Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2131

dabrafenib 50mg and 75mg hard capsules (Tafinlar®)

Novartis Pharmaceuticals UK Ltd

11 January 2019

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

dabrafenib (Tafinlar®) is accepted for use within NHSScotland.

Indication under review: In combination with trametinib for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Relapse-free survival was significantly longer in the dabrafenib plus trametinib group compared with placebo in a phase III study of patients with completely resected, stage III melanoma with BRAF V600E or V600K mutations.

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

Chairman
Scottish Medicines Consortium

Indication

In combination with trametinib for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.[1]

Dosing Information

The recommended dose of dabrafenib, when used in combination with trametinib, is 150mg twice daily. The recommended dose of trametinib, in combination with dabrafenib, is 2mg once daily. In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity.

If a dose of dabrafenib is missed, it should not be taken if it is less than 6 hours until the next scheduled dose. If a dose of trametinib is missed, when dabrafenib is given in combination with trametinib, the dose of trametinib should only be taken if it is more than 12 hours until the next scheduled dose.

The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation. See summary of product characteristics (SPC) for further details.

Treatment with dabrafenib should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.[1]

Product availability date

27 August 2018

Dabrafenib in combination with trametinib meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Dabrafenib inhibits rapidly accelerated fibrosarcoma (RAF) kinases and trametinib inhibits mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity, preventing the growth of mutated BRAF V600 cells.[1] Trametinib in combination with dabrafenib is accepted for restricted use within NHSScotland for the first-line treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (SMC 1161/16). Dabrafenib monotherapy is accepted for restricted use in patients with unresectable or metastatic BRAF V600 mutation-positive metastatic melanoma who have received no prior therapy (SMC 1023/15).

The evidence supporting this indication is from COMBI-AD, a randomised, double-blind, placebo-controlled phase III study. COMBI-AD recruited adult patients with completely resected, histologically confirmed stage IIIA (with lymph-node metastasis >1mm), IIIB or IIIC cutaneous melanoma (according to the criteria of the American Joint Committee on Cancer, seventh edition) with BRAF V600E or V600K mutations confirmed in primary-tumour or lymph-node tissue by a central reference laboratory. Patients had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual regional node disease within 12 weeks before

randomisation. They had not received previous systemic anticancer treatment or radiotherapy for melanoma and were required to have an Eastern Cooperative Oncology Group performance (ECOG) status of 0 or 1.[2, 3]

Patients were randomised equally to receive oral dabrafenib 150mg twice daily plus trametinib 2mg once daily (n=438) or two matched placebo tablets (n=432) for 12 months (stratified according to BRAF mutation status [V600E or V600K] and stage of disease [IIIA, IIIB, or IIIC]). Treatment continued unless disease recurrence, unacceptable toxic effects, withdrawal of consent, or death occurred. [2, 3] Dose changes or interruptions were allowed for non-haematologic adverse events of grade 2 or higher that could not be managed with routine supportive care. Patients were followed up for disease recurrence until the first recurrence and then followed up for survival.[2]

The primary outcome was relapse-free survival, which was assessed in all randomised patients, with data censored for patients lost to follow-up, those who were alive without evidence of relapse and those who started subsequent anti-cancer therapy prior to disease recurrence (censored at the date of last efficacy assessment before the initiation of subsequent anti-cancer therapy). [2, 3]

At the time of the primary analysis the minimum length of follow-up was 2.5 years (median 2.8 years). Disease recurrence was reported in 37% (163/438) of patients in the dabrafenib plus trametinib group and in 57% (247/432) of patients in the placebo group. Death had occurred in 14% (60/438) of patients in the dabrafenib plus trametinib group and 22% (93/432) of the placebo group. Melanoma was the most common cause of death in 12% and 18% of the respective groups.

Investigator assessed relapse-free survival was significantly longer in the dabrafenib plus trametinib group than in the placebo group, estimated hazard ratio for relapse or death was 0.47 (95% confidence interval [CI] 0.39 to 0.58, p<0.001). Median relapse-free survival had not yet been reached in the dabrafenib plus trametinib group and was 16.6 months in the placebo group. The estimated rates of relapse-free survival were 88% at 1 year, 67% at 2 years, and 58% at 3 years in the dabrafenib plus trametinib group, compared with 56%, 44%, and 39%, respectively, in the placebo group. [2, 3]

At the first interim analysis of overall survival, carried out at the time of the primary analysis, median duration of overall survival had not been reached in either group. The estimated rate of overall survival was 97% at 1 year, 91% at 2 years, and 86% at 3 years in the dabrafenib plus trametinib, compared with rates of 94%, 83%, and 77%, respectively, in the placebo group (hazard ratio for death, 0.57; 95% CI, 0.42 to 0.79; p=0.0006, this was not considered statistically significant because it did not cross the pre-specified conservative interim boundary of p=0.000019).

Fewer patients had distant metastases or died in the dabrafenib plus trametinib group than in the placebo group (25% versus 35%; hazard ratio, 0.51; 95% CI, 0.40 to 0.65; p<0.001).[2] Median distant metastases-free survival was not reached in either treatment group due to low event rates.[3]

Health-related quality of life was assessed using the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire and visual analogue scale (VAS). During treatment and follow-up VAS scores remained similar to baseline with no clinically meaningful differences between groups.[4] The European Medicines Agency (EMA) noted that since disease-related symptoms are not expected in an adjuvant setting, this suggests that the treatment has no negative impact on quality of life.[3]

A post-hoc analysis after an additional 10 months of follow-up (data cut-off April 2018) was conducted. Median follow-up was 44 months in the dabrafenib plus trametinib group and 42 months in the placebo group. Results for relapse-free survival at this data cut-off were consistent with the primary outcome, estimated hazard ratio was 0.49 (95% CI: 0.40 to 0.59). At this data cut-off, 40% (174/438) of patients in the dabrafenib plus trametinib group had a relapse compared with 59% (253/432) of patients in the placebo group. As of April 2018, three patients had died in the dabrafenib plus trametinib group and one in the placebo group without prior tumour recurrence.[3]

Summary of evidence on comparative safety

At least one adverse event was reported in 97% (422/435) of patients in the dabrafenib plus trametinib group compared with 88% (380/432) of patients in the placebo group. Serious adverse events occurred in 36% and 10% of the dabrafenib plus trametinib and placebo groups respectively. Adverse events leading to permanent discontinuation of the study drug occurred in 26% and 3%, adverse events leading to dose reduction in 38% and 3% and adverse events leading to dose interruption in 66% and 15% of patients in the respective groups.[2]

Commonly reported adverse events that occurred more frequently in the dabrafenib plus trametinib group included pyrexia (63% versus 11%), fatigue (47% versus 28%), nausea (40% versus 20%), headache (39% versus 24%), chills (37% versus 4%), diarrhoea (33% versus 15%), vomiting (28% versus 10%), arthralgia (28% versus 14%) and rash (24% versus 11%).[2]

Summary of clinical effectiveness issues

The global incidence of melanoma is increasing.[5] Ultra violet (UV) light exposure (both natural and artificial sunlight) is considered to be the main risk factor for cutaneous melanoma. It has a relatively young age distribution and often affects people of working age. Different activating mutations have been described in melanoma and approximately 45% of patients with cutaneous melanoma carry a BRAF V600 mutation. Melanoma can be curable if recognised and treated with surgery at an early stage however prognosis for patients with advanced melanoma is poor with 5-year survival between 40% and 80%.[3, 6] Interferon alfa is licensed in Scotland for the treatment of resected melanoma in the adjuvant setting, but is not recommended for this use by the Scottish Intercollegiate Guidelines Network (SIGN) other than in a trial setting. In patients who undergo complete resection there is no standard adjuvant treatment in current practice and most patients

are managed through routine surveillance.[6] Nivolumab has recently been licensed for this indication.

Clinical experts consulted by SMC considered that dabrafenib plus trametinib fills an unmet need in this therapeutic area as these patients are at a high risk of recurrence and currently there are no adjuvant therapies in use for this indication. Dabrafenib in combination with trametinib meets SMC orphan equivalent criteria.

In the pivotal COMBI-AD study in adult patients with completely resected, stage III melanoma with BRAF V600E or V600K mutations, investigator assessed relapse-free survival was significantly longer in the dabrafenib plus trametinib group than the placebo group. The EMA accepts that recurrence free survival is a valid outcome in melanoma studies but notes that overall survival should also be reported as adjuvant treatment may limit subsequent treatment options. Overall survival data are immature, however the EMA considered that they show a trend towards a favourable outcome in the dabrafenib plus trametinib group.[3]

Investigator assessment was used for all disease-recurrence analyses in the COMBI-AD study which could have introduced bias. Patients with stage IIIA disease were excluded from the study if their lymph node metastases were <1mm therefore potentially patients with slightly better prognosis were excluded. The licensed indication includes all patients with stage III disease. Patients with cardiovascular risk were excluded from the COMBI-AD study which could potentially affect the generalisability of the results to some of the Scottish population. In addition, patients with ocular and mucosal melanoma were excluded from the study but are included in the licensed indication. Patients were required to have an ECOG status of 0 or 1 therefore it is unclear whether the results would apply to patients with a poorer performance status (≥2).

The COMBI-AD study compared dabrafenib plus trametinib with placebo, which can be considered a proxy for routine surveillance, the most relevant comparator. The impact of the use of dabrafenib plus trametinib as adjuvant therapy on subsequent treatment in the metastatic setting is not known. The optimal treatment sequencing is not known.

Clinical experts consulted by SMC considered that dabrafenib plus trametinib is a therapeutic advancement due to significantly reducing the risk of relapse in this patient group. They considered that the place in therapy is adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection. Dabrafenib plus trametinib is taken for 12 months which may impact on the patient due to the requirement for visits to the treatment centre. Treatment is associated with more potential adverse events compared with routine surveillance however the EMA noted that health-related quality of life outcomes from COMBI-AD suggest that the treatment has no negative impact on quality of life. Prior to initiation of dabrafenib plus trametinib patients must have confirmed BRAF V600 positive mutation using a validated test. Clinical experts consulted by SMC considered that the introduction of this medicine may impact on service delivery as capacity in oncology clinics would be required although patient numbers will be small.

Summary of comparative health economic evidence

The company submitted a cost utility analysis that evaluated dabrafenib in combination with trametinib as adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. The analysis compared dabrafenib in combination with trametinib against a strategy of routine surveillance.

A four state model was constructed comprising recurrence free survival (RFS), local recurrence (LR), distant recurrence (DR) and death. Upon DR a simplifying assumption was made whereby fixed costs and outcomes were applied in the model, based on previous NICE technology appraisals. This approach was considered appropriate as outcomes associated with DR are related to the efficacy of metastatic treatments, which are not the subject of this appraisal. Treatment continues for 12 months as in the clinical study, COMBI-AD. Clinical evidence for the model was based principally on the COMBI-AD study. The model begins with a patient mean age of 50 years, and 55% male (as in the COMBI-AD study) and adopts a 50 year time horizon.

RFS is modelled up to 50 months based on the clinical study Kaplan-Meier data, to which the company fitted parametric functions. A range of functions was explored, with the base case adopting a log-logistic unrestricted mixture model, allowing RFS to be modelled independently for each arm. Following 50 months, data from the placebo arm of the EORTC 18071 study[7] were used to extrapolate RFS over the lifetime time horizon. The proportion of RFS events that were LR, DR, or deaths, was applied based on arm specific data in the COMBI-AD phase and EORTC data subsequently. Scenario analyses applied parametric extrapolations in place of the EORTC data. Data were not available to model the LR to DR transition, however data for LR to death were available and these data were used to calibrate RFS in LR using a hazard ratio such that OS post LR accorded with that seen in the study.

The company noted that among patients who experienced a recurrence event (excluding death), similar proportions of patients in both treatment arms received any type of systemic anti-cancer therapy post-recurrence; more patients in the dabrafenib plus trametinib arm received immunotherapy compared to placebo (52% vs 38%). Post DR, overall survival showed no statistically significant differences between the arms. The company's clinical experts suggested that a visual difference in the post-DR OS could potentially be explained by the different mix of treatments (e.g. immunotherapies or targeted therapies) received at the point of recurrence. However, these experts expected post-DR OS to be similar in the long-term irrespective of initial treatment. The proportions of patients receiving immunotherapy and targeted therapy after DR were taken from the COMBI-AD study and were used to calculate the one-off cost and quality-adjusted life years (QALYs) assigned at the point of recurrence. The company emphasises that although alternative assumptions could have been applied the simplified approach used in the base case was reasonable as post-DR OS does not impact on costs and QALYs and the approach used was supported by clinical opinion. Though OS assumptions have no impact given the model design, however, differing assumptions as to the long term pay-offs could impact the model result.

EQ-5D-3L assessments were conducted in COMBI-AD. There was no difference between treatment arms in changes from baseline. A generalized estimating equation included covariates for baseline EQ-5D and health state (RFS on and off treatment, LR, and DR). Utility estimates for DR are not applicable within the model due to the use of fixed QALY pay-offs in order to simplify the model structure. The final utility estimates were 0.854 and 0.869 for RFS on and off treatment respectively, and 0.836 for LR. The company noted the relatively minor decrement for LR, and that

this may have been influenced by small numbers of relevant observations and timing of assessment in relation to recurrence. No separate application of utility decrements for adverse events was applied. Upon DR a weighted average 3.23 QALYs was assigned (44% immunotherapy – 2.96 QALYs and 56% targeted therapy – 3.44 QALYs.)

The main costs were treatment acquisition and administration costs, disease management costs and management of adverse events. Cumulative dose was used to calculate drug costs (time on treatment data were complete). No administration costs were applied for the oral therapy, however monthly pharmacy costs were estimated. Monitoring and follow up costs for routine surveillance was based on UK consensus guidelines, and clinical experts for the company advised monitoring for patients treated with dabrafenib in combination with trametinib would be more intensive, returning to parity on completion of treatment. On LR it was assumed 90% of patients would undergo surgical resection, and of the remainder 70% would be treated with immunotherapy and 30% targeted therapy. For DR total discounted costs were taken from previous NICE appraisals of pembrolizumab (immunotherapy) and dabrafenib plus trametinib (for targeted therapy) respectively, and weighted according to subsequent therapy use in COMBI-AD, providing a one-off cost of £142,699.

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. The base case results with PAS and key scenario analyses are presented in the tables below.

Table 3: Base case and selected scenario analyses results dabrafenib plus trametinib versus to routine surveillance

Base case	£19,725 per QALY	
Sensitivity analysis		
Variable	Lower	Upper
Expected discounted cost of DR ±25%	22,295	17,154
Hazard for RFS after 50 months ±25%	17,605	21,820
HR applied to RFS events for LR vs RFS ±25%	21,610	18,706
Expected discounted QALYs after DR ±25%	18,640	20,944
Disutility for RFS on treatment vs off treatment ±25%	18,703	20,864
Scenario analysis	Scenario:	
Time horizon	20 years	24,342
RFS for observed COMBI-AD period	Direct KM	22,286
RFS for observed period cut-off	41 months	19,276
Post observation period recurrence hazard function	Exponential (M)	12,709
	Lognormal (M)	18,929
Parametric RFS functions for lifetime	Loglogistic (R)	12,147
	Gen gamma (R)	10,355
Event types after observed period	Pooled COMBI-AD	19,729
HR Transition from LR	1.5	23,622
	4.5	17,768
DR as % of events after LR	100%	20,074
Post-DR costs and QALYs – equal in each arm	TA366	23,546

	TA396	16,624
	50%:50% IO:TT	20,145
	75%:25% IO:TT	21,860
Post-DR costs and QALYs – assuming may differ by arm	D+T: 25%:75% IO:TT PBO: 50%:50% IO:TT	28,947
	D+T: 75%:25% IO:TT PBO: 50%:50% IO:TT	10,490
Drug costs	No wastage	20,763

IO: immunotherapy; TT: targeted therapy.

- The main weakness in the economic case relates to immaturity of overall survival data. In the model survival estimates are generated via recurrence. Several analyses for RFS were conducted but their results not reported due to their being deemed clinically implausible. This appeared to relate mainly to the fact of the treatment curves crossing in the extrapolation and the company argued that too few relapses will occur in later periods for these scenarios to be credible. On request the omitted analyses were provided by the submitting company and accepted as being seemingly implausible.
- The model design, in its adoption of fixed pay-offs at DR appears reasonable, and alternative approaches that might have involved complex modelling in the DR phase based on limited evidence are justifiably avoided. Nevertheless there is unavoidable uncertainty involved in the use of this approach. This is explored by varying the common pay-offs applied in the model, with little impact on the incremental cost-effectiveness ratio (ICER). All such analyses were undertaken varying the pay-offs equally for both model arms. If treatment pathways in DR are in fact conditional on prior treatment this may be a restrictive assumption. Alternative scenarios in which the distribution of post DR therapies were not assumed equal demonstrated some sensitivity of the ICER. Optimal strategies for management of metastatic disease are unknown, however, and the base case assumption of equal use of immunotherapy and targeted therapy in each arm following DR may be reasonable.

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

After considering all the available evidence and after application of the appropriate SMC modifier, the Committee accepted dabrafenib for use in NHS Scotland.

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

Summary of patient and carer involvement

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

- We received patient group submissions from Melanoma UK, and Melanoma Action and Support Scotland (MASScot). Melanoma UK is a registered charity and MASScot is a Scottish Charitable Incorporated Organisation (SCIO).

- Melanoma UK has received 8% pharmaceutical company funding in the past two years, including from the submitting company. MASScot has not received any pharmaceutical company funding in the past two years.
- Melanoma patients with advanced disease can struggle greatly. A diagnosis can often mean that a patient has to give up work which can have an enormous impact on a family, especially a family with young children on a low income. The disease can also have a massive psychological impact, especially when it comes to scarring - scarring and lymphedema are huge issues for patients. Often, patients who are living with this disease suffer greatly, the stress of reaching stage 3 and knowing that there are limited options available is a terrifying situation for a patient to be in.
- In many other cancers there is an adjuvant therapy available which gives hope of preventing recurrence. There has not been such a therapy for these B-Raf +ve patients until now. The current 'watch & wait' approach is often not favoured by patients. If patients can have a treatment and one which is showing promise, they want to have that choice. The watch and wait approach is just not one that sits well in the patient community.
- Taking a treatment helps patients feel that "something is being done", with the alternative being the current method of watch and wait. That this combination therapy is oral and potentially has few side effects and that these are manageable was highlighted as being particularly welcomed by patients. Taking treatment each day can also increase confidence that recurrence is likely to be less of a threat. This adds up to an increased feeling of hope and quality of life for patients and family.

Additional information: guidelines and protocols

The most up to date published guidelines for the assessment and management of melanoma of the skin includes: The Scottish Intercollegiate Guidelines Network (SIGN) 'Clinical Guidelines for Cutaneous Melanoma' (SIGN 146, 2017);[6] The European Society for Medical Oncology (ESMO) 'Cutaneous Melanoma Clinical Practice Guidelines' (2015)[8] and The National Institute for Health and Care Excellence (NICE) 'Clinical Guidelines for the Management of Melanoma' (2015).[9] All these publications predate the availability of dabrafenib plus trametinib as adjuvant treatment for resected stage III melanoma with a BRAF V600 mutation, and none provides recommendations on their use for this indication. With regards to the management of resected stage III melanoma the main recommendations are as follows:

SIGN, NICE and ESMO guidelines recommend that adjuvant radiotherapy should be considered for patients with completely resected stage IIIB and IIIC melanoma after discussion of the risk of local recurrence and if a reduction in such risk outweighs the significant adverse events and risks associated with radiotherapy. Adjuvant radiotherapy is not recommended for patient in stage IIIA melanoma.[6, 8, 9]

While SIGN guidelines do not recommend the use of interferon, unless it is in a trial setting,[6] the ESMO guidelines indicate that, awaiting the results of prospective randomised trials, patients with resected stage III melanomas should be evaluated for adjuvant interferon.[8] NICE guidelines do not make any recommendation regarding the use of adjuvant interferon. It is noted in the SIGN

guideline that there are a number of ongoing well-designed trials of adjuvant immunotherapy (including ipilimumab, nivolumab and pembrolizumab). [6]

With regards to follow-up, the ESMO guidelines state that there is no consensus on the optimal schedule of frequency of follow-up visits, or on the utility of imaging and blood tests for patients with resected melanoma.[8] This is reflected in the recommendations by SIGN and NICE. SIGN recommends follow-up every three months for five to ten years and suggests that decisions on routine imaging are made at a regional managed clinical network level after identifying and agreeing any additional imaging resources required in addition to consideration of other patient factors, including patient choice.[6] NICE recommends follow-up, with imaging, every three months for the first three years and then every six months for the next two years, followed by discharge at the end of five years.[9]

Additional information: comparators

Routine surveillance

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
Dabrafenib and trametinib	**Dabrafenib: 150mg twice daily.** **Trametinib: 2mg once daily** **Patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity.**	**131,040**

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 05 November 2018. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 43 patients eligible for treatment with dabrafenib and trametinib in year 1 rising to 50 in year 5. Of patients eligible under the license, 80% are assumed to be treated in year 1 rising to 85% in years 2-5.

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 14 December 2018.

**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.