Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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ibrutinib 140mg hard capsule (Imbruvica®) SMC No. (1150/16)

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 ultra-orphan medicine processes

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

Indication under review: Treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

In a randomised, open-label, phase III study ibrutinib significantly prolonged progression-free survival, the primary endpoint, compared to a chemotherapy treatment, in patients with relapsed or refractory MCL.

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.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 08 August 2016

Indication

Treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

Dosing Information

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

Ibrutinib 560mg (four, 140mg capsules) orally once daily. Treatment should continue until disease progression or no longer tolerated by the patient.

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.

Product availability date

5 November 2014
Ibrutinib has been designated an orphan medicine by the European Medicines Agency (EMA). It also meets SMC end of life and ultra-orphan criteria.

Background

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 mantle cell lymphoma (MCL).[1,2]

Ibrutinib is indicated for the treatment of relapsed/refractory MCL, where there is currently no standard of care. Temsirolimus is the only other medicine specifically licensed for relapsed/refractory MCL but was not recommended for use by SMC in April 2010, as the result of non-submission.

Nature of condition

MCL, an aggressive subtype of non-Hodgkin's lymphoma (NHL), represents approximately 6% of all new NHL cases per year. The majority of patients present with advanced disease. There are no treatments that provide a cure for MCL and there are no standard second-line chemotherapy regimens in relapsed MCL, where choice is generally individualised for each patient.[1,2] Clinical experts consulted by SMC reported a range of treatments used, including chemotherapy (bendamustine, fludarabine plus cyclophosphamide, chlorambucil, cyclophosphamide + doxorubicin + vincristine + prednisone [CHOP]) ± rituximab.

PACE participants reported that, in advanced disease, quality of life and normal daily functions can be significantly impacted and can be extremely difficult to cope with emotionally and

physically. Patients with MCL have poor outcomes and tend to have only short periods of remission.

The incidence of MCL increases with age and is highest in patients aged 70 to 79 years. In patients with relapsed MCL treated with salvage therapies, the median overall survival is one to two years.[1] Ibrutinib meets SMC ultra-orphan criteria and is an EMA designated orphan medicine. Ibrutinib also meets SMC end of life criteria. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, as there are few efficacious treatments in patients who have relapsed.

Impact of new technology

Summary of evidence on comparative efficacy

Evidence of efficacy in MCL comes from MCL-3001, a randomised controlled, open-label, phase III study comparing ibrutinib with temsirolimus in 280 patients with relapsed or refractory MCL, confirmed by central pathology.[3] Patients had received at least one previous rituximab-containing chemotherapy regimen and had documented relapse or disease progression after the last anti-MCL treatment. In addition they had measurable disease by Revised Response Criteria for Malignant Lymphoma, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Haematology and biochemical values were required to be within pre-specified limits.

Patients were randomised equally to ibrutinib 560mg orally once daily, continuously (n=139) or temsirolimus 175mg intravenously (IV) on days 1, 8 and 15 of cycle one and then 75mg IV on days 1, 8 and 15 of subsequent 21-day cycles (n=141). Patients were treated until disease progression or death, adverse event, patient decision or investigator/funder decision. Randomisation was stratified by the number of previous lines of therapy (one or two versus three or more) and simplified mantle-cell lymphoma international prognostic index (sMIPI) score (low risk [0–3] versus intermediate risk [4–5] versus high risk [6–11]). During the study the protocol was amended to allow crossover of patients treated with temsirolimus to the ibrutinib group if they had independent review committee (IRC)-confirmed disease progression.

The primary endpoint was progression free survival (PFS), defined as the interval from date of randomisation to date of progression (assessed by masked IRC) or death, whichever came first and irrespective of subsequent treatments. It was assessed in the intention-to-treat (ITT) population. After a median follow-up of 20 months, median PFS was 14.6 months for ibrutinib and 6.2 months for temsirolimus; hazard ratio 0.43, 95% CI: 0.32 to 0.58, $p<0.0001$. At the two-year landmark analysis, PFS rate was 41% versus 7% for ibrutinib and temsirolimus respectively. The effect of ibrutinib was generally consistent across the pre-planned subgroups.[3]

Secondary endpoints included response rate, median duration of response and overall survival. The overall response rate was assessed by IRC using revised International Working Group (IWG) for NHL criteria and included complete plus partial responses. The proportion of patients with an overall response was 72% (100/139) for ibrutinib and 40% (57/141) for temsirolimus; difference 32% (95% CI: 20% to 42%), $p<0.0001$. The proportion of patients with a complete response was 19% (26/139) for ibrutinib versus 1.4% (2/141) for temsirolimus. The median duration of response had not been reached in the ibrutinib group and was 7.0 months for the temsirolimus group. Median overall survival had not been reached in the ibrutinib group and was 21.3 months for the temsirolimus group; hazard ratio 0.76 (95% CI: 0.53 to 1.09), $p=0.1324$. The

proportion of patients who died was 42% (59/139) in the ibrutinib group and 45% (63/141) in the temsirolimus group. Analysis after long-term follow-up will be reported at the end of the study.[3]

Quality of life was measured using the FACT-Lym tool as well as the EQ-5D-5L utility score and visual analogue scale (VAS). FACT-Lym measures lymphoma symptoms (range 0 to 60) with a clinically meaningful improvement/worsening defined as ≥5 point increase/decrease respectively from baseline. The proportion of patients with a clinically meaningful improvement in lymphoma symptoms was 62% (86/139) for ibrutinib and 35% (50/141) for temsirolimus, and the median time to clinically meaningful improvement was 6.3 weeks versus 57.3 weeks respectively ($p<0.0001$). The proportion of patients with a clinically meaningful worsening in lymphoma symptoms was 27% (37/139) for ibrutinib and 52% (73/141) for temsirolimus, and the median time to clinically meaningful worsening was not reached versus 9.7 weeks respectively ($p<0.0001$). Generally there were improvements or stable quality of life for patients treated with ibrutinib, when measured using the EQ-5D-5L utility values and VAS; the differences versus temsirolimus were statistically significant up to week 49 for the EQ-5D-5L utility score and to week 106 for EQ-5D-5L VAS.[3, 4]

Supportive data come from study PCYC1104, an open-label, non-randomised, single-arm, phase II study in patients with MCL. Patients had received one to five previous lines of treatment with no partial or better response to the most recent treatment regimen or with disease progression after the most treatment regimen. In addition, they had measurable disease (lymph node diameter ≥2cm), an ECOG performance status of 0 to 2 and adequate organ function. Patients were classified according to prior bortezomib use: cohort 1 (no prior bortezomib, defined as <2 complete cycles or no prior bortezomib therapy) and cohort 2 (prior bortezomib, ≥2 cycles). All patients received ibrutinib 560mg orally daily until disease progression or until unacceptable adverse events. A total of 111 patients received treatment (cohort 1, n=63 and cohort 2, n=48).[1, 5]

The primary endpoint was investigator-assessed overall response which included complete plus partial responses according to revised IWG for NHL criteria. At a median follow-up of 15.3 months, the proportion of patients with an overall response was 68% (75/111); complete responses (21% [23/111]) and partial responses (47% [52/111]). Secondary endpoints included duration of response (median, 17.5 months; 15.8 months in cohort 1 and not reached in cohort 2) and PFS (median, 13.9 months; 7.4 months in cohort 1 and 16.6 months in cohort 2). In an updated analysis (median follow-up 26.7 months) median PFS was 13 months and the median overall survival was 22.5 months. The two-year Kaplan-Meier estimate of PFS was 31% and overall survival was 47%.[5, 6]

Summary of evidence on comparative safety

In the MCL-3001 study, treatment emergent adverse events were reported in 99% of patients in each group, and those of at least grade 3 occurred in 68% (94/139) and 87% (121/139) of patients in the ibrutinib and temsirolimus groups respectively. Treatment discontinuation due to adverse events occurred in 6.5% (9/139) and 26% (36/139) of patients respectively. Median treatment duration was longer for ibrutinib (14.4 months) than temsirolimus (3.0 months).[3]

Haematological adverse events (of at least grade 3) were (in the ibrutinib and temsirolimus groups respectively): thrombocytopenia (9.4% and 42%), anaemia (7.9% and 20%) and neutropenia (13% and 17%). Non-haematological adverse events (any grade) were (in the ibrutinib and temsirolimus groups respectively): diarrhoea (29% and 31%), fatigue (22% and 29%), cough (22% each), pyrexia (17% and 21%), nausea (14% and 22%), peripheral oedema (13% and 22%), epistaxis (8.6% and 24%) and stomatitis (2.9% and 21%). Although major

bleeding occurred in a higher proportion of ibrutinib than temsirolimus patients, when adjusted for exposure, the event rate for any major bleeding treatment-emergent adverse event was 0.8 events per 100 patient-months for ibrutinib and 1.1 events per 100 patient-months for temsirolimus.

The proportion of patients who died during treatment or within 30 days of last dose of study drug was 17% (24/139) versus 11% (15/139). Disease progression was the most common cause of death in the ibrutinib group and adverse events in the temsirolimus. In the first six months of treatment, the proportion of patients with a treatment-emergent adverse event with an outcome of death was 5.8% (8/139) and 7.9% (11/139) in the ibrutinib and temsirolimus groups respectively.[3]

Summary of clinical effectiveness issues

In the pivotal study, conducted in patients with relapsed or refractory MCL who had received at least one previous rituximab-containing chemotherapy regimen, median PFS was significantly longer for ibrutinib than temsirolimus. It has been reported that PFS correlates with overall survival in NHL.[7] Overall survival data are currently immature and confounded by crossover, which occurred in 23% of patients in the temsirolimus group at the time of the primary analysis.

In patients who received subsequent treatments (excluding those who received crossover treatment with ibrutinib or temsirolimus), the overall response rate was 20% (8/40) in the ibrutinib group and 20% (10/50) in the temsirolimus group, indicating that patients not responding to ibrutinib (or temsirolimus) have a poor prognosis.[3]

The pivotal study was of open-label design; however, the primary outcome of PFS was assessed by blinded independent review which should minimise potential bias. The median age of patients in the MCL-3001 study was 68 years.[3] Furthermore, the summary of product characteristics notes that patients with severe cardiovascular disease were excluded from ibrutinib clinical studies.[8] Therefore, the study population (with respect to patient age and co-morbidities) may not truly reflect patients who will be eligible for ibrutinib in clinical practice.

Study PCYC1104, of single arm open-label design, provides supportive data for the submission to SMC. However, the EMA granted marketing authorisation based on this study, as at the time, study MCL-3001 was ongoing. The EMA considered that the results for overall response rate and duration of response were exceptional.

Temsirolimus, the comparator in the study MCL-3001, is not used in clinical practice in NHS Scotland and was not considered a relevant comparator. Consequently an adjusted indirect treatment comparison (ITC) using Bucher methodology was conducted to compare ibrutinib with physician's choice using temsirolimus as a common comparator. Results of the indirect comparison were used to derive estimates for PFS and overall survival for the physician's choice arm in the base case economic evaluation. Two studies were included in the indirect comparison and the efficacy endpoints reported were overall response rate, PFS and overall survival. Results indicate that ibrutinib was superior to physician's choice for overall response rate and PFS, with no difference between groups for overall survival. The ITC has limitations. Treatments used in the physician's choice arm do not reflect treatments now used in clinical practice which makes generalisability uncertain. Also, there was heterogeneity in outcomes between the common control arms (temsirolimus) of the studies. Therefore, the results should be interpreted with caution. Given this, the use of temsirolimus data from MCL-3001, may be an appropriate option as a proxy for physician's choice in the economic evaluation.

The introduction of ibrutinib for MCL 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. They considered that a range of treatments are likely to be displaced.

At the PACE meeting, participants highlighted the quality of life (QoL) improvements seen in practice and considered that the pivotal study did not fully capture real life QoL. Compared with current chemotherapy and/or supportive care, ibrutinib offers improvement in QoL due principally to its markedly reduced toxicity profile. This means a reduced need for family and carer support and greater independence for patients.

*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 end of life and ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- MCL is a rare and aggressive form of non-Hodgkin's lymphoma. It is often diagnosed in the late stages of disease with poor outcomes and where quality of life is significantly impacted with symptoms such as overwhelming fatigue, fever, and abdominal pain.

- PACE participants highlighted a clear unmet need for treatment in view of limited effective options. Chemotherapy treatments have a significant toxicity profile and responses are poor. Each subsequent relapse is more difficult to treat and progression is common.

- Ibrutinib has a unique mechanism of action and is a well tolerated, remarkably effective treatment. Clinicians reported that in practice, patients experienced fewer adverse effects than seen in the clinical studies and fewer infective complications are seen, particularly in the elderly. Patients are also less likely to be admitted to hospital for effects of toxicity. The pivotal study did not fully capture real life QoL and clinicians observed a marked improvement in the QoL of their ibrutinib treated patients compared to combination chemotherapy.

- Ibrutinib is administered orally which is more convenient for patients and their carers, allowing greater independence.

- Ibrutinib would be considered particularly beneficial in patients who are elderly, frail and with poor bone marrow reserve but clinicians emphasised that it would be the first-line choice for all refractory and relapsed MCL patients.

- Ibrutinib is an effective, well tolerated and easy to administer treatment which can offer high response rates and may offer a survival benefit in patients for whom there are no other effective tolerable treatment options.

Additional patient and carer involvement
We received a patient group submission from the Lymphoma Association. The patient group has received <8% pharmaceutical company funding in the past two years, including from the submitting company. A representative from the patient group also participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Value for money

The submitting company presented a cost-utility analysis comparing ibrutinib with physician's choice (PC) for the treatment of adult patients with relapsed or refractory MCL. In terms of efficacy, PC included: 51% gemcitabine, 28% fludarabine, 7% chlorambucil, 7% cladrabine and 7% etoposide. For the purpose of costing, PC consisted of: 46% R-CHOP (rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone), 31% FCR (fludarabine + cyclophosphamide + rituximab), 13% BR (bendamustine + rituximab) and 10% R-CVP (rituximab + cyclophosphamide + vincristine + prednisone). SMC clinical experts have commented that the rituximab regimes may be the most likely to be displaced.

A three state *de novo* model was developed consisting of three health states (PFS, post-progression (PPS) and death) over a 15-year time horizon. The clinical data used to inform the economic evaluation were taken from the pivotal study and the ITC described above. Specifically, the hazard ratio for PFS for each arm was taken from the ITC. PPS was assumed to be the same for both arms (ie the same risk of death post-progression). This method suggests that the survival benefit is being driven by the treatment effect in PFS, and that these benefits would not differ post-progression. Several possible forms for parametric distributions were considered to extrapolate and the choice was made based on advice from a panel of clinical experts convened by the submitting company as well as goodness-of-fit statistics. In the base case for PFS and PPS, the exponential parametric distribution was fitted to extrapolate the data.

Quality of life data were collected in the MCL-3001 clinical study described above, and thus informed the PFS health state. Utility decrements associated with PPS and AEs were taken from the published literature. The utility values applied to the PFS health state were 0.730 for PC, and 0.779 for the ibrutinib arm. The PPS utility value was 0.636. Costs were included in the analysis based on response rates taken from the ITC. Resource use data covered NHS costs of giving drug treatment and of on-going routine care. The assumptions used in the modelling of routine care were based on expert opinion from an on-line survey. The costs varied according to the response (partial/complete/non-responder) status of the patient, which in turn was informed by the response rate data from the MCL-3001 and the ITC.

A complex Patient Access Scheme (PAS) was proposed by the submitting company and assessed as acceptable for implementation in NHS Scotland. The PAS offered a discount on the price of the medicine. The base case analysis estimated a cost per quality adjusted life year (QALY) for ibrutinib compared to PC to be £41,798 with the PAS. SMC would wish to present the QALY gain and incremental cost estimates that informed the SMC decision but is unable to publish these figures as the company has intimated that these are commercial in confidence.

The incremental cost-effectiveness ratio (ICER) was most sensitive to the following scenarios;

- Fitting a lognormal distribution to both PFS and overall survival increased the with-PAS ICER to £53k.
- As a proxy for the PC arm, data were taken from the temsirolimus arm of the MCL-3001 study, and this increased the with-PAS ICER to £48k.
- Assuming that the routine follow-up costs are the same regardless of response status, the with-PAS ICER increased to £48k.
- Removal of the incremental utility associated with being in the PFS state on ibrutinib treatment resulted in an ICER of £45k with PAS.

The following weaknesses in the company's base case were noted:

- The therapies included as the basis for estimating costs in the PC arm are not the same therapies as those included to inform the efficacy underpinning the model and there was a concern that the efficacy of PC could be underestimated by using the therapies in the ITC rather than the rituximab-based regimens, which represent current practice. Discussions at the New Drugs Committee (NDC) suggested that the efficacy of temsirolimus may be similar to the rituximab regimens and thus the temsirolimus arm of the MCL-3001 study may be a more appropriate proxy for physician's choice. As noted above, when the temsirolimus arm of the MCL-3001 study is used as a proxy for PC in the model, the with-PAS ICER increased to £49k as a result of lower predicted QALY gains.
- The method the company has used to model PFS and PPS assumes that the likely benefit of treatment is only accrued in PFS and that PPS would be the same for both treatment arms. The company has provided a scenario analysis taking the PFS from the MCL-3001 study and the HR from the ITC to project overall survival. A log-normal distribution was fitted to the data to extrapolate. In this scenario, the with-PAS ICER increased to £53k; however, it is noted that the log-normal curve produced estimates that may be clinically implausible, with 10% of patients being progression-free after 10 years.
- The routine care costs were applied in the model based on responder, partial responder and non-responder state, and informed by the ITC. If the rituximab regimens used in practice are likely to have greater response rates, then the costs in the PC arm in the base case analysis could be overestimated, thus biasing the analysis in favour of ibrutinib. Assuming the same routine costs regardless of response increased the with-PAS ICER to £48k.
- There is some uncertainty associated with the utility values used for the PFS state given that the PC value will reflect the use of temsirolimus in the MCL-3001 study rather than the rituximab-based treatments used in clinical practice. The direction and magnitude of any differences is not known but, conservatively, removing the increment associated with ibrutinib increased the ICER to £45k.

Following discussion, it was felt that the analysis using the temsirolimus arm as a proxy for the efficacy of current treatments was likely to be more appropriate than the base case which used the ITC. This gave a base case ICER of £48k with the PAS. Some sensitivity analysis was provided around this ICER. For example, the with-PAS ICER rose to £53k when the upper limit of the confidence interval for the hazard ratio for PFS for ibrutinib versus temsirolimus was used, reflecting some uncertainty associated with the extrapolation of longer term treatment effects. Additionally, a very conservative scenario was provided with an ICER of £90k when the assumptions were combined, using the PFS and overall survival extrapolated using a log-normal distribution, the temsirolimus arm of the MCL-3001 study as a proxy for PC, routine

follow-up costs assumed to be the same regardless of response rate and applying the same utility value of 0.73 to both arms.

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

Impact beyond direct health benefits and on specialist services

PACE participants highlighted that MCL is often diagnosed in the late stages of disease and QoL is significantly impacted. MCL can be extremely difficult to cope with emotionally and physically for patients as well as their carers and families. Current treatments include chemotherapy, which can often have a significant toxicity profile, affecting a patients ability to work, and also impacts on the burden of carers' responsibility. Elderly patients often suffer treatment toxicity thereby spending more time in hospital.

Ibrutinib can improve QoL and is well tolerated compared to chemotherapy, enabling patients to potentially perform more activities of daily living and relieving input from carers. Ibrutinib is an oral treatment and can be self-administered by patients at home. It does not require frequent hospital visits for infusion or monitoring. There is a corresponding reduced need for patient travel and attendance in hospital for treatment which may require carer support.

Costs to NHS and Personal Social Services

The submitting company estimated there would be would be 82 patients eligible for treatment with ibrutinib in year 1 and 84 patients in year 5, to which confidential estimates of treatment update were applied.

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.**

Conclusion

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 ultra-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 use in NHS Scotland.

Additional information: guidelines and protocols

In 2012 the British Committee on Standards in Haematology (BCSH) published guidelines for the investigation and management of MCL. These recommend that where possible, patients with MCL should be managed within the context of a clinical trial. The guideline acknowledges that "*that there is no-gold standard therapy for relapsed MCL, and clinicians will choose the treatment most appropriate for the individual patient. The choice of therapy will be determined by patient age, performance status, initial therapy, bone marrow reserve and history of infections*." Potential treatment options recommended for relapsed or refractory disease in the guidelines include rituximab, bortezomib, temsirolimus and combination chemotherapy.[2] This guideline predates the availability of ibrutinib.

In 2014 the European Society for Medical Oncology (ESMO) published clinical practice guidelines for diagnosis, treatment and follow-up of newly diagnosed and relapsed MCL. The guidelines recommend that for early relapses or in refractory patients, combined targeted therapies (such as bortezomib, ibrutinib, temsirolimus, lenalidomide) should be considered. In younger patients, an allogeneic transplantation should be considered among possible options.[9]

Additional information: comparators

There is no standard of care for the treatment of relapsed or refractory MCL. Treatments include chemotherapy (bendamustine, fludarabine plus cyclophosphamide, chlorambucil, CHOP) usually in conjunction with rituximab. Many of these treatments are used off-label. Temsirolimus is indicated for the treatment of adult patients with relapsed and/or refractory MCL. However it has not been recommended for use by SMC and is not considered a relevant comparator.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per course (£)
Ibrutinib¥	**560mg orally once daily continuously**	**-**	**85,848**
Rituximab*	375mg/m^2 IV on day 1 of each cycle for 6 to 8 cycles	1,222	7,332 to 9,776
Bendamustine* (± rituximab)	90mg/m^2 (with rituximab) or 120mg/m^2 (monotherapy) IV, on days 1 and 2, every 3 weeks for up to 6 cycles	1,242 (without R) 2,190 (with R)	7,452 (without R) 13,140 (with R)
Bortezomib* (± rituximab)	1.3mg/m^2 IV or SC on days 1, 4, 8 and 11 every 3 weeks, for up to 6 cycles	3,050 (without R) 4,272 (with R)	18,300 (without R) 25,632 (with R)
Fludarabine* plus cyclophosphamide* (± rituximab)	Fludarabine 40mg/m^2 orally plus cyclophosphamide 250mg/m^2 orally daily for 5 consecutive days every 28 days, for up to 6 cycles	714 (without R) 1,936 (with R)	4,284 (without R) 11,616 (with R)
Chorambucil*^ (± rituximab)	10mg/m^2 orally daily for 7 days every 28 days for up to 6 to 8 cycles	102 (without R) 1,324 (with R)	612 to 816 (without R) 7,944 to 10,592 (with R)
CHOP* (± rituximab)	cyclophosphamide 750mg/m^2 IV, doxorubicin 50mg/m^2 IV, vincristine 1.4mg/m^2 (maximum 2mg) IV on day 1 plus prednisolone 100mg orally for 5 days, every 3 weeks for up to 6 to 8 cycles	210 (without R) 1,432 (with R)	1,260 to 1,680 (without R) 8,592 to 11,456 (with R)

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis and DM&D on 26 February 2016 and are calculated based on a body surface area of 1.8m^2, 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 mantle cell lymphoma.

IV=intravenous, SC=subcutaneous, R=rituximab

¥ Ibrutinib is costed for a treatment course of 14 months (based on the median treatment exposure from MCL3001 study of 14.4 months)

* Not specifically licensed for MCL or not licensed in relapsed/refractory MCL

^treatment regimen is off-label.

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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This assessment is based on data submitted by the applicant company up to and including 30 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.