Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2380

pembrolizumab 25mg/mL concentrate for solution for infusion (Keytruda®)

Merck Sharp & Dohme (UK) Limited

08 October 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

pembrolizumab (Keytruda®) is accepted for restricted use within NHS Scotland.

Indication under review: as monotherapy for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

SMC restriction: treatment with pembrolizumab is subject to a two-year clinical stopping rule.

In a phase III study, pembrolizumab increased progression free survival compared with an antibody-drug conjugate medication in patients with relapsed/refractory classical Hodgkin lymphoma who were ineligible for or had relapsed after ASCT.

This advice applies only in the context of an approved NHS Scotland 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.

Vice Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.[1]

Dosing Information

The recommended dose of pembrolizumab in adults is either 200mg every 3 weeks or 400mg every 6 weeks administered as an intravenous infusion over 30 minutes.

The recommended dose in paediatric patients aged 3 years and older with classical Hodgkin lymphoma is 2mg/kg bodyweight (up to a maximum of 200mg), every 3 weeks administered as an intravenous infusion over 30 minutes.

Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity. Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Treatment with pembrolizumab must be initiated and supervised by specialist physicians experienced in the treatment of cancer.[1]

Product availability date

6 October 2021

Pembrolizumab meets SMC orphan equivalent criteria

Summary of evidence on comparative efficacy

Pembrolizumab is a humanised monoclonal antibody which blocks the interaction between programmed cell death-1 (PD-1) receptor and its ligands PD-L1 and PD-L2. This results in the functional activity of the target lymphocytes being enhanced to facilitate immune-mediated anti-tumour activity.[1] The indication under review is for an extension to the previous indication. Pembrolizumab has previously been reviewed by the Scottish Medicines Consortium (SMC) as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed (ASCT) and brentuximab vedotin, or who are transplant-ineligible and have failed brentuximab vedotin (SMC 1296/18).

KEYNOTE-204 is an international, randomised, active-controlled, open-label, phase III study which evaluated the efficacy and safety of pembrolizumab compared with brentuximab vedotin in 304 adult patients with relapsed or refractory classical Hodgkin lymphoma who were ineligible for or had relapsed after ASCT. Patients were required to have measurable disease, an Eastern

Cooperative Oncology Group (ECOG) performance status 0 or 1, and adequate organ function. Patients were randomised equally to receive pembrolizumab 200mg intravenously every three weeks (n=151) or brentuximab vedotin 1.8mg/kg (max 180mg) intravenously every 3 weeks (n=153). Treatment in both groups was to continue for up to 35 cycles or until documented disease progression, unacceptable toxic effects, or investigator decision. Randomisation was stratified according to previous autologous HSCT (yes versus no) and status after front-line therapy (primary refractory versus relapsed <12 months versus relapsed ≥12 months).[2]

The co-primary outcomes were progression-free survival (PFS) (defined as time from randomisation to the first documented disease progression or death due to any cause, whichever occurs first) assessed by blinded independent central review according to the International Working Group criteria, including clinical and imaging data following autologous or allogeneic HSCT; and overall survival (defined as time from randomisation to death due to any cause). Efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomisation and controls were in place for type 1 errors.

After a median follow-up of 2 years, pembrolizumab demonstrated a significant improvement in PFS versus brentuximab vedotin. PFS sensitivity analyses were consistent with the primary analysis. See Table 1 for details of primary and key secondary outcomes. Overall survival data are immature and were not formally tested during this interim analysis.[3]

Table 1. Summary of efficacy results for KEYNOTE-204 (ITT population) (data cut: Jan 2020).[2, 3]

	Pembrolizumab (n=151)	**Brentuximab vedotin (n=153)**
Median follow-up	24.9 months	24.3 months
PFS (blinded independent central review per International Working Group 2007 criteria)		
Events (n)	81	88
Median PFS	13.2 months	8.3 months
Hazard Ratio (95% CI), p-value	0.65 (0.48 to 0.88) p=0.003	
KM estimated PFS at 24 months	35%	25%
ORR (blinded independent central review by International Working Group 2007 criteria)		
ORR	66%	54%
Complete response	24%	24%
Partial response	41%	30%
Duration of response		
Median	20.7 months	13.8 months

CI = confidence interval; ITT= intention-to-treat; KM=Kaplan-Meier ORR = objective response rate; PFS = progression-free survival

The submitting company provided subgroup analysis for patients receiving treatment in the third line or later (licensed indication) (82% of ITT patients, n=249). In line with the ITT population, PFS was longer in the pembrolizumab group compared with the brentuximab vedotin group (Table 2).

Table 2. Efficacy results for KEYNOTE-204 for patients receiving treatment in the third line or later subgroup (data cut: Jan 2020).[3,4]

	Pembrolizumab (n=124)	Brentuximab vedotin (n=125)
PFS (blinded independent central review per International Working Group 2007 criteria)		
Events (n)	68	75
Median PFS	12.6 months	8.2 months
Hazard Ratio (95% CI)	0.66 (0.47 to 0.92)	
KM estimated PFS at 24 months	35%	24%
ORR (blinded independent central review by International Working Group 2007 criteria)		
ORR	65%	54%
Complete response	27%	22%
Partial response	39%	33%

CI = confidence interval; KM=Kaplan-Meier; ORR = objective response rate; PFS = progression-free survival

Health Related Quality of Life (HRQoL) was assessed using 2 questionnaires: European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and European Quality of Life Five Dimensions Questionnaire (EQ-5D). In general, there were trends towards improvement with pembrolizumab while, conversely, a trend towards deterioration was reported in the brentuximab vedotin group in EORTC QLQ-C30. Pre-specified time to deterioration analysis showed an improvement with pembrolizumab in the general health state/quality of life score (HR 0.40; 95% CI 0.22 to 0.74) and physical functioning score (HR 0.56; 95% CI 0.32 to 0.97). Results from the EQ-5D questionnaire were consistent with those of the EORTC QLQ-C30 questionnaire.[3]

KEYNOTE-051 is a multicentre, non-randomised, open-label, single-arm, phase I/II study in paediatric patients with multiple tumour types, including patients with relapsed/refractory classical Hodgkin lymphoma. Patients received pembrolizumab intravenously 2mg/kg every 3 weeks (n=22). The primary outcome was ORR assessment according to the IWG response criteria; secondary outcomes included duration of response (DOR, defined as the time from first RECIST 1.1 response to documented progressive disease or death due to any cause, whichever occurs first, in participants who achieve a PR or better), disease control rate (DCR, defined as the proportion of participants with a response of CR, PR, or SD), PFS by RECIST 1.1, and overall survival. The ORR based on IWG response criteria as per investigator assessment was 54%; DCR based on IWG criteria as per investigator assessment was 82%; median DOR was 17.4 months by KM estimation; median PFS based on IWG 2007 criteria was 8.3 months based on KM estimation; median overall survival had not been reached.[3]

Summary of evidence on comparative safety

In the KEYNOTE-204 study at data cut-off January 2020, the median duration of treatment in the pembrolizumab group was 305 days and in the brentuximab vedotin group was 146.5 days. Any treatment-emergent adverse event (AE) was reported by 74% (110/148) of patients in the

pembrolizumab group and 77%% (117/152) in the brentuximab vedotin group; patients reporting a grade 3 to 5 AE were 44% versus 43%; patients with a reported serious AE were 30% versus 21%; and patients discontinuing therapy due to an AE was 14% versus 18%.[2, 3]

The most frequently reported AEs (incidence >10%) were as follows in the pembrolizumab and brentuximab vedotin groups: diarrhoea (20% versus 16%), pyrexia (20% versus 13%), hypothyroidism (19% versus 2.6%), upper respiratory tract infection (19% versus 14%), pruritus (18% versus 12%), cough (17% versus 13%), fatigue (16% versus 18%), nausea (14% versus 24%), vomiting (14% versus 20%), back pain (13% versus 12%), nasopharyngitis (12% versus 5.3%), urinary tract infection (11% versus 2.6%), headache (10% versus 10%), constipation (7.4% versus 12%), neutropenia (6.8% versus 13%), and peripheral neuropathy (4.1% versus 18%).[3]

The overall side effect profile of pembrolizumab observed in KEYNOTE-204 was generally consistent with what has previously been reported in patients with classical Hodgkin lymphoma. No new safety signals were identified in the paediatric patients. When adjusted for exposure, pembrolizumab had lower rates than brentuximab vedotin for most AEs.[3]

Summary of clinical effectiveness issues

Hodgkin lymphoma is a lymphoid malignancy characterised by the presence of multinucleated Reed Sternberg cells in the context of a mixed inflammatory background, which comprises lymphocytes (T-cells are usually predominant), eosinophils, neutrophils, macrophages, plasma cells and fibroblasts. The majority of cells in the tumour tissue are a mixed infiltrate of various lymphoid cells, including effector and regulatory T-cells and macrophage. Classical Hodgkin lymphoma accounts for about 95% of cases of Hodgkin lymphoma.[3] The indication under review represents the third-line and later treatment lines, i.e. patients who have had at least two prior lines of therapy with or without prior ASCT. The most relevant comparator in this setting is brentuximab vedotin. Pembrolizumab meets SMC orphan equivalent criteria.

In KEYNOTE-204 pembrolizumab demonstrated a statistically significant improvement in PFS when compared with current standard of care brentuximab vedotin. The 4.9 month gain in PFS in the ITT population can be considered clinically meaningful. Sensitivity analysis, secondary outcomes (ORR and DOR), and data in paediatric patients were considered supportive. Although second-line patients were included in KEYNOTE-204, numbers were limited and consequently the EMA did not approve pembrolizumab for use in this subgroup. [3]

There are some limitations to the evidence presented. Overall survival data are currently not available. DOR data are immature; 40% of patients were informative according to the EMA. HRQoL outcomes should be interpreted with caution as KEYNOTE-204 was open-label and HRQoL outcomes were not adjusted for multiplicity.[3]

There are limited data in paediatric patients with relapsed/refractory classical Hodgkin lymphoma; only 22 relevant patients were evaluated in KEYNOTE-051. However, results have been consistent

with the adult population and the EMA state anti-tumour activity has been confirmed. Additionally, data in patients aged ≥65 years are limited.[1]

There were some potential generalisability issues with KEYNOTE-204. Approximately 5% of patients had previously responded to treatment with brentuximab vedotin. Patients are not routinely offered brentuximab vedotin in the front-line setting in Scotland. However, due to the low numbers this was unlikely to have affected the overall results of the study. Furthermore, brentuximab vedotin could be continued for up to 35 treatment cycles, which differs from the licensed posology and subsequently Scottish clinical practice which states that 8 to 16 cycles are recommended in patients who respond to treatment. The number of patients that received >16 cycles of brentuximab vedotin was low (12% of brentuximab vedotin group); median number of cycles in the brentuximab vedotin group was 7. Due to the low numbers of patients that received <8 or >16 cycles of brentuximab vedotin, and that detailed analysis of these patients showed no significant issues, the impact on the overall study results was felt to be limited by the EMA.[2, 3]

In KEYNOTE-204 pembrolizumab was continued for up to 35 treatment cycles (approximately 2 years) however the SPC indicates that treatment can continue until disease progression or unacceptable toxicity. Data for treatment with pembrolizumab beyond 2 years for this indication are limited.[3]

Clinical experts consulted by SMC considered that service implications are likely to be minimal. Pembrolizumab can be given as a 3 weekly or 6 weekly treatment cycle. The latter may be advantageous for suitable patients as the frequency of hospital visits for administration would be reduced.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis that evaluated pembrolizumab in patients with relapsed or refractory classical Hodgkin lymphoma who have received ASCT or at least two prior therapies when ASCT is not a treatment option (3L+ population). The comparator in the analysis was brentuximab vedotin. The model was designed as a standard three state partitioned survival model. The analysis adopted an NHSScotland perspective over a 50-year time horizon (patients entered the model age 39 years), with weekly model cycles.

The sources of clinical data used in the model primarily included progression free survival data in the 3rd line population of KEYNOTE-204 and overall survival for brentuximab vedotin from the key clinical study relating to SMC 845/12.[7] The latter was employed due to the unavailability of overall survival data from KEYNOTE-204 in the relevant interim analysis. Overall survival was modelled as a log-normal distribution fitted to digitised data from Gopal et al, with the same modelled overall survival applied in both arms, in the absence of overall survival evidence from KEYNOTE-204. Progression free survival was based on analysis of the third line population in the KEYNOTE-204 study. Proportional hazards was assessed by standard means, and rejected for the model, so that each arm was modelled independently. A piecewise approach to modelling PFS was adopted

whereby the observed KM data is applied until week 52, with parametric functions applied beyond this point. The log-normal was selected as providing plausible clinical outcomes in accordance with clinical advice, as well as a good visual fit to observed data. There is likely to be considerable uncertainty in the PFS modelling due to comparatively low numbers at risk in the period to which the data was fit.

The duration of treatment for both pembrolizumab and brentuximab vedotin is based directly on the evidence from KEYNOTE-204. According to the submitting company there is no evidence regarding the optimal duration of treatment with pembrolizumab, however, the KEYNOTE-204 protocol mandated a maximum of 35 cycles for both pembrolizumab and brentuximab vedotin, though the licensed treatment duration for brentuximab vedotin is 16 cycles, rather than the 35 applied in KEYNOTE-204 and the model. As KM data were available up until week 88 for the brentuximab vedotin arm and up until week 103 for the pembrolizumab arm, separate parametric curves were fitted to extrapolate the Time on Treatment (ToT) until the maximum duration of treatment.

In both the pre- and post-progression state, treatment-specific utilities were applied, based on mean EQ-5D-3L values in KEYNOTE-204. In the progression-free state pembrolizumab and brentuximab vedotin were assigned treatment-specific utility values, and with separate treatment-specific utility values applied in the post-progression state. In scenario analysis pooled (treatment-independent) estimates were applied for the progression and post-progression states. One-off disutilities were assigned to adverse events, each of which was assigned an average duration.

The model includes costs of subsequent treatment lines after treatment discontinuation or failure on the initial intervention. Patients in the KEYNOTE-204 study received a mix of subsequent treatments, however, according to the submitting company, practice in Scotland is different. Based on the current relapsed or refractory classical Hodgkin lymphoma treatment pathway in Scotland, pembrolizumab (SMC 1296/18) and nivolumab (SMC 1240/17) are approved fourth line treatment options following disease progression after treatment with brentuximab vedotin. Therefore, subsequent treatment costs were assumed to be for brentuximab vedotin in the pembrolizumab arm of the model, and nivolumab or pembrolizumab (depending on prior ASCT) in the brentuximab vedotin arm. Health state costs are applied to each weekly cycle in the model for the proportion of patients in the progression-free and progressed disease health states, based on costs of providing routine follow-up care and monitoring of patients with relapsed or refractory classical Hodgkin lymphoma. In each arm a proportion of patients are assumed to undergo SCT, and end of life costs were also considered.

A Patient Access Scheme (PAS) was submitted by the 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. A PAS discount is in place for brentuximab vedotin and this was included in the results used for decision-making by using estimates of the comparator PAS price.

The base case and scenario analyses results are presented in Table 3 and

Table ***4***, respectively, below. The results presented do not take account of the PAS for brentuximab vedotin or the PAS for pembrolizumab. However, these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for brentuximab vedotin due to commercial confidentiality and competition law issues.

Table 3 Base case results vs brentuximab vedotin (list price for all medicines)

	Pembrolizumab	Brentuximab vedotin	Incremental
Total cost (£)	£167,324	£165,667	£1,657
QALYs	4.14	3.56	+0.58
Cost per QALY (£)	£2,852		

QALY: Quality-adjusted life year

Sensitivity analyses were consistent with the base case analysis. The scenarios of greatest interest are presented in
Table ***4***.

Table 4 Scenario analyses versus brentuximab vedotin (list price for all medicines)

		Pembrolizumab		Brentuximab vedotin		Incremental		
		Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Costs (£)	QALYs	ICER (£)
Base case		167,324	4.14	165,667	3.56	-1,657	0.58	2,852
1	PFS fully parametric fit	168,444	4.09	164,108	3.48	4,336	0.6	7,170
2	Pooled utilities post-progression	167,324	4.14	165,667	3.76	1,657	0.3	5,464
3	No vial wastage	165,182	4.14	157,846	3.56	7,336	0.58	12,626
4	BV maximum cycles set to 16	167,324	4.14	156,188	3.56	11,136	0.58	19,166
5	Subsequent treatments based on KEYNOTE-204	149,532	4.14	133,071	3.56	16,461	0.58	28,331

QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; PFS: progression-free survival; BV: brentuximab vedotin

The analysis is subject to certain limitations:

- the impact of pembrolizumab on overall survival is yet to be demonstrated, and the analysis assumes equivalent overall survival under both treatment regimens – though this may appear a conservative assumption this is nevertheless a limitation;
- while the cost-saving appears to be most heavily impacted by the brentuximab vedotin maximum treatment duration, incremental QALYs are sensitive to pooled post-progression utilities, and it is unclear how less favourable assumptions regarding utilities might impact the

analyses when combined with a 16-cycle maximum for brentuximab vedotin;

- it is uncertain how alternative PFS scenarios may impact the analysis, for example whether less favourable PFS distributions or assumptions might be countered by further cost savings.

Despite the limitations outlined above, the economic case was demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Lymphoma Action, which is a registered charity.

- Lymphoma Action has received 12.7% pharmaceutical company funding in the past two years, with none from the submitting company.

- Relapsed or refractory Hodgkin lymphoma is a rare condition, with symptoms including swollen lymph nodes, fevers, night sweats and weight loss. Fatigue is a commonly reported symptom and it can persist for many years. Patients report that this affects their work, physical activity and social activities. Patients with Hodgkin lymphoma are often young. As a result, it can have a financial impact on patients and their families. The emotional impact of lymphoma is also considerable.

- Current treatments for relapsed or refractory Hodgkin lymphoma are typically very intensive and incur serious side effects. Targeted treatments are not routinely available to under 18s. More toxic treatments (such as stem cell transplants) place a huge burden on patients and their families.

- Patients feel that pembrolizumab has the potential to offer a convenient, outpatient treatment with high response rates. The favourable safety profile of pembrolizumab is viewed as an important advantage, with the potential to allow greater participation in normal life as well as a reduced burden on family and carers.

Additional information: guidelines and protocols

The British Committee for Standards in Haematology (BCSH) and the British Society of Blood and Marrow Transplantation published "Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma" in October 2013.[5] This guideline makes the following recommendations:

- ASCT is the standard treatment for patients with relapsed or primary resistant disease who achieve an adequate response to salvage therapy. ASCT is not recommended in those failing to achieve an adequate response (currently defined as a partial response).

- Current evidence does not support the use of maintenance cytotoxic therapies post-ASCT.
- Allogeneic transplantation using a reduced intensity conditioning regimen is the treatment of choice for younger patients with a suitable donor and chemo-sensitive disease following failure of ASCT.
- A second ASCT is a reasonable clinical option in selected patients with late relapse following ASCT.
- In patients not eligible for ASCT, combined modality therapy should be considered, especially in early stage relapse and in patients who have not received prior radiotherapy or who have relapsed outside of the initial radiotherapy field.
- In patients unlikely to tolerate the toxicities associated with more intensive regimens, palliation with either a single agent or with a multi-agent oral regimen with or without IV vinblastine should be considered.

The European Society for Medical Oncology (ESMO) updated its "Hodgkin's lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in 2018.[6] This guideline makes the following recommendations:

- For most patients with refractory or relapsed Hodgkin lymphoma, high-dose chemotherapy followed by ASCT can be regarded as the treatment of choice.
- Salvage regimens such as dexamethasone/high-dose cytarabine/cisplatin (DHAP), ifosfamide/ gemcitabine/vinorelbine/dexamethasone (IGEV) or ifosfamide/carboplatin/etoposide (ICE) are given to reduce the tumour burden and mobilise stem cells prior to high-dose chemotherapy and ASCT.
- Brentuximab vedotin is an option for patients failing ASCT.
- Nivolumab and pembrolizumab are approved for the treatment of patients with disease recurrence after HDCT followed by ASCT and brentuximab vedotin therapy.
- Allogeneic stem cell transplantation represents a potentially curative treatment option for patients failing high-dose chemotherapy and ASCT.
- In a palliative setting, acceptable remission rates, satisfying quality of life and prolonged survival can be achieved by gemcitabine-based chemotherapy and/or regional radiotherapy. Brentuximab vedotin can also be considered for the treatment of Hodgkin lymphoma patients with disease recurrence after at least two lines of treatment who are not candidates for high-dose chemotherapy followed by ASCT.

Additional information: comparators

Brentuximab vedotin

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per cycle (£)
Pembrolizumab	200mg IV every 3 weeks or 400mg IV every 6 weeks	£5,260

Costs from BNF online on 04 August 2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be between 17 and 18 patients eligible for treatment with pembrolizumab in each of years 1 to 5. The estimated uptake rate was 48% in year 1 and 50% subsequently, leading to 8 to 9 patients treated per annum.

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. This template does not incorporate any PAS discounts associated with comparator medicines.

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

References

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7. Gopal AK, Chen R, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood. 2015;125(8):1236-43.

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