Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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ibrutinib 140mg hard capsules (Imbruvica®) SMC No. (1151/16)

Janssen-Cilag Ltd

10 March 2017

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

ADVICE: following a resubmission assessed under the end of life and orphan medicine process

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

Indication under review: the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

SMC restriction: patients with relapsed/refractory CLL and for whom fludarabine-based regimens are inappropriate.

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.

This resubmission relates to use as a single agent for the treatment of adult patients with CLL who have received at least one prior therapy. SMC published advice in August 2016 that ibrutinib was accepted for restricted use as a single agent for patients with 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy (SMC 1151/16).

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 10 April 2017

Indication

As a single agent or in combination with bendamustine and rituximab (BR) for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.[1]

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.[1]

Product availability date

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).[1]

This resubmission relates to the treatment of adult patients with CLL who have received at least one prior therapy (i.e. relapsed or refractory disease). SMC has previously accepted the use of ibrutinib in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.The submitting company has requested that SMC considers ibrutinib when positioned for use in patients with relapsed/refractory CLL and for whom fludarabine-based regimens are inappropriate. The ibrutinib licence also permits treatment in combination with bendamustine and rituximab;[1] this resubmission relates to ibrutinib use as a single agent only.

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.[2,3] 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, which was defined as

the presence of at least one criterion listed in Figure 1. Patients had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1.

Figure 1: Factors determining suitability for treatment/retreatment with purine-based regimen.[2,3]

Response to prior purine-based and anti-CD20-containing regimen (after ≥2 cycles)	Failure to respond (either stable disease or disease progression on treatment) or Progression-free interval <3 years
Age and fitness	≥70 years or ≥65 years plus the presence of co-morbidities (Cumulative Illness Rating ≥6 or creatinine clearance <70mL/min) provided at least two cycles of alkylating agent- or purine analogue-based anti-CD20-containing regimen received
Toxicity	History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia
Adverse genetic marker	17p deletion

Patients 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 cross over to ibrutinib treatment on disease progression confirmed by an independent review committee (IRC).[2,3]

The primary outcome was progression-free survival (PFS), defined as the time from randomisation to disease progression or death from any cause, whichever occurred 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, IRC-assessed PFS was significantly longer for patients treated with ibrutinib when compared with ofatumumab (Table 1). A consistent treatment effect with ibrutinib over ofatumumab was found across all pre-specified subgroups. In the subgroup of patients with disease refractory to purine analogues (n=175), the hazard ratio for PFS was 0.18 (95% confidence interval [CI]: 0.10 to 0.32).[2,3] 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.[2,3]

The key secondary outcomes were overall survival and overall response rate (ORR). At the time of the interim analysis, 29% (57/196) ofatumumab patients had crossed over to receive ibrutinib. Results of the primary analysis of overall survival in which patients were censored at crossover are presented in Table 1. Sensitivity analysis, with patients not censored at crossover, was similar (hazard ratio 0.39 [95% CI:0.22 to 0.70], 12 month survival rate 90% and 79% respectively).[1-3] At the updated analysis, 61% (120/196) of ofatumumab patients had crossed over to ibrutinib; when censored, the 18-month survival rates were 85% versus 78% respectively.[4]

Table 1: Survival outcomes from RESONATE[2-4]

Outcome			ibrutinib (n=195)	ofatumumab (n=196)
Interim analysis (median follow-up 9.4 months)	PFS* (IRC-assessed)	Event rate	18% (35/195)	57% (111/196)
		Median	Not reached	8.1 months
		Hazard ratio (95% CI)	0.22 (0.15 to 0.32), p<0.001	
	Overall survival[#]	Event rate	8.2% (16/195)	17% (33/196)
		Median	Not reached	Not reached
		12-month survival	90%	81%
		Hazard ratio (95% CI)	0.43 (0.24 to 0.79), p=0.005	
Updated analysis (median follow-up 16 months)	PFS (investigator-assessed)	Event rate, %	NR	NR
		Median	Not reached	8.1 months
		12-month PFS rate	84%	19%
		Hazard ratio (95% CI)	0.11 (0.07 to 0.15), p<0.0001	

*Primary outcome. [#]Analysis which censored patients at crossover.
IRC = independent review committee, CI = confidence interval. NR = not reported

ORR was 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 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.[1-3] 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.[3]

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 Questionnaire-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.[3] Numerically more ibrutinib than ofatumumab patients achieved a clinically meaningful improvement in FACiT-fatigue (increase of ≥3points), in the EORTC QLQ-C30 global health score (improvement ≥10 points) and in EQ-5D-5L.[5,6]

Haematological improvements were assessed in the subset of patients with cytopenia(s) at baseline (haemoglobin ≤110g/L, platelets ≤100x10^9/L, or absolute neutrophil count (ANC) ≤1.5x10^9/L), the proportion of patients with sustained hematological improvement (defined as

improvement in cytopenia by ≥50%, or haemoglobin >110g/L, ANC >1.5x10^9/L, platelets >100x10^9/L, with the duration of improvement lasting for at least two 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.[2,3]

Supportive data comes from the phase Ib/II PCYC-1102 study plus three-year extension (PCYC-1103). Patients with relapsed/refractory CLL/SLL (n=101), or treatment-naive (n=31) were treated with either ibrutinib 420mg or 840mg once daily until disease progression or unacceptable toxicity. In patients taking either dose of ibrutinib, after a median follow-up of 39 months, investigator-assessed ORR for relapsed/refractory patients was 86%, of which 10% were complete responses. Median duration of response was 45 months. Median PFS was 52 months and the 5-year PFS rate was estimated to be 43%.[7-9]

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 at least 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. At the time of the interim analysis (9.4 months data-cut), the median duration of treatment was longer in the ibrutinib group (8.6 months) than in the ofatumumab group (5.3 months).[2,3]

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%).[3]

Haemorrhagic events were reported in 44% of ibrutinib and 12% of ofatumumab patients, and were classified as major (defined as ≥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 at least 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%).[2,3]

Summary of clinical effectiveness issues

Ibrutinib is a first-in-class medicine for the treatment of CLL. This resubmission relates to the treatment of adult patients with CLL who have received at least one prior therapy (i.e. relapsed or refractory disease). The submitting company has asked SMC to consider ibrutinibfor patients for whom fludarabine-based regimens are inappropriate. The ibrutinib licence also permits treatment in combination with bendamustine and rituximab; this resubmission focuses on ibrutinib use as a single agent only.

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.[10] Idelalisib, in combination with anti-CD20 monoclonal antibody, either rituximab or ofatumumab, is also indicated for relapsed or refractory CLL. 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 patients with CLL, through a patient access programme and is sometimes used. Clinical experts consulted by SMC advised that there is no standard treatment option for patients who have received at least one prior therapy; examples of treatments used included re-treatment with first-line therapy, chlorambucil-, bendamustine-based regimens and idelalisib plus rituximab. The experts advised that idelalisib plus rituximab was the treatment most likely to be replaced by ibrutinib but also noted the utilisation of idelalisib plus rituximab in Scottish clinical practice has recently been limited by its associated toxicity. 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.

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 subgroups. Overall survival was a secondary outcome and immature data suggest 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 group 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, although the non-comparative phase Ib/II studies provide supportive longer-term outcome data for ibrutinib. The immature overall survival data are further limited by crossover of patients from ofatumumab to ibrutinib.The primary overall survival analysis censored patients at crossover and estimated the HR as 0.43. Adverse events associated with ibrutinib, although common, did not lead to substantial discontinuations of treatment.

The RESONATE study population represented the proposed positioning for relapsed or refractory CLL in patients not considered suitable for fludarabine-based regimens.

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.[3,10] The summary of product characteristics (SPC) notes that patients with severe cardiovascular disease were excluded from ibrutinib clinical studies.[1]

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 company submission considered physician's choice (PC) to be the primary comparator and idelalisib plus rituximab as another relevant comparator. To support the economic case, the submitting company presented indirect comparisons of ibrutinib versus physician's choice (PC) and versus idelalisib plus ofatumumab. Due to lack of relevant data, idelalisib plus ofatumumab was used as a proxy for idelalisib plus rituximab. In this indirect comparison, PC consisted of a range of regimens including rituximab in combination with cyclophosphamide, vincristine and prednisolone (R-CVP), alemtuzumab, bendamustine plus rituximab, fludarabine plus cyclophosphamide and rituximab.

The indirect comparisons used Bucher methodology with ofatumumab as a common comparator and the reported efficacy outcomes were ORR, PFS and overall survival. Each indirect comparison comprised two studies including RESONATE. The indirect comparison of ibrutinib with PC suggested that ibrutinib was superior for overall response rate, PFS and overall survival. The indirect comparison with idelalisib plus ofatumumab suggested superiority of ibrutinib for PFS.

Limitations with the analyses warrant cautious interpretation of the results. The treatments used as PC may not reflect clinical practice, and idelalisib plus ofatumumab was used as a proxy for idelalisib plus rituximab. However, SMC clinical experts generally considered that these assumptions were reasonable. The relative outcomes may be confounded by differing length of study follow-up and data maturity (particularly in the comparisons of overall survival). There were differences in the outcome results for the common ofatumumab group suggesting different disease severity/prognosis across the studies. Heterogeneity of study populations was most prominent in the comparison with PC. To address this, the company conducted a sensitivity analysis in which the patient population from the RESONATE study was restricted according to the eligibility criteria of the PC study. The result of the sensitivity analysis suggested ibrutinib was superior to PC for all three outcomes. This analysis addressed heterogeneity between the study populations; however, other limitations remain (e.g. differing data maturity).

The introduction of ibrutinib for CLL would offer patients an effective oral agent for the treatment of relapsed/refractory disease. 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.

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

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. PACE participants considered there is significant unmet need in patients with relapsed/refractory CLL.

- 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.

- Recent safety concerns surrounding the use of idelalisib may influence selection of agent in the relapsed/refractory group and further reduce available options.

- 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 study. In addition, the clinical study 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 with 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 with other treatment options.

Additional Patient and Carer Involvement

We received patient group submissions from Bloodwise, Leukaemia CARE and the Chronic Lymphocytic Leukaemia Support Association (CLLSA); all three are registered charities. Bloodwise has received 0.29% pharmaceutical company funding in the past two years, including from the submitting company. Leukaemia CARE has received 10.6% pharmaceutical company funding in the past two years, including from the submitting company. CLLSA has received 65% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all three charities attended the PACE meeting. The key points of their submissions have been included in the full PACE statement.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis using a partitioned survival model over a 20-year time horizon in adult patients with CLL who have received at least one prior therapy and for whom fludarabine-based regimens are inappropriate. The comparators included were PC and idelalisib plus rituximab (IR). PC 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).

The model consisted of three health states: PFS, post-progression survival (PPS) and death. Patients received ibrutinib until disease progression or until treatment was no longer tolerated. Patients initiated to PC received treatment until progression or until the maximum treatment duration had been reached. The economic model also assumed that 42% 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 economic model included clinical data from the RESONATE study, which was used to generate PFS and overall survival estimates for ibrutinib.[2,3] The hazard ratios were adjusted for crossover to capture the impact of ofatumumab patients in the RESONATE study switching treatment to ibrutinib after disease progression. In the absence of direct data versus PC and IR, indirect comparisons versus PC and idelalisib plus ofatumumab (IO) were presented. Due to the lack of relevant data, efficacy data for IO were used as a proxy for IR.

In order to extrapolate the data, a number of parametric functions were fitted. The choice of curve was determined by goodness of fit statistics, visual inspection and the clinical plausibility of the longer term predictions. For PFS, the Weibull curve was identified as the most appropriate curve for use in the analysis. For overall survival, the log-normal curve was fitted for the first three years and then the exponential was used thereafter. In order to provide a comparison against IR and PC, the hazard ratios from the ITC were applied to the ibrutinib PFS and overall survival curves. 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.[5,6,13] 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 simple Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price of ibrutinib. A PAS is in place for idelalisib and an estimate of the PAS price was included in the results used for SMC decision-making. The results of the base case and key sensitivity analyses are presented in table 2.

Table 2: Base case results and key sensitivity analyses

Analysis	ICER vs. PC (with ibrutinib PAS)	ICER vs. IR (using list price for all medicines)
Base case	£33,943	£51,494
Exponential curve to estimate PFS	£45,780	£75,808
Restricting the benefit of ibrutinib to 6 years	£44,688	£68,347
Restricting the benefit of ibrutinib to 7 years	£42,796	£65,123
Reducing the time horizon to 10 years	£41,604	£71,261
Assume no cost benefit due to response	£43,672	£60,563
Removing non-significant differences	n/a	£442,511

ICER = incremental cost-effectiveness ratio, PC = physician's choice, IR = idelalisib plus rituximab, PAS = patient access scheme, PFS = progression-free survival

Note that the results versus IR presented in table 2 do not take account of the PAS for either ibrutinib or idelalisib. SMC is unable to present these results due to commercial confidentiality and competition law issues.

The following limitations were noted:

- The company considered that PC is the most relevant comparator and the comparison with IR was provided as a secondary analysis, but SMC clinical expert responses suggest that IR is the primary comparator. Both PC and IR are considered relevant comparators that could be displaced by ibrutinib.
- 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 may not be entirely reflective of Scottish practice, and the data that informed the efficacy of IR were based on patients initiated to IO and not IR. SMC clinical experts were requested to comment on the efficacy assumptions used in the indirect comparison and economic analysis and, although 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. The company provided a sensitivity analysis which used the exponential curve for both PFS and overall survival (see table 2). The long term data are limited as in the RESONATE study relatively few patients had progressed or died. Therefore, the extrapolation was associated with uncertainty and based on relatively immature data.
- The analyses included non-significant differences, and the results were sensitive to removing these differences (see table 2). The company suggested that due to a lack of data in the condition few significant differences can be demonstrated and therefore this analysis should be interpreted 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 and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted ibrutinib for restricted use in NHS Scotland.

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

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.[10]In patients with relapsed/refractory disease, treatment should only be started in symptomatic patients. First-line treatment may be repeated if the relapse or progressionoccurs at least 24 to 36 months after chemo-immunotherapyand if TP53 mutation or 17p deletion is excluded. If relapse occurs within 24 to 36 months after chemo-immunotherapy,or if the disease does not respond to any first-linetherapy, the therapeutic regimen should be changed to one of the following options: B-cell antagonists alone or in combination within a clinical study; ibrutinib; idelalisib plus rituximab or other chemo-immunotherapy combinations (which should onlybe administered if TP53 mutation/17p deletion is excluded). Patients not responding nor progressing upon therapy withkinase inhibitors might be switched to a different kinase inhibitoror to B-cell 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. Allogeneic stem-cell transplantation should be considered in patients achieving remission with kinase inhibitors or B-cell antagonists after early relapse from chemoimmunotherapy and/or with 17p deletion 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.[11] Further studies are required to evaluate the role of bendamustine in combination with an anti-CD20 antibody in fit patients with relapsed disease. Patients relapsing after chlorambucil can be retreated with chlorambucil. Entry into trials that include bendamustine or chlorambucil and an anti-CD20 antibody is strongly recommended. In the absence of a suitable trial, bendamustine plus rituximab should be considered for patients who are refractory to chlorambucil. Other options for patients who are refractory to chlorambucil and unable to tolerate myelosuppressive therapy include high dose corticosteroids, alone or in combination with rituximab, and alemtuzumab. The guidelines also note that treatment for high-risk CLL (which includes those who relapse within two years of, or are refractory to purine-analogue based therapy) should ideally be as part of a clinical trial. Outside of trials, alemtuzumab in combination with pulsed high dose glucocorticoid is the treatment of choice. Allogeneic stem-cell transplantation should be considered as consolidation therapy for all fit patients with high-risk CLL and should ideally be performed in the setting of a secure remission. For patients for whom allogeneic transplantation is not an option, re-treatment with alemtuzumab should be considered in those patients who relapse more than 12 months after initial treatment. Treatment options for patients who fail or relapse early after alemtuzumab-based therapy are limited. Active agents include ofatumumab, lenalidomide and high-dose steroids with or without rituximab. Corticosteroids given at conventional dose can provide useful short-term disease control and

improve CLL-related symptoms. The choice of therapy depends on patient fitness, previous treatment and drug availability.[11]

A recent interim statement in 2015 aims to update the guidance in response to the advances in CLL treatments which have recently become available.[12] Idelalisib plus rituximab 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 bendamustine plus rituximab or FCR.

Additional information: comparators

For patients with relapsed CLL, treatment options include idelalisib plus rituximab, bendamustine ± rituximab, fludarabine plus cyclophosphamide plus rituximab, chlorambucil ± rituximab, alemtuzumab (unlicensed) ± high dose corticosteroids.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 28-day cycle (£)
ibrutinib	**420mg orally once daily continuously**	**4,292**
idelalisib plus rituximab	idelalisib 150mg orally twice daily continuously rituximab 375mg/m^{2}IV cycle 1, 500mg/m^{2}cycles 2 to 6	Cycle 1: 4,130 Cycles 2 to 6: 4,479 Cycle 7-: 2,907
fludarabine plus cyclophosphamide plus rituximab	40mg/m^2 orallydaily for 5 days every 28 days 250mg/m^{2}orallydaily for 3 days every 28 days 375mg/m^{2}IV cycle 1, 500mg/m^{2}cycles 2 to 6	Cycle 1: 1,933 Cycles 2 to 6: 2,282
bendamustine plus rituximab	90m^2 IV daily for 2 days every 28 days 375mg/m^{2}IV cycle 1, 500mg/m^{2}cycles 2 to 6	Cycle 1: 1,318 Cycles 2 to 6: 1,668
chlorambucil plus rituximab	10mg/m^{2}daily orally for 7days every 28 days 375mg/m^{2}IV cycle 1, 500mg/m^{2}cycles 2 to 6	Cycle 1: 1,330 Cycles 2 to 6: 1,680

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis and MIMSonline on 7 December 2016 and are calculated based on a body surface area of 1.8m^2, where appropriate.Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes or VAT into consideration. This is not an exhaustive list of regimens used for the treatment of CLL. IV=intravenous

Additional information: budget impact

The submitting company estimated there would be 170 patients eligible for treatment with ibrutinib in year 1, rising to 173 patients in year 5. The estimated uptake rate was 20% in year 1 (34 patients), rising to 88% in year 5 (152 patients).

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

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

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This assessment is based on data submitted by the applicant company up to and including 20 February 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

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.