. (1151/16)

Janssen-Cilag Ltd

08 July 2016

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 assessed under the end of life and orphan medicine process

**ibrutinib (Imbruvica®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.

**SMC restriction:** patients with 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy.

In an open-label, phase III study, ibrutinib significantly increased progression-free survival compared with an anti-CD20 antibody in patients with relapsed or refractory CLL.

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

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

The license holder has indicated their intention to resubmit for relapsed or refractory disease.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

## Indication

For the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.

## Dosing Information

The recommended dose of ibrutinib is 420mg (three capsules) once daily. Treatment should continue until disease progression or no longer tolerated by the patient. Ibrutinib should be administered orally once daily with a glass of water approximately at the same time each day. The capsules should be swallowed whole with water and should not be opened, broken, or chewed and must not be taken with grapefruit juice or Seville oranges.

See summary of product characteristics for information on dose modifications when co-administered with CYP3A4 inhibitors or in event of non-haematological and haematological toxicity.

Treatment with ibrutinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

## Product availability date

3 November 2014

Ibrutinib has been designated an orphan medicine by the European Medicines Agency (EMA) and also meets SMC end of life criteria.

## Summary of evidence on comparative efficacy

Ibrutinib is a first-in-class inhibitor of Bruton's tyrosine kinase (BTK). BTK is an important signalling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways; the BCR pathway is implicated in the pathogenesis of several B cell malignancies, including chronic lymphocytic leukaemia (CLL).

This submission relates to the treatment of adult patients with CLL who have received at least one prior therapy (i.e. relapsed or refractory disease) and also to treatment-naïve patients who have 17p deletion or TP53 mutation and are unsuitable for chemo-immunotherapy<sup>1,2</sup> Within the former group, the submitting company has requested that SMC considers ibrutinib when positioned for use in patients with relapsed CLL and for whom fludarabine-based regimens are inappropriate. The ibrutinib licence has subsequently been extended to cover first-line use in all CLL patients and this extension will be considered in a future SMC submission.

The evidence comes from one pivotal, randomised, open-label, phase III study (RESONATE) which compared ibrutinib with ofatumumab in patients with relapsed or refractory CLL.<sup>2,3</sup> Eligible patients were aged at least 18 years with active CLL or small lymphocytic lymphoma (SLL) requiring treatment according to the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) 2008 criteria. They had received at least one previous therapy for CLL/SLL and were not appropriate for treatment/retreatment with purine analogue-based therapy. This was defined by failure to respond, a progression-free interval of <3 years after treatment with at

least two cycles of a chemo-immunotherapy or age  $\geq 70$  years. The definition also included patients aged  $\geq 65$  years with the presence of co-morbidities (Cumulative Illness Rating Scale [CIRS]  $\geq 6$  or creatinine clearance  $< 70$  mL/min) provided they had received at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemo-immunotherapy, a history of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia or presence of 17p deletion. Patients had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1. They were randomised equally to receive ibrutinib (420mg orally once daily) until disease progression or unacceptable toxicity or ofatumumab for up to 24 weeks (300mg intravenously [IV] at week one, followed by 2,000mg IV every week for seven weeks and then every four weeks for 16 weeks). Randomisation was stratified by the presence of 17p deletion and refractoriness to purine analogues administered in combination with an anti-CD20 monoclonal antibody. Patients in the ofatumumab group were allowed to crossover to ibrutinib treatment on disease progression confirmed by an independent review committee (IRC).

The primary outcome was progression-free survival (PFS), defined as the time from randomisation to disease progression or death from any cause, whichever occurs first. Disease progression that occurred for any reason except lymphocytosis was verified by the IRC according to IWCLL criteria. At the time of an interim analysis (cut-off date 6 November 2013), after a median follow-up of 9.4 months, 18% (35/195) of ibrutinib and 57% (111/196) of ofatumumab patients had died or had disease progression. PFS (IRC assessed) was significantly increased in the ibrutinib group compared with the ofatumumab group; adjusted hazard ratio 0.22 (95% confidence interval [CI]: 0.15 to 0.32),  $p < 0.001$ . Using Kaplan-Meier methods, median PFS was not reached in the ibrutinib group and was 8.1 months in the ofatumumab group. A consistent treatment effect with ibrutinib over ofatumumab was found across all pre-specified subgroups. In the subgroup of patients with 17p deletion ( $n=127$ ), the hazard ratio for PFS was 0.25 (95% CI: 0.14 to 0.45) and for those with disease refractory to purine analogues ( $n=175$ ), the hazard ratio was 0.18 (95% CI: 0.10 to 0.32).<sup>2,3</sup> Since results from the interim analysis crossed the pre-specified superiority boundary, the independent data monitoring committee recommended that the study was stopped early and that patients in the ofatumumab group have access to ibrutinib.<sup>2,3</sup> Results from an updated analysis, after a median follow-up of 16 months, found that investigator-assessed median PFS was significantly longer in the ibrutinib group compared with the ofatumumab group (median not reached versus 8.1 months respectively, hazard ratio 0.11 [95% CI: 0.07 to 0.15,  $p < 0.0001$ ]).<sup>4</sup>

The key secondary outcomes were overall survival and overall response rate (ORR: defined as the proportion of patients who achieve a complete response, complete response with incomplete haematopoietic recovery, nodular partial response, or partial response) assessed by the IRC using the IWCLL criteria. At the time of the interim analysis, 8.2% (16/195) of ibrutinib patients and 17% (33/196) of ofatumumab patients had died. Median overall survival had not been reached in either group. At this time, 29% (57/196) ofatumumab patients had crossed over to receive ibrutinib. The hazard ratio was 0.43 (95% CI: 0.24 to 0.79),  $p = 0.005$ , when patients who had crossed over were censored: 12-month survival rates of 90% in the ibrutinib group and 81% in the ofatumumab group. Sensitivity analysis, with patients who crossed over not censored, was similar (hazard ratio 0.39 [95% CI: 0.22 to 0.70], 12 month survival rate 90% and 79% respectively).<sup>1,2,3</sup> At the updated analysis, 61% (120/196) ofatumumab patients had crossed over to ibrutinib; when censored, the 18 month survival rates were 85% versus 78% respectively.<sup>4</sup>

At the interim analysis, an ORR was achieved by 43% (83/195) of ibrutinib and 4.1% (8/196) of ofatumumab patients: odds ratio 17.4 (95% CI: 8.1 to 37.3),  $p < 0.001$ . All responses were

partial.<sup>1,2,3</sup> When assessed by the investigator, the ORR were higher in both groups: 70% (136/195) of ibrutinib patients and 21% (42/196) of ofatumumab patients.<sup>3</sup>

Quality of life was assessed using the functional assessment of chronic illness therapy (FACiT)-Fatigue questionnaire, the European Organisation for Research and Treatment of Cancer Quality of Life-30 (EORTC QLQ-C30) and the EQ-5D-5L. There were improvements from baseline in both treatment groups for all three outcomes. There was no significant difference between the two treatment groups in FACiT-Fatigue score and so the hierarchical statistical testing was stopped.<sup>2</sup> However, numerically more ibrutinib than ofatumumab patients achieved a clinically meaningful improvement in FACiT-fatigue (increase of  $\geq 3$  points), in the EORTC QLQ-C30 and in EQ-5D-5L.<sup>5,6,7</sup>

Haematological improvements were assessed in the subset of patients with cytopenia(s) at baseline (haemoglobin  $\leq 11$  g/dL, platelets  $\leq 100,000$ /microlitre, or absolute neutrophil count (ANC)  $\leq 1500$ /microlitre), the proportion of patients with sustained hematological improvement (defined as improvement in cytopenia by  $\geq 50\%$ , or haemoglobin  $> 11$  g/dL, ANC  $> 1500$ /microlitre, platelets  $> 100,000$ /microliter, with the duration of improvement lasting for at least 2 months without blood transfusion or growth factors) was achieved by more ibrutinib than ofatumumab patients. Improvement of neutropenia was reported in 63% versus 32% of patients respectively and improvement of thrombocytopenia in 72% versus 22% of patients respectively.<sup>2,3</sup>

In a supportive open-label, single-arm, phase II study in patients with CLL and 17p deletion, all patients were treated with ibrutinib 420mg orally daily until disease progression or unacceptable toxicity.<sup>8</sup> Of the 51 patients enrolled in this study, 35 patients were treatment-naïve. The primary outcome was overall response at 24 weeks based on modified IWCLL 2008 criteria. In the 33 evaluable patients who were treatment-naïve, this was achieved by 55% (18/33) of patients (all partial responses). Best response was a secondary outcome achieved by 82% (27/33) treatment-naïve patients, including four complete responses. The estimated overall survival at 24 months was 84% in the treatment-naïve patients.

## Summary of evidence on comparative safety

During treatment in the RESONATE study, adverse events were reported by 99% (194/195) of ibrutinib and 98% (187/191) of ofatumumab patients, and these were considered treatment-related in 84% (164/195) and 79% (150/191) of patients respectively. Serious adverse events occurred in 42% (81/195) and 30% (58/191) of patients respectively. Adverse events with a severity of  $\geq$  grade 3 were reported in 57% (111/195) and 47% (90/191) of patients respectively. Discontinuation due to adverse events occurred in 4% of patients in both treatments groups. The median duration of treatment was longer in the ibrutinib group (8.6 months) than in the ofatumumab group (5.3 months).<sup>2,3</sup>

The most frequently reported adverse events in the ibrutinib and ofatumumab groups respectively included: diarrhoea (48% and 18%); fatigue (28% and 30%); nausea (26% and 18%); pyrexia (24% and 15%); anaemia (23% and 17%); neutropenia (22% and 15%); cough (19% and 23%); thrombocytopenia (17% and 12%); arthralgia (17% and 6.8%); upper respiratory tract infection (16% and 10%); constipation (15% and 9.4%); vomiting (14% and 6.3%); headache (14% and 5.8%); petechiae (14% and 1.0%); muscle spasm (13% and 8.4%) and dyspnoea (12% and 10%). The most frequently reported serious adverse events in the ibrutinib and ofatumumab groups were pneumonia (8.7% and 6.3% respectively); pyrexia (3.1%

versus 2.1%); atrial fibrillation (3.1% versus 0.5%); lung infection (2.6% versus 0); lower respiratory tract infection (2.1% versus 1.0%); urinary tract infection (2.1% versus 0); febrile neutropenia (1.5% versus 2.1%) and anaemia (1.0% versus 2.1%).<sup>3</sup>

Haemorrhagic events were reported in 44% of ibrutinib and 12% of ofatumumab patients and were classified as major (defined as  $\geq$  grade 3 or requiring red cell transfusion or hospitalisation) in 1.0% and 1.6% of patients respectively. Basal-cell and squamous-cell carcinomas were reported in 4% of ibrutinib and 2% of ofatumumab patients, and 2.6% and 1% of patients respectively had non-skin cancers during treatment. There was a higher incidence of atrial fibrillation in the ibrutinib group than in the ofatumumab group (5.1% versus 0.5%), which was of  $\geq$  grade 3 severity in 3.1% of ibrutinib patients only. Fatal serious adverse events were reported in 6.2% of ibrutinib and 8.4% of ofatumumab patients and these were most commonly due to pneumonia (1.5% versus 1.0%), progression of CLL (1.0% in each group) and sepsis (1.0% versus 0%).<sup>2,3</sup>

## Summary of clinical effectiveness issues

Ibrutinib is a first-in-class medicine for the treatment of CLL. This submission relates to the treatment of adult patients with CLL who have received at least one prior therapy (i.e. relapsed or refractory disease) and also to treatment-naïve patients who have 17p deletion or TP53 mutation and are unsuitable for chemo-immunotherapy.<sup>1,2</sup> Within the former group, the submitting company has asked SMC to consider ibrutinib for patients for whom fludarabine-based regimens are inappropriate. The ibrutinib licence has subsequently been extended to cover front-line use in all CLL patients and this extension will be considered in a future SMC submission.

CLL is the most common form of adult leukaemia and mainly affects older people. It has a variable course with some patients experiencing long periods of remission, while others have an aggressive form of the disease. Initial management of CLL is usually watchful waiting with treatment only started for advanced symptomatic and active disease. Treatment for relapsed/refractory disease should only be started in symptomatic patients and depends on previous treatment, time since previous treatment (which may be repeated if sufficient duration of initial response), fitness of patient and presence of genetic mutations.<sup>9</sup> Patients with 17p deletion or TP 53 mutation are a small, high risk group of CLL. Idelalisib, in combination with rituximab (IR), is also indicated for relapsed or refractory CLL and for first-line treatment of patients with 17p deletion or TP53 mutation (ie cytogenetic markers of high-risk disease) unsuitable for chemo-immunotherapy. Alemtuzumab was previously licensed for the treatment of CLL but the marketing authorisation was withdrawn by the company for commercial reasons, not related to efficacy or safety. It is now available for oncology indications, such as CLL, through a patient access programme and is sometimes used. Ibrutinib has been designated an orphan medicine by the EMA and meets SMC end of life criteria.

Clinical experts consulted by SMC considered there is unmet need in this therapeutic area for effective, and possibly better tolerated, alternatives to current options. During the SMC assessment of ibrutinib, the EMA started a review of idelalisib and issued provisional advice including a recommendation that idelalisib should not be started in previously untreated patients with CLL with 17p deletion or TP53 mutation.<sup>10</sup> This further limits treatment options for this group of patient.

In the pivotal study, conducted in patients who had received at least one previous treatment, ibrutinib significantly improved the primary outcome of PFS compared with ofatumumab and this effect was consistent across groups, including those with 17p deletion. Overall survival was a secondary outcome and immature data indicate that this may also be improved with ibrutinib. Due to positive results from the interim analysis, the study was stopped early; median PFS in the ibrutinib and median overall survival in both groups had not been reached. Therefore, it is possible that the treatment effect of ibrutinib with respect to these outcomes has not been fully characterised. The immature overall survival data are further limited by crossover of patients from ofatumumab to ibrutinib.

Although ofatumumab is licensed for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab, it is not used in Scottish clinical practice and is therefore not considered to be a relevant comparator. The RESONATE study population represented the proposed positioning for relapsed or refractory CLL patients. However, the first-line treatment of patients with CLL and 17p deletion or TP53 mutation is not represented by the RESONATE study population since patients were not treatment-naïve. The RESONATE study did not include patients with TP53 mutation but results would be expected to be similar. There are very limited available data for the licensed population who are treatment-naïve and have genetic mutations. However, the European Public Assessment Report (EPAR) notes that there are limited treatment options (eg fludarabine or alemtuzumab) for these patients which may be too toxic for many, so the benefit-risk for ibrutinib was considered clearly favourable for patients with 17p deletion or TP53 mutation not suitable for immuno-chemotherapy regardless of prior treatment experience. The positive results in these patients were considered of particular importance and support an indication in first line for those patients who are unsuitable for chemo-immunotherapy.<sup>2</sup> However, the actual treatment effect of ibrutinib in these patients is unclear and there are no comparative data with IR which may be an alternative treatment option in this population.

The study was of open-label design; however, the primary outcome of PFS was assessed by blinded independent review which should minimise potential bias.

RESONATE excluded patients with active clinically significant cardiovascular disease and, since the CLL population has a median age at diagnosis of 72 years, this may affect the generalisability of the results to clinical practice.<sup>3,9</sup> The summary of product characteristics (SPC) notes that patients with severe cardiovascular disease were excluded from ibrutinib clinical studies.<sup>1</sup>

The company submission acknowledges that ofatumumab is not a relevant comparator for Scottish practice in patients with relapsed/refractory CLL and the submitting company has presented indirect comparisons of ibrutinib versus physician's choice (PC) and versus IR. These used Bucher methodology with ofatumumab as a common comparator and the reported efficacy outcomes were overall response rate, PFS and overall survival. Two studies were included in each indirect comparison. Due to lack of relevant data, a study comparing idelalisib plus ofatumumab (IO) versus ofatumumab was used, in which the combination arm was used as a proxy for IR for data inputs in the economic analysis. Results suggest that ibrutinib was superior to PC for overall response rate, PFS and overall survival, and superior to IO for PFS only. There are limitations with the comparisons including: the treatments used as PC may not reflect clinical practice, IO was used as a proxy for IR (although SMC clinical experts generally considered that this was reasonable), differences between study populations and also differences in outcome results in the common ofatumumab group.



The submitting company considered that ofatumumab was a comparator for first-line treatment in patients with 17p deletion or TP53 mutation. However, the company was asked to provide a comparison with IR in CLL patients with genetic mutations. A naive indirect comparison was provided which suggests that ibrutinib and IO were not significantly different in terms of PFS and overall survival. The comparison is limited by its naive methodology and lack of common control arm, and the use of IO as a proxy for IR (although SMC clinical experts generally considered that this was reasonable). In addition, due to limited available data in treatment-naive patients, data from relapsed/refractory CLL patients with 17p deletion were used as a proxy.

The introduction of ibrutinib for CLL would offer patients an effective oral agent for the treatment of relapsed/refractory disease. In patients with 17p deletion, the treatment effect was similar and ibrutinib can be used first-line in these higher risk patients. Oral administration may offer advantages to the patient and service over alternative treatments which are administered intravenously in hospital. Generally, there were improvements in quality of life for patients treated with ibrutinib. Clinical experts consulted by SMC considered that ibrutinib is a therapeutic advancement as it is efficacious and well tolerated.

## Summary of 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 ibrutinib as an orphan and end of life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- CLL is a rare and debilitating disease. Patients with the presence of 17p deletion or TP53 mutation are a small, high risk sub-group who have an especially poor prognosis. PACE participants considered there is significant unmet need in both subsets of the ibrutinib indication.
- Recent safety concerns surrounding idelalisib further reduce available options for patients within both subsets of the ibrutinib indication. Indeed, in the first-line indication for patients with 17p deletion or TP53 mutation, there are currently no other SMC accepted options for new patients. It was noted that patients who did not initially express these mutations can develop them as CLL progresses.
- Relapsed CLL is difficult to treat. Current combination chemotherapy is associated with low response rates and significant toxicities and may be unsuitable for more elderly patients and those with multiple co-morbidities.
- PACE participants noted the speed of benefit of ibrutinib, with a rapid reduction in symptoms within days of initiation. They commented that the beneficial impact of ibrutinib on fatigue was not fully captured in the clinical trial. In addition, the clinical trial did not use a suitable comparator and therefore the quality of life benefit was also expected to be underestimated.
- The toxicity profile and monitoring requirements for ibrutinib are more favourable compared to idelalisib and other chemotherapy treatments. Ibrutinib does not appear to interfere with immune functions and therefore has potential benefits in avoiding infective complications.

- Ibrutinib is orally administered which has benefits for patients, carers and the wider NHS in reducing travel needs, hospital attendance and burden on carers and family, compared to other treatment options.

#### **Additional patient and carer involvement**

We received patient group submissions from the Leukaemia Care, Chronic Lymphocytic Leukaemia Support Association (CLLSA) and Bloodwise. Leukaemia Care has received <10% pharmaceutical company funding in the past two years, including from the submitting company. CLLSA has received approximately 70% pharmaceutical company funding in the past two years, including from the submitting company. Bloodwise has received 0.5% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from each patient group also participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

### **Summary of comparative health economic evidence**

The submitting company presented a cost-utility analysis using a survival partition model over a 20 year time horizon in two subpopulations of patients with CLL. For adult patients with CLL who have received at least one prior therapy and for whom fludarabine-based regimens are inappropriate, ibrutinib was compared against PC, IR and ofatumumab. The PC comparator consisted of a range of therapies which included alemtuzumab, bendamustine plus rituximab (BR), rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), fludarabine, cyclophosphamide plus rituximab (FCR), chlorambucil, methylprednisolone and rituximab (R+HDMP). For adult patients who were treatment naive and have 17p deletion or TP53 mutation, ibrutinib was initially compared against ofatumumab. However, upon request, the company also provided a comparison versus IR in this subgroup as SMC clinical expert responses indicated IR was the appropriate comparator.

In terms of model structure, the model consisted of three health states: PFS, post-progression disease (PPS) and death. Patients received ibrutinib until disease progression or until treatment was no longer tolerated by the patient. Patients initiated to PC would receive treatment until progression or until the maximum treatment duration had been reached. The economic model also assumed that 41.9% of patients who transitioned to the PPS health state received a subsequent treatment until disease progression, while the remainder of patients in the health state received BSC. In addition, patients in the PPS health state who had progressed on a subsequent treatment were also treated with BSC. The subsequent line of treatment patients received in the post-progression health state included R+HDMP and HDMP.

The clinical data used in the economic model included the RESONATE study which was used to generate PFS estimates for ibrutinib and ofatumumab in both subgroups of patients as well as overall survival for ibrutinib in the treatment naive and 17p deletion or TP53 mutation subgroup. Overall survival for ibrutinib in the at least one prior therapy and fludarabine-based regimens inappropriate subgroup was estimated using the PCYC1102/1103 study data. In order to estimate overall survival for ofatumumab in both subgroups, the hazard ratios for ibrutinib versus ofatumumab derived from the RESONATE study were used in the analysis. The hazard ratios were adjusted for crossover to capture the impact of ofatumumab patients in the RESONATE study switching treatment to ibrutinib beyond disease progression. In the absence of direct head to head data versus PC and IR, the analysis used hazard ratios from the indirect comparison in order to estimate PFS and overall survival for these comparators. The available



clinical study data were also extrapolated using parametric functions in order to derive overall survival and PFS estimates beyond the study period for use in the economic model. The economic analysis also used the ORR odds ratios from the indirect comparison to model the impact response may have on medical recourse use for PC and IR.

Utility estimates were derived from EQ-5D-5L data collected as part of the RESONATE study combined with published literature. The analysis also included a disutility for adverse events. The analysis included medicines costs as well as administration, routine follow-up care, adverse event, subsequent treatment and terminal care costs.

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. The PAS offered a discount on the price of the medicine.

For adult patients who have received at least one prior therapy and for whom fludarabine-based regimens are inappropriate versus PC, the incremental cost-effectiveness ratio (ICER) was £45,745 with PAS. The ICER for ibrutinib versus IR was >£50k without PAS. A PAS is in place for idelalisib and this was included in the base case analysis by using an estimate of the relevant price of idelalisib. SMC would wish to present the exact results provided by the company which used an estimate of the PAS price for idelalisib but owing to commercial-in-confidence issues, this result cannot be presented.

SMC would also wish to present the QALY gain and incremental cost estimates that informed the SMC decisions. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these figures.

For adult patients who are treatment naive and have 17p deletion or TP53 mutation, the company did not initially present results versus IR which may be considered a primary comparator in this subgroup. However, the company did provide a naive indirect comparison versus IR upon request. The analysis generated an ICER of >£50k without PAS. A PAS is in place for idelalisib and this was included in the analysis by using an estimate of the relevant price of idelalisib. As above, SMC would wish to present the exact results provided but owing to commercial-in-confidence issues this result cannot be presented.

The economic model was most sensitive to the following changes:

Analysis	ICER vs. PC (all ICERs with ibrutinib PAS)	ICER vs. IR (at least one prior therapy subgroup)	ICER vs. IR (treatment naïve and 17p del/TP53 subgroup)
Exponential curve to estimate PFS	£61,875	>£50k without PAS	>£50k without PAS
Restricting the benefit of ibrutinib treatment to 6 years	£61,340	>£50k without PAS	>£50k without PAS
Restricting the benefit of ibrutinib to 7 years	£58,544	>£50k without PAS	>£50k without PAS
Reducing the time horizon to 10 years	£57,109	>£50k without PAS	>£50k without PAS
Assume no cost benefit due to response	£55,480	>£50k without PAS	>£50k without PAS

The company also provided a comparison versus ofatumumab in both subgroups of patients. For adult patients who have received at least one prior therapy and for whom fludarabine-based regimens are inappropriate, the ICER for ibrutinib versus ofatumumab was £47,897. For adult patients who are treatment naïve and have 17p deletion or TP53 mutation, the ICER was £40,942 with PAS. A PAS is in place for ofatumumab and this was included in the analysis by using an estimate of the relevant price of ofatumumab. Both analyses were sensitive to using alternative parametric functions to extrapolate PFS, restricting the benefit of ibrutinib to 6 and 7 years respectively, reducing the time horizon, and changing assumptions regarding the impact of response on medical resource use.

The main weaknesses were:

- Previous SMC advice and SMC clinical expert responses to this submission suggested that IR is a relevant comparator in both subgroups of patients (though the EMA's recent provisional advice that idelalisib should not be started in previously untreated patients with CLL with 17p deletion or TP53 mutation is noted). The company did not initially present a comparison versus IR in the treatment naïve and 17p deletion population, but this was subsequently provided alongside sensitivity analyses testing the robustness of the result. It is also worth noting that although IR was identified as a relevant comparator in both groups of patients, the recent SMC review of idelalisib (1026/15) requested an analysis versus alemtuzumab. Alemtuzumab is no longer licensed for the treatment of CLL as the licence was withdrawn voluntarily by the submitting company for commercial reasons, but responses from some SMC clinical experts suggest it is a treatment option for some patients.
- The indirect comparisons which informed the comparative efficacy of ibrutinib versus PC and IR were associated with a number of weaknesses. For example, the mix of treatments which represented PC in the indirect comparison was not reflective of Scottish practice and the data that informed the efficacy of IR was based on patients initiated to IO and not IR. A further weakness with the clinical data used in the economic model was that the data used to estimate PFS and overall survival for ibrutinib in the treatment naïve and 17p deletion group were based on relapsed or refractory patients and not treatment naïve patients. SMC clinical experts were requested to comment on the efficacy assumptions used in the indirect comparison and economic analysis and, although initial responses were mixed, they were generally supportive of the approach adopted by the company.
- In order to estimate PFS and overall survival beyond the study period, parametric functions were fitted to the available study data. However, a number of curves were presented which represented a similar fit to the data and few curves were tested as sensitivity analyses. The company provided a sensitivity analysis which used the exponential curve for both PFS and overall survival which generated an ICER of £62,837 with PAS vs. PC and >£50k without PAS versus IR in the at least one prior therapy and treatment naïve and 17p deletion subgroups. The long-term data are limited as the RESONATE study was stopped early and relatively few patients had progressed or died. Therefore the extrapolation was associated with considerable uncertainty because of the immaturity of the data and in the most appropriate method to use for extrapolation, and this increased the uncertainty of the ICER.
- The analyses included non-significant differences and, when these were removed, the ICERs increased to >£50k without PAS versus IR in the at least one prior therapy, and treatment naïve and 17p deletion subgroups. The company suggested that due to a lack of data in the condition few significant differences can be demonstrated and therefore

the analyses should be treated with caution.

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

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted ibrutinib for restricted use in NHS Scotland. Use is restricted to patients with 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy.

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

The European Society for Medical Oncology (ESMO) published Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up in 2015.<sup>9</sup> The guidelines recommend a watch and wait strategy for patients with early disease. For patients with advanced disease, treatment should only be started when the disease is symptomatic and active. The guidelines recommend first-line treatment with ibrutinib or idelalisib and rituximab in patients with TP53 mutation/17p deletion. In patients with relapsed/refractory disease, treatment should only be started in symptomatic patients. First-line treatment may be repeated if the relapse or progression occurs at least 24 to 36 months after chemo-immunotherapy and if is excluded. (First-line treatments in patients without TP53 mutation/17p deletion include FCR, BR, chlorambucil plus an anti-CD20 antibody). If relapse occurs within 24 to 36 months after chemo-immunotherapy, or if the disease does not respond to any first-line therapy, the therapeutic regimen should be changed to one of the following options: BCL2 antagonists alone or in combination within a clinical study; ibrutinib; IR or other chemo-immunotherapy combinations (which should only be administered if TP53 mutation/17p deletion is excluded). Patients not responding nor progressing upon therapy with kinase inhibitors might be switched to a different kinase inhibitor or to BCL2 antagonists when available (according to clinical trials). Fit patients achieving second remission following the second application of an inhibitor should proceed to allogeneic haematopoietic stem-cell transplantation. An allogeneic stem-cell transplantation should be considered in patients achieving remission with kinase inhibitors or BCL2 antagonists after early relapse from chemoimmunotherapy and/or with del(17p) or TP53 mutation. In this situation, long-term treatment with inhibitors is an alternative option.

The British Committee for Standards in Haematology (BCSH) published guidelines on the diagnosis and management of CLL in 2012.<sup>11</sup> However a recent interim statement in 2015 aims to update the guidance in response to the advances in CLL treatments which have recently become available.<sup>12</sup> This includes a recommendation for IR or ibrutinib as the first-line treatment of choice for patients with TP53 disruption. If these agents are not available, alemtuzumab with/without corticosteroids remains preferable to chemotherapy. In addition, IR or ibrutinib, is recommended as the first-line treatment of choice for patients with relapsed CLL who meet the pivotal idelalisib or ibrutinib study criteria. For patients not meeting these criteria, chemotherapy with/without rituximab is recommended, mainly BR or FCR. The revised BCSH CLL guidelines were expected before the end of 2015.

## Additional information: comparators

For patients with 17p deletion and/or TP53 mutation unsuitable for chemo-immunotherapy, first-line treatment would be IR or alemtuzumab (unlicensed) plus pulsed high dose corticosteroids. For patients with relapsed CLL, treatment options include IR, bendamustine ± rituximab, FCR, chlorambucil ± rituximab, alemtuzumab (unlicensed) ± high dose steroids.

## Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per course (£)*
<b>Ibrutinib</b>	<b>420mg orally once daily continuously</b>	-	<b>40,011</b>
Idelalisib Rituximab (IR)	150mg orally twice daily continuously 375mg/m <sup>2</sup> IV cycle 1, 500mg/m <sup>2</sup> cycles 2 to 6	- 1,222 - 1,572	11,939 9,082
Fludarabine Cyclophosphamide Rituximab (FCR)	40mg/m <sup>2</sup> orally daily for 5 days every 28 days 250mg/m <sup>2</sup> orally daily for 3 days every 28 days 375mg/m <sup>2</sup> IV cycle 1, 500mg/m <sup>2</sup> cycles 2 to 6	706 5 1,222 - 1,572	4,236 29 9,082
Bendamustine Rituximab (BR)	90m <sup>2</sup> IV daily for 2 days every 28 days 375mg/m <sup>2</sup> IV cycle 1, 500mg/m <sup>2</sup> cycles 2 to 6	968 1,222 - 1,572	5,808 9,082
Chlorambucil Rituximab	10mg/m <sup>2</sup> daily orally for 7days every 28 days 375mg/m <sup>2</sup> IV cycle 1, 500mg/m <sup>2</sup> cycles 2 to 6	102 1,222 - 1,572	612 9,082

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis and BNF on 2 March 2016 and are calculated based on a body surface area of 1.8m<sup>2</sup>, where appropriate.

Costs do not take any patient access schemes into consideration. This is not an exhaustive list of regimens used for the treatment of CLL.

IV=intravenous

\* the cost per course is based on a treatment course of 8.6 months with ibrutinib (based on the median treatment exposure in the RESONATE study); a treatment course of 3.8 months with idelalisib (based on the median dose in the pivotal study) and of six cycles of FCR, BR and chlorambucil plus rituximab.

## **Additional information: budget impact**

*Adult patients who were treatment naive and have 17p deletion or TP53 mutation:*

The company estimated there would be 34 patients eligible for treatment with ibrutinib in each year, to which confidential estimates of treatment uptake were applied. Note, this figure relates to first-line use and does not take account of patients who may develop 17p deletion or TP53 mutation as CLL progresses.

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

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

## References

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

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4. Brown JR, Hillmen P, O'Brien S, et al. Updated efficacy including genetic and clinical subgroup analysis and overall safety in the phase 3 RESONATE™ trial of ibrutinib versus ofatumumab in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma. American Society of Hematology Annual Meeting; December 7, 2014; San Francisco, CA2014.
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8. Farooqui ZH, Valdez J, Martyr S et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. Lancet Oncol 2015;16:169-76.
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12. Follow GA, Bloor A, Dearden C et al. Interim statement from the BCSH CLL guidelines panel, 2015. [www.bcsguidelines.com](http://www.bcsguidelines.com)

This assessment is based on data submitted by the applicant company up to and including 16 May 2016.



*\*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal*

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

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

**Advice context:**

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

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