Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2387

ibrutinib 140mg, 280mg and 420mg film-coated tablets (Imbruvica®)

Janssen-Cilag Ltd

05 November 2021

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission under the orphan medicine process

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

Indication under review: as a single agent for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy.

SMC restriction: for use in patients who have received at least one prior therapy.

In a phase II study, in previously treated patients with Waldenström's macroglobulinaemia, ibrutinib was associated with an overall response rate of 87% to 90%.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

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

Chairman
Scottish Medicines Consortium

Indication

As a single agent for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy.[1]

Dosing Information

The recommended dose of ibrutinib is 420mg 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 tablets should be swallowed whole with water and should not be broken or chewed. Ibrutinib must not be taken with grapefruit juice or Seville oranges.

Treatment with this medicinal product should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. Refer to the SPC for further details.[1]

Product availability date

3 July 2015

Ibrutinib has been designated an orphan medicine for lymphoplasmacytic lymphoma (also known as Waldenström's macroglobulinaemia) by the Medicines and Healthcare products Regulatory Agency (MHRA) (PLGB00242/0687-0691/OD3). Ibrutinib meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Waldenström's macroglobulinaemia is a rare B-cell cancer. Ibrutinib is a covalently binding inhibitor of Bruton's tyrosine kinase (BTK). BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is involved in the pathogenesis of several B-cell cancers. Ibrutinib is the first medicine to be licensed for the treatment of Waldenström's macroglobulinaemia, both in combination with rituximab and as monotherapy.[1, 2] Ibrutinib in combination with rituximab has been accepted for restricted use by SMC for use in patients who have received at least one prior therapy (SMC2259). This submission is for ibrutinib as a single agent and the submitting company has requested that SMC considers ibrutinib when positioned for use in patients who have received at least one prior therapy.

The evidence for monotherapy use for Waldenström's macroglobulinaemia comes from one open-label, single-arm, phase II study (1118E). Patients were aged ≥18 years with a diagnosis of Waldenström's macroglobulinaemia which met consensus panel criteria for treatment. They had measurable disease, defined as the presence of immunoglobulin M (IgM) at ≥2 times the upper limit of normal (ULN) and an Eastern Co-operative Oncology Group (ECOG) performance status ≤2. They had received at least one prior therapy for Waldenström's macroglobulinaemia. Eligible

patients were treated with ibrutinib 420mg orally daily (n=63) for up to 40, four-week cycles, until disease progression or unacceptable toxicity, however, patients could continue to receive commercially available ibrutinib after that.

The primary outcome was the overall response rate (ORR) which was defined in terms of reduction in serum IgM levels as a complete response, a very good partial response (≥90% reduction), a partial response (≥50% reduction) and minor response (≥25% reduction) as defined by the Third International Workshop on Waldenström's macroglobulinaemia. ORR was assessed by investigator and the primary outcome was assessed 6 months after the last patient had enrolled. Efficacy and safety analyses were performed in the all-treated population which comprised all patients who received at least one dose of study treatment.[2, 3] The key secondary outcome was major response rate (defined as ≥50% reduction in serum IgM levels). Other secondary outcomes included time to response, progression-free survival (PFS), overall survival and sustained (for ≥ 8 weeks) haemoglobin improvement (defined as an increase to > 110 g/L with at least a 5 g/L improvement or an increase of ≥ 20 g/L for patients with baseline haemoglobin ≤ 110 g/L; an increase of ≥ 20 g/L for patients with baseline value > 110 g/L without blood transfusion or growth factors).

There are no published results at a cut-off after 40 cycles. At the time of the primary analysis (cut-off date February 2014), the median duration of follow-up was 14.8 months and patients had received a median of 11.7 months (range 0.5 to 21.1) of ibrutinib treatment. Results have also been published after a median follow-up of 24 months (median 19.1 months of treatment) and at a final analysis, after a median follow-up of 59 months (duration of treatment not reported). Details are presented in Table 1.

Table 1: Results for the primary and secondary outcomes of the 1118E study[2-4]

	Primary analysis (n=63)	Updated analysis (n=63)	Final analysis (n=63)
Median duration of follow-up, months	14.8	24	59
ORR, investigator-assessed, (95% CI)	87% (77% to 94%)	90% (80% to 96%)	90% (NR)
Major response rate, investigator-assessed, (95% CI)	70% (57% to 81%)	73% (60% to 83%)	79% (NR)
Time to ORR, months	1.0	1.0	0.9
Haemoglobin improvement, %	59%	NR	NR

ORR=overall response rate; CI=confidence interval; NR=nor reported

At the time of the final analysis, median PFS and overall survival were not estimable. The Kaplan-Meier estimated rates for PFS were 83% at 18 months, 69% at 24 months and 54% at 60 months; corresponding overall survival rates were 93%, 95% and 87% respectively.[2-4]

Health related quality of life was not assessed during the 1118E study.

The company presented a naïve indirect comparison of ibrutinib monotherapy (using results from the 1118E study) with ibrutinib plus rituximab (using results from a relapsed/refractory subgroup of the iNNOVATE study [n=41] which compared ibrutinib plus rituximab with placebo plus rituximab) in patients with Waldenström's macroglobulinaemia.[3-5] Treatments were compared

using two outcomes of PFS and overall survival. The resulting confidence intervals for the hazard ratio of the difference in PFS and overall survival between treatments were both wide and include one making it challenging to draw a conclusion on relative efficacy.

Summary of evidence on comparative safety

The EMA concluded that the safety profile of ibrutinib in patients with Waldenström's macroglobulinaemia is consistent overall with what is already known in ibrutinib treated patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma and mantle cell lymphoma. No new safety signals have been observed.[2]

There are no comparative safety data. At the primary analysis of the 1118E study, after a median follow-up of 14.8 months, the median duration of treatment with ibrutinib was 11.7 months. Any treatment-emergent adverse event (AE) was reported by 100% (63/63) of ibrutinib treated patients and these were considered treatment-related in 67%. A grade 3 or higher AE was reported by 29% of patients and a serious AE by 38%. Eleven percent of patients required a dose reduction due to treatment-emergent AEs and 9.5% of patients discontinued therapy due to an AE.[2]

The most frequently reported treatment-emergent AEs of any grade were diarrhoea (37%), neutropenia (25%), nausea, fatigue, and muscle spasms (21% each), epistaxis, sinusitis and upper respiratory tract infection (19% each), thrombocytopenia (18%) and anaemia (16%).[2]

These details were not reported at later analyses which included the incidence of grade 2 to 4 AEs only.[3, 4]

Summary of clinical effectiveness issues

Waldenström's macroglobulinaemia is a rare incurable B-cell cancer accounting for 1% to 2% of non-Hodgkin lymphomas and is considered to be a lymphoplasmacytic lymphoma. It is considered a disease of the elderly with reported median age at diagnosis of 63 to 75 years. The International Prognostic Scoring System (IPSS) categorises risk as low, intermediate or high for new patients and 5-year survival rates of 87% in low-risk, 68% in intermediate risk and 36% in high-risk patients have been reported.[2, 6] There has been no standard treatment pathway for this condition until ibrutinib received marketing authorisation. Treatment was determined on an individual patient basis with first-line generally including chemotherapy in combination with rituximab. Treatment at relapse may include an alternative chemo-immunotherapy regimen. High dose chemotherapy followed by autologous stem cell transplant (ASCT) may be appropriate for some younger patients with aggressive disease.[2, 6] After receiving its marketing authorisation, ibrutinib has been accepted by SMC (SMC2259) for restricted use in combination with rituximab for the treatment of Waldenström's macroglobulinaemia in patients who have received at least one prior therapy. The submitting company has requested that SMC considers the use of ibrutinib as monotherapy in patients who have received at least one prior therapy. Ibrutinib meets SMC orphan criteria for this indication.

Evidence from the 1118E study has demonstrated high responses rates with an ORR achieved by 87% of patients at the primary analysis and 90% of patients at the final analysis. No patients achieved a complete response but the major response rate was high (70% and 79% at the respective time-points). This is supported by improvements in haemoglobin which was considered an outcome of high clinical relevance. At the final analysis, median PFS and overall survival had not been reached. However 5-year, Kaplan-Meier estimates were 54% for PFS and 87% for overall survival. The EMA considered that the efficacy of ibrutinib in this patient population was clinically relevant.

This evidence comes from one open-label, single-arm, phase II study, which is prone to various biases. Interpretation of all outcomes was hampered by the lack of a control group. The open-label design limits assessment of subjective outcomes and the primary outcome of ORR was investigator assessed, although was supported by similar results when assessed independently. Health-related quality of life was not assessed.

The 1118E study enrolled patients with Waldenström's macroglobulinaemia who had received at least one prior systemic therapy, reflecting the company's proposed positioning. However study patients had received a median of two previous lines of therapy (range one to nine, with 25% of patients having received at least five lines). The study population may be more heavily pre-treated than patients eligible for treatment in practice who must have received at least one prior treatment.

The study population had a median age of 63 years and may be at the younger end of patients eligible for treatment in practice where the reported median age at diagnosis is 63 to 75 years. Subgroup analysis found that ORR was higher in patients with MYD88 mutations (100% in patients with mutated MYD88, wild-type CXCR4 [n=36] and 86% in patients with mutated MYD88 [n=22]) than with MYD88 wild-type (50%, n=4), but the number of patients with wild-type was small. In practice, approximately 90% of patients with Waldenström's macroglobulinaemia are thought to have the $MYD88^{L265P}$ mutation.[4, 6]

Because of the study design, there are no comparative data, so the company performed a naïve indirect comparison with ibrutinib plus rituximab which is considered the most relevant comparator. The relative results for PFS and overall survival had wide confidence intervals, including one, from which it was difficult to draw any conclusions on relative efficacy. In addition, the indirect comparison was limited by its naïve methods, small patient numbers (including a subgroup of the ibrutinib plus rituximab patients), immature survival results for ibrutinib and differences in patient populations particularly level of pre-treatment. Due to these limitations, the company's conclusions are uncertain.

The introduction of ibrutinib monotherapy would offer patients with Waldenström's macroglobulinaemia, who have received at least one prior therapy, another licensed treatment option. This would provide an alternative to ibrutinib plus rituximab which may be an advantage for patients considered unsuitable for rituximab. Ibrutinib monotherapy is an oral treatment avoiding the need for frequent hospital visits for rituximab administration. This may offer an advantage to patients and the service.

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 medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Waldenström's macroglobulinaemia is a rare, incurable form of blood cancer that is associated with major disease-related symptoms that have a substantial impact on patients' daily activities. Symptoms, particularly fatigue, can be intense and disabling, and the burden of disease negatively impacts patients' quality of life including their ability to perform daily activities, socialise and participate in family life. Although Waldenström's macroglobulinaemia generally affects an older population, some patients are of working age and the burden of disease has affected some patients' ability to work with significant financial implications.
- There is a high unmet need for effective, convenient and well-tolerated treatment options for previously treated patients with Waldenström's macroglobulinaemia. Chemotherapy and chemo-immunotherapy are associated with significant toxicity and are not suitable for all patients, including older patients and younger patients who may not be able to continue to work during treatment.
- Patients with Waldenström's macroglobulinaemia who receive ibrutinib may achieve effective, durable disease control with minimal side effects. Responding patients may be able to return to normal daily activities, including normal family, social and working life. This may relieve the overwhelming burden of the disease and its treatment on patients and their families and improve quality of life. Patients treated with ibrutinib have described this as life-changing.
- Ibrutinib monotherapy is an oral treatment that can be taken at home, offering convenience and reducing the burden of treatment and hospital visits for patients and their families. It is well-tolerated and is associated with less toxicity than chemotherapy or chemo-immunotherapy.
- PACE clinicians highlighted that ibrutinib as monotherapy would be their preferred treatment and would reflect clinical practice. The omission of rituximab is not expected to reduce efficacy but instead reduce the harm associated with increased toxicity of rituximab and reduced quality of life.
- Ibrutinib is a well-established medicine and the service already has experience in managing and monitoring treatment for other haematology patients.

Additional Patient and Carer Involvement

We received a joint patient group submission from Lymphoma Action and WMUK. Lymphoma Action and WMUK are both registered charities. Lymphoma Action has received 12.7% pharmaceutical company funding in the past two years, including from the submitting company. WMUK has received 12% pharmaceutical company funding in the past two years, including from

the submitting company. A representative from WMUK participated in the PACE meeting. The key points of the submission from both organisations have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis and a cost-utility analysis of ibrutinib monotherapy for the treatment of adult patients with Waldenström's macroglobulinaemia who have received at least one prior therapy. The economic analysis was performed against a comparator of ibrutinib plus rituximab, which is the only licensed treatment accepted for use by SMC for this indication.

The model consisted of five mutually exclusive health states; a starting health state in which patients are treated with ibrutinib monotherapy or ibrutinib plus rituximab; first subsequent treatment; second subsequent treatment, best supportive care (BSC) and death. Patients either remain in state, transition to subsequent treatment, BSC or death at the end of each cycle.

The cycle length was four weeks with patients either remaining in state, or transitioning to a subsequent treatment state or death at the end of each cycle. An NHS perspective and a 30-year lifetime horizon were selected in the base case of the economic model.

Study 1118E, iNNOVATE, and a European Chart Review study were the primary clinical data sources used in the economic analysis.[3-5, 7] The efficacy of the two treatments was captured in terms of PFS (probability of progression or death) and probability of death and these variables were informed by iNNOVATE and the Chart Review study. PFS and probability of death were used to derive the probability of progression.

The lack of patient level data for study 1118E and its single arm nature meant that efficacy results could not be directly applied to the model. Instead, relative effectiveness for ibrutinib monotherapy was derived from a naïve indirect comparison versus ibrutinib plus rituximab. The naïve comparison used available PFS and overall survival data from 1118E (59 months median follow up) and iNNOVATE (49.7 months median follow up). The wide confidence intervals indicate that it is challenging to conclude Ibrutinib monotherapy is definitively more or less efficacious than ibrutinib plus rituximab. The cost-minimisation analysis shows the results of assuming there are no differences between the treatments in terms of overall survival or PFS.

PFS and overall survival for the ibrutinib plus rituximab arm was directly extrapolated using parametric curves from the iNNOVATE Kaplan-Meier data. Curve selection was based on statistical goodness of fit, visual inspection and clinical plausibility. The exponential curve was found to be best-fitting on this basis for both PFS and overall survival.

PFS for ibrutinib monotherapy was estimated by applying the HR from the naïve comparison to the PFS extrapolation for the comparator. Overall survival for ibrutinib monotherapy was estimated by applying an assumed HR of 1. This was in place of the HR from the naïve comparison, which would have implied better overall survival but worse PFS for monotherapy, which would be clinically counterintuitive and implausible.

Utility scores were not collected as part of Study 1118E and the utility values from iNNOVATE were not used in the base case analysis due to the small sample size. Instead, utility inputs in the model were informed by an external study of ibrutinib in relapsed or refractory chronic lymphocytic leukaemia, in which EQ-5D data were collected during the course of treatments.[8] Adverse event related utility decrements were applied in the base case.

Acquisition costs for ibrutinib and rituximab were included in the analysis, as were the costs associated with any subsequent treatments. Unit costs for disease management, managing adverse events, end of life care were also accounted for.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price for ibrutinib.

In the cost-minimisation analysis, which assumed equal efficacy between ibrutinib monotherapy and ibrutinib plus rituximab, a cost saving with the use of ibrutinib monotherapy in place of ibrutinib plus rituximab was estimated.

The cost-effectiveness analysis presented by the submitting company produced a southwest quadrant incremental cost-effectiveness ratio (ICER) of £128,056 inclusive of PAS. The incremental net monetary benefit (NMB) of ibrutinib monotherapy was £8,605 with PAS. This represents the additional value gained by the health system using an example willingness to pay threshold of £30K per quality-adjusted life-year (QALY).

Table 2: Cost-utility analysis results at PAS price

Technologies	ICER (£/QALY)	NMB
ibrutinib		
ibrutinib + rituximab	£128,056*	£8,605

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; NMB, net monetary benefit
* Southwest quadrant ICER: ibrutinib monotherapy is estimated to be cost-saving but less effective.

Table 3: Selected scenario analysis at PAS price

	Scenario	ICER (with PAS)
	Base Case	***£128,056****
1	Alternate PFS parametric distribution – Log-normal	£140,209*
2	Overall survival HR = PFS HR	£19,095*
3	Overall survival HR based on naïve comparison point estimate	dominant
4	Alternate TTD distribution - Weibull	£70,905*
5	Inclusion of vial sharing	£137,792*

Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression free survival; TTD, time to treatment discontinuation.
* Southwest quadrant ICERs: ibrutinib monotherapy is estimated to be cost-saving but less effective.

There were a number of limitations with the analysis which include the following:

- Direct comparative evidence between ibrutinib monotherapy and ibrutinib plus rituximab is lacking. The company considered that a robust indirect treatment comparison was not feasible and the naïve comparison performed, which generated a HR suggesting that there was no statistically significant difference between the two treatments is uncertain. SMC considered that the evidence base to support the use of the cost-minimisation analysis (ie no differences between treatments) was particularly uncertain and was not a suitable basis for decision-making.
- In the cost-effectiveness analysis, PFS for ibrutinib monotherapy was based on a constant HR against ibrutinib plus rituximab. This HR was derived from the point estimates based on a naïve comparison. However, the confidence intervals for the HR estimate were very wide and included 1, which reflects weakness of the underlying data. There is, therefore, uncertainty regarding the predicted PFS in the model.
- The analysis assumed equivalence in OS between ibrutinib monotherapy and ibrutinib plus rituximab in the cost- utility and cost-minimisation analyses. A HR of 1.0 was applied in the model because the point estimate derived from the naïve comparison indicated superior OS for ibrutinib monotherapy and was counterintuitive to the PFS HR. This further highlights the weakness in the data underlying the naïve comparison and the uncertainty with respect to estimating relative effectiveness. Varying the OS HR in the scenario analysis predictably had a major impact on the results and in the absence of better comparative data it is difficult to know which HR is the most appropriate.
- There is some uncertainty associated with estimating pre-progression mortality in the ibrutinib arm because of limitations in the data available. The rate of death during PFS for ibrutinib plus rituximab was also applied to ibrutinib monotherapy but this may not be appropriate.

The Committee also 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 NHSScotland.

Additional information: guidelines and protocols

The British Committee for Standards in Haematology (BCSH) published updated Guidelines on the diagnosis and management of Waldenström's macroglobulinaemia in 2014.[9] This guidance recommends that only symptomatic patients who have relapsed following initial therapy should be treated, irrespective of evidence of serological disease progression. Symptomatic patients should be treated with a rituximab-containing regimen if CD20 expression has been documented. The guidance recommends the following regimens as appropriate: fludarabine plus rituximab (FR);

fludarabine plus cyclophosphamide plus rituximab (FCR); cladribine plus rituximab (Clad-R); bendamustine plus rituximab (BR); dexamethasone plus rituximab plus cyclophosphamide (DRC). The choice of regimen should be guided by performance status, clinical features (including renal function), comorbidities, and potential candidacy for stem cell transplantation (SCT). The guidance also states that in some patients retreatment with the initial therapy may be appropriate. The use of bortezomib-containing regimens is recommended as suitable in the relapse setting with weekly regimens being preferable due to the neurological toxicity associated with the biweekly schedules. The guidance recommend prophylaxis against herpes zoster virus reactivation. The BCSH guideline also highlights that alemtuzumab is a potential option in refractory disease and that surveillance for cytomegalovirus (CMV) reactivation is recommended.

This guideline predates the availability of ibrutinib.

The European Society for Medical Oncology (ESMO) published guidance on the treatment of Waldenström's macroglobulinaemia in 2018.[6] This guidance recommends treatment with ibrutinib for patients who have relapsed within <1 year and between 1 and 3 years since treatment. The guidance notes that patients with wild-type MYD88 may have no significant benefit from ibrutinib but that this is based on data from limited numbers of patients and that patients with non-$MYD88^{L265P}$ mutation may also benefit from ibrutinib therapy. In patients who are ineligible for treatment with ibrutinib consideration can be given to the use of an alternative rituximab-based combination. In patients who relapse >2-3 years after treatment with a rituximab-based regimen, consideration can be given to the use of an alternative rituximab-based combination: if rituximab with cyclophosphamide was used (DRC), rituximab with either bendamustine (BR) or bortezomib either with or without dexamethasone (BDR or VR) may be used. The ESMO guidance states that rituximab plus nucleoside analogues (FR, FCR) is an “active but also toxic combination and therefore should be used cautiously.” In patients who have a prolonged remission (>4 years) the reinstitution of a prior treatment regimen can be considered. The guidance also recommends that high dose therapy with autologous stem cell transplantation (ASCT) can be considered in select younger patients with aggressive disease, who have either failed or are resistant to BTK inhibitors.

Additional information: comparators

Ibrutinib plus rituximab

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost year (£)
ibrutinib	420mg orally daily	55,801

Costs from MIMS online on 3 August 2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The company estimated there would be 2 patients eligible for treatment with ibrutinib monotherapy in year 1 and 5 patients in year 5, to which confidential uptake rates 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 confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 17 September 2021.

**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*

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

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine 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 NHSScotland 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 NHSScotland 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.