Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2136

cabozantinib 20mg, 40mg, and 60mg film-coated tablets (Cabometyx®)

Ipsen Ltd UK

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 resubmission considered under the end of life process

cabozantinib (Cabometyx®) is not recommended for use within NHSScotland.

Indication under review: advanced renal cell carcinoma (RCC) in treatment-naïve adults with intermediate or poor risk.

In a phase II study, in treatment-naïve adults with advanced RCC with intermediate or poor risk as defined by the International Metastatic RCC Database Consortium risk group categories, cabozantinib was superior to another tyrosine kinase inhibitor for progression free survival.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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

Chairman
Scottish Medicines Consortium

Indication

The treatment of advanced renal cell carcinoma (RCC) in treatment-naïve adults with intermediate or poor risk.[1]

Dosing Information

The recommended dose of cabozantinib is 60mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary treatment interruption and / or dose reduction. When dose reduction is necessary, it is recommended to reduce to 40mg daily, and then to 20mg daily. See the summary of product characteristics (SPC) for further information.[1]

Cabozantinib tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least two hours before, through one hour after, taking cabozantinib.

Cabometyx (cabozantinib) tablets and Cometriq (cabozantinib) capsules are not bioequivalent and should not be used interchangeably.

Cabozantinib should be initiated by a physician experienced in the administration of anticancer medicinal products.[1]

Product availability date

May 2018
Cabozantinib meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy

Cabozantinib inhibits multiple receptor tyrosine kinases, including vascular endothelial growth factor (VEGF), and hepatocyte growth factor receptor protein (MET). Inhibition of these kinases may inhibit tumour growth, angiogenesis, metastatic progression and pathological bone remodeling.[1, 2] The indication under review is an extension to the licensed indication for the treatment of renal cell carcinoma (RCC). Cabozantinib has previously been accepted by the SMC for the treatment of advanced RCC in adults following prior VEGF-targeted therapy.

CABOSUN (Alliance for Clinical Trials in Oncology A031203) was a randomised, open-label, phase II collaborative study conducted in the United States.[3] To be eligible for inclusion in the study patients were required to meet the following criteria; adults with systemic, treatment-naïve, locally advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC with a clear-cell component, measurable disease per investigator (using Response Evaluation Criteria in

Solid Tumors [RECIST] version 1.1), International Metastatic RCC Database Consortium (IMDC) classification of intermediate or poor risk disease, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, appropriate organ function and no uncontrolled significant illnesses, and have archival tumour tissue.[2, 3] The risk factors considered for classification of risk using the IMDC tool are;

- time from diagnosis of RCC to systemic treatment less than one year
- haemoglobin less than lower limit of normal
- corrected calcium greater than upper limit of normal (ULN)
- Karnofsky's performance score less than 80%
- neutrophil count greater than ULN
- platelet count greater than ULN

Intermediate risk disease is defined as meeting one or two of the risk factors, while poor risk is defined as meeting three or more risk factors.[1] Patients were randomised equally to receive oral cabozantinib 60mg once daily continuously (n=79) or oral sunitinib 50mg once daily for four weeks, followed by two weeks off treatment to complete six-week continuous cycles (n=78). Doses could be reduced for adverse effects (AEs): cabozantinib could be reduced to 40mg or 20mg once daily, and sunitinib could be reduced to 37.5mg or 25mg once daily. Treatment was continued until radiographic evidence of disease progression assessed by the investigator, intolerance to treatment, or withdrawal of consent. Randomisation was stratified by the presence of bone metastases (yes or no) and IMDC risk group (intermediate or poor). Investigators and patients were not blinded to treatment but the Independent Review Committee (IRC) was blinded.[2, 3] The primary end-point was investigator-assessed progression free survival (PFS) in the intention-to-treat population. PFS was defined as the time from randomisation to radiographic progression of the disease per RECIST version 1.1 or death due to any cause, whichever occurred first.[2, 3] PFS assessed by IRC was conducted at a later time point. The investigator assessments did not censor data for non-protocol systemic anti-cancer treatments or if there were at least two assessments missing. The IRC assessments did censor for these considerations. The results of the primary outcome are described in Table 1 below.

Table 1. Results of primary outcome, progression free survival, as assessed by investigator and independent review committee

	cabozantinib (n=79)	**sunitinib (n=78)**
Investigator assessed median PFS, data cut-off 11 April 2016, following investigator adjudged 123 PFS events[4]	8.2 months	5.6 months
	HR 0.66, 95% CI: 0.46 to 0.95 p=0.012	
IRC assessed median PFS, data cut-off 15 September 2016, following IRC adjudged	8.6 months	5.3 months
	HR 0.48, 95% CI: 0.32 to 0.73 p<0.001	

92 PFS events, in accord with EMA censoring[1, 3]		
Investigator assessed median PFS, data cut-off 15 September 2016, following investigator adjudged 107 PFS events[3, 5]	8.3 months	5.4 months
	HR 0.56 ,95% CI: 0.37 to 0.83 p=0.004	

PFS = progression free survival, HR = Hazard ratio, CI = confidence interval, IRC = independent review committee, EMA = European Medicines Agency

Subgroup analyses based on IRC assessment of PFS at data-cut off 15 September 2016 for risk groups intermediate and poor, with and without bone metastases, and MET status positive and negative, were consistent with the results in the overall population.[3]

The proportion of patients obtaining an objective response (OR) based on the IRC assessment at data-cut off 15 September 2016 was 20% (16/79) in the cabozantinib group and 9% (7/78) in the sunitinib group; all were partial responses with no patient obtaining a complete response. The proportions with stable disease were 54% (43/79) with cabozantinib and 38% (30/78) with sunitinib. Six patients in the cabozantinib group and 18 in the sunitinib group did not have evaluable images for IRC OR and were classed as non-responders. These patients did not receive, or discontinued study treatment; the imbalance was primarily due to withdrawal of consent.

At the 01 July 2017 data cut-off, the median follow-up was 35.4 months, 90 deaths were reported (43/79 patients in the cabozantinib group and 47/78 patients in the sunitinib group) and median overall survival (OS) was 26.6 months with cabozantinib and 21.2 months with sunitinib; stratified HR 0.80, 95% CI: 0.53 to 1.21, p=0.29.[2, 3] The overall survival data are immature and the study was not powered for this outcome.[1] Subsequent anti-cancer therapies were similar for both groups of patients.[3]

The CABOSUN study did not record patient reported outcomes on health-related quality of life.

Summary of evidence on comparative safety

At the 15 September 2016 data cut-off of the CABOSUN study, the median duration of treatment in the cabozantinib (n=78) and sunitinib (n=72) groups was 6.5 months and 3.1 months respectively. Dose reductions were reported for 46% and 35% of the patients and treatment discontinuation due to AEs was reported for 21% and 22% in the respective safety analysis sets. In the cabozantinib and sunitinib groups respectively, 68% and 65% reported grade 3 or 4 AEs, and grade 5 AEs were reported for 4% and 10%.[3]

The most common grade 3 or 4 AEs in the cabozantinib and sunitinib groups respectively were hypertension (28% versus 21%), diarrhoea (10% versus 11%), hand-foot syndrome (8% versus 4%),

fatigue (6% versus 17%), platelet count decreased (1% versus 11%) and hyperglycaemia (0% versus 6%).[3] There were three treatment-related deaths in the cabozantinib group (acute renal failure, jejunal perforation and sepsis), and six in the sunitinib group (including sepsis, respiratory failure, angiopathy and sudden death).[2] The AEs associated with cabozantinib in CABOSUN are similar to the other tyrosine kinase inhibitors used to treat RCC and the known AE profile of cabozantinib.

Summary of clinical effectiveness issues

RCC is the most common type of kidney cancer accounting for approximately 90% of kidney neoplasms and it most commonly occurs between the ages of 60 and 70 years. Clear cell RCC is responsible for approximately 75% of RCC cases.[2] At the time of diagnosis approximately 25 to 30% of patients have metastatic disease with a 10% chance of 5-year survival.[6] Surgical resection is most commonly used in localised disease and targeted therapies are most commonly recommended in metastatic disease.[3] The median overall survival in the IMDC risk categories range from eight months in patients with poor risk to four years in patients with a favourable risk score. Morbidity of advanced RCC is significantly affected by the extent and location of metastases.[2] SMC clinical experts advised that the tyrosine kinase inhibitors, pazopanib and sunitinib, are currently the first line systemic treatment options for patients in all risk categories with advanced or metastatic RCC in Scotland. Cabozantinib meets SMC end of life criteria in this setting.

Cabozantinib was associated with a statistically significant advantage over sunitinib in terms of PFS in treatment-naïve patients with advanced RCC and IMDC risk category intermediate or poor. This did not translate to a significant benefit in overall survival, although the study was neither powered, nor were the data sufficiently mature, to make firm conclusions about the relative efficacy of cabozantinib for this endpoint.[3]

There are some limitations to the evidence described in the clinical efficacy section. CABOSUN was an open-label phase II study that enrolled a small number of patients relative to the condition.[7] Phase II studies are at a higher risk of reporting a false positive result,[8] and a higher proportion of patients randomised to sunitinib withdrew prior to receiving treatment (1% from the cabozantinib versus 8% in from the sunitinib group), possibly due to the open label design.[1, 3, 8] The CABOSUN study reported median PFS for sunitinib was not in line with other published estimates of sunitinib median PFS for RCC patients but some of these studies included patients in the IMDC favourable risk group.[8] CABOSUN included a relatively high proportion of patients with poor prognostic factors such as bone metastases, greater number of metastatic sites and ECOG PS 2, which are not accounted for in the IMDC criteria.[3] The intermediate risk group was heterogeneous and could include patients with either one or two of the six IMDC risk factors. There is some evidence that there are differences in PFS between patients with one and two IMDC risk factors when treated with sunitinib.[8]

The overall survival data reported for the CABOSUN study are immature, at the most recent data cut-off in July 2017, 57% of patients had died.[2] Overall survival data for patients who receive a first line treatment are likely to be confounded by the effects of subsequent lines of treatment. Some studies conducted in patients with metastatic RCC have reported an association between treatment effect on PFS and treatment effects on OS.[9, 10]

The inclusion and exclusion criteria of the CABOSUN study may reduce the generalisability to the Scottish population, particularly to patients with cardiovascular disease, history of thromboembolism, gastrointestinal disease and those receiving treatment with CYP3A4 modulating medicines.

The CABOSUN study did not record patient reported outcomes such as data on health-related quality of life. A lower proportion of patients in the cabozantinib group of the CABOSUN study reported fatigue compared with the sunitinib group (6% versus 17%), which may represent a meaningful benefit to patients. The open-label study design may have affected the reporting of adverse events.

There are no direct study data comparing cabozantinib with pazopanib, a relevant comparator for NHSScotland. The submitting company presented an indirect treatment comparison (ITC) of cabozantinib and pazopanib in patients with treatment-naïve advanced or metastatic RCC for efficacy outcomes. It compared hazard ratios modelled by fractional polynomials for PFS and OS using a Bayesian framework and fixed effects model. The network connected the CABOSUN[3] and COMPARZ[7] studies using the sunitinib arm of each study. Results of the ITC suggest that cabozantinib was associated with a greater median PFS compared with pazopanib. There was insufficient evidence of a difference in OS, and the credible intervals for median OS overlapped. Limitations of the ITC include differences in the patient populations (COMPARZ included patients with favourable risk, according to Memorial Sloan-Kettering Cancer Centre categorisation, 27% of overall population), and potential ascertainment bias for PFS. Tumour assessment varied across the studies; differing versions of RECIST were used, and differing assessment schedules (6- versus 12-weekly). The cabozantinib group PFS reported in the ITC is higher than the cabozantinib group PFS reported in the CABOSUN study, which was the reference study for the ITC. The COMPARZ study included many more patients (greater than six-times) and was conducted in a phase III setting whereas CABOSUN was conducted in a phase II setting. Pazopanib was non-inferior to sunitinib for PFS in the COMPARZ study, and OS was similar with both treatments.[7] Despite these concerns it was felt that an assumption of comparable efficacy for sunitinib and pazopanib was reasonable.

Cabozantinib would provide another treatment option for treatment-naïve patients with advanced or metastatic RCC, IMDC risk category intermediate and poor, and has been associated with a PFS advantage over sunitinib (direct data) and pazopanib (indirect data).

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 cabozantinib, as an end of life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Advanced RCC affects patients from a wide range of ages. It is an incurable disease which causes significant morbidity and only 10% of patients will survive for five years or more. The cancer related symptoms are often difficult to manage, may require hospitalisation and impact on general well-being. Employment can become difficult as health deteriorates, with families facing a loss of income in addition to the psychological burden of the disease.

- There is an unmet need for patients with intermediate or poor risk as defined by IMDC risk group categories, as many have a poor response to standard tyrosine kinase inhibitors. Approximately 50% of patients are not suitable to go on to receive a second line of therapy following disease progression on first line treatment. First line treatment options with improved time to cancer progression are required.

- Cabozantinib has been associated with improved time to progression and improved response rate over sunitinib and this is likely to provide patients and families with a psychological boost which may have quality of life benefits.

- Clinicians have experience of cabozantinib in the second line setting and are familiar with managing associated adverse events.

- This therapeutic area is changing rapidly and clinicians suggest the availability of cabozantinib as a first and second line treatment option would be beneficial as patient factors may mean some treatment options are unsuitable for some patients.

We received patient group submissions from Kidney Cancer Scotland, Kidney Research UK, and the Kidney Cancer Support Network (KSCN). All three organisations are registered charities. KCSN has received 61% pharmaceutical company funding in the past two years, including from the submitting company. Kidney Cancer Scotland has received 9% pharmaceutical company funding in the past two years, with none from the submitting company. Kidney Research UK has received 15.5% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all three organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing cabozantinib to sunitinib and pazopanib for the treatment of advanced RCC in treatment-naïve adults with intermediate or poor risk as per IMDC criteria. Based on SMC clinical expert responses sunitinib and pazopanib appear to be the comparators most likely displaced in Scotland.

The economic analysis used a 20 year partitioned survival model which consisted of three health states (pre-progression, post-progression and death). The proportion of patients in each health state was based on parametric survival curves fitted to clinical data on PFS and OS. The clinical data used in the economic analysis were derived from two sources, that is the pivotal study,[3, 4] for the comparison versus sunitinib, and an indirect treatment comparison for the comparison versus pazopanib. For the comparison versus sunitinib, PFS estimates were derived by applying parametric functions to the IRC Kaplan-Meier data for cabozantinib and sunitinib (median modelled PFS 10.15 months versus 5.37 months for cabozantinib and sunitinib respectively). The log normal function was used for both arms. The base case cost-effectiveness results used OS data from the July 2017 data cut and an exponential function was used for both arms. It is worth noting that OS data were not mature and credible intervals included one.

For the comparison versus pazopanib, the company derived PFS and OS estimates from the indirect treatment comparison, whereby data for pazopanib were adjusted to reflect patients in the sunitinib arm of the pivotal study.[3, 4] To extrapolate results over time, the company adopted a modelling approach using fractional polynomials. Based on this analysis cabozantinib resulted in median PFS of 10.36 months while pazopanib and sunitinib resulted in median PFS of 5.40 months and 5.58 months respectively. Given some potential limitations with the indirect comparison, the company also provided a base case analysis under an assumption that the data for pazopanib were equivalent to those of sunitinib.

Medicine acquisition costs and monitoring costs were included in the analysis. Within the model, costs were estimated using time to treatment discontinuation and subsequent lines of therapy were also included in the analysis using treatment patterns from the CABOSUN study and other sources. Monitoring costs included outpatient consultations, CT scans and blood tests. No administration costs were included as all treatments are taken orally. Grade 3 and 4 adverse event costs were included in the model.

The utility values used in the model were 0.726 for pre-progression health state and 0.649 for the post-progression health state respectively. These values were derived from published NICE guidance for tivozanib and values are reflective of patients included in the TIVO-1 study, that is adult patients with RCC.[11] Disutility associated with grade 3 and 4 adverse events was included in the model.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. PASs are in place for sunitinib and pazopanib and these were included in the analysis by using an estimate of the PAS prices of sunitinib and pazopanib based on information that is in the public domain.

Table 2. Base case results (cabozantinib versus sunitinib using CABOSUN data) PAS price

Medicine	Incremental Costs	Incremental QALYs	ICER
Sunitinib	-	-	-
Cabozantinib	£5,422	0.419	£12,928

Table 3. Base case results (cabozantinib versus pazopanib using ITC results) PAS price

Medicine	Incremental Costs	Incremental QALYs	ICER
Pazopanib			
Cabozantinib	£14,424	0.526	£27,415

Table 4. Base case results (cabozantinib versus pazopanib using CABOSUN sunitinib data for pazopanib/equal efficacy assumption) PAS price

Medicine	Incremental Costs	Incremental QALYs	ICER
Pazopanib			
Cabozantinib	£4,700	0.576	£11,266

Table 5. Scenario analysis versus sunitinib (PAS price included for both medicines)

Scenario	ICER
OS curve based on ITC (alternative fractional polynomial method- 2nd order model P1=-0.5, P2=0)	£18,683
Weibull curve used to model OS (log normal used in base case)	£14,929
Alternative pattern of subsequent therapies based on clinical expert view	£18,861
Removal of non-significant differences in OS (that is no survival gain assumed)	£33,421

Table 6. Scenario analysis versus pazopanib (PAS price included for both medicines)

Scenario	ICER
OS curve based on ITC (alternative fractional polynomial method- 2nd order model P1=-0.5, P2=0)	£38,681
ITC base case: PFS and OS estimated using the Weibull curve	£45,402

Removal of non-significant differences in OS (that is no survival gain assumed)	£163,922
ITC base case: 10 year time horizon	£30,811

The company provided a number of other sensitivity analyses including one-way and scenario analyses. Results were not overly sensitive to variation in most parameters. The ICERs did show some variation in the use of different extrapolation methods for OS and PFS but the ICERs all remained under £20,000 versus sunitinib and versus pazopanib when using the equal efficacy assumption analysis.

There were a number of limitations with the data used in the analysis which include the following;

- Based on the results of the pivotal study[3, 4] and the indirect treatment comparison, cabozantinib resulted in a non-significant difference for OS, versus both sunitinib and pazopanib. While the data are immature, there is some uncertainty surrounding the validity of OS estimates used in the economic analysis. As shown above, analysis which removed all survival benefit resulted in considerable increases in the cost-effectiveness ratios. Further, in relation to the PFS benefits of cabozantinib over sunitinib, as noted above there may be some concerns regarding the sunitinib value from the CABOSUN study.
- As noted above, the company included two methods of estimating the outcomes in the comparison with pazopanib; either using the ITC method, or by assuming comparable efficacy of pazopanib and sunitinib and therefore using CABOSUN sunitinib data for pazopanib). As there is some uncertainty surrounding the appropriateness of the company's method of adjusting data from the ITC to reflect patients in the pivotal study, it was helpful to have the alternative analysis using the equal efficacy assumption, however, given some concerns about the sunitinib values as noted, some uncertainty may still exist.
- There is some uncertainty associated with the subsequent treatments used in the model and whether they reflect the treatment pathways in NHSScotland. Sensitivity analysis showed some change in the ICERs from the use of alternative assumptions.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept cabozantinib for use in NHS Scotland.

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

Additional information: guidelines and protocols

The European Society of Medical Oncology (ESMO) produced a clinical practice guideline in 2016 titled 'Renal cell carcinoma: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up' which was updated in 2017. The guideline advises partial or radical nephrectomy for patients with local or locoregional RCC. Radiofrequency ablation, cryoablation and active surveillance are alternative options for some patient groups. Radical nephrectomy is suggested for patients with locally advanced disease. For the management of patients with metastatic disease the guideline notes that the recommendations primarily relate to patients with clear cell histology, as most studies were conducted in this group of patients. For patients with metastatic disease and good or intermediate prognosis; sunitinib or pazopanib monotherapy (most commonly used), or bevacizumab with interferon are recommended first line treatments. High dose interleukin-2, sorafenib and low dose interferon with bevacizumab are listed as alternative first line treatment options. For patients with a poor prognosis temsirolimus is the preferred option with sunitinib, pazopanib and sorafenib as alternative options. Best supportive care is also a management option in patients with poor prognosis.[12] These recommendations pre-date the licensing of cabozantinib for use in treatment naïve patients with advanced RCC.

The European Association of Urology (EAU) guidelines on renal cell carcinoma were most recently updated in 2018. The recommendations in this guideline for the first line treatment of metastatic clear cell RCC are more recent than in the ESMO recommendations above. This guideline advises the use of ipilimumab plus nivolumab in treatment-naïve patients with clear-cell metastatic RCC of IMDC intermediate and poor risk, stating that this combination leads to superior survival compared to sunitinib (the evidence to support this recommendation is considered strong). It also recommends cabozantinib and sunitinib for this patient group (evidence considered weak) and pazopanib is recommended to use it patients with IMDC intermediate risk only (evidence considered weak). Sunitinib and pazopanib are recommended for IMDC favorable risk disease (evidence considered strong). Sunitinib is recommended for patients requiring treatment for non-clear cell RCC.[13]

Additional information: comparators

Sunitinib and pazopanib are the relevant comparators for treatment-naïve advanced RCC patients with intermediate or poor risk as per IMDC in Scottish practice.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
cabozantinib	**60mg orally daily**	**62,402**
sunitinib	50mg orally daily for four weeks followed by a 2-week treatment free period to complete a six week cycle	27,203
pazopanib	800mg orally daily	27,203

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 company estimated there would be 1,242 patients eligible for treatment within year 1 rising to 1,709 patients in year 5. The assumed market share was 10.3% in year 1 (128 patients) rising to 51.7% in year 5 (884 patients).

Without PAS
The gross impact on the medicines budget was estimated to be £5.9m in year 1 rising to £41.2m in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £3.0m in year 1 rising to £20.8m in year 5.

It should be noted that the net budget impact estimates do not take account of any PAS applicable to comparator medicines.

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

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This assessment is based on data submitted by the applicant company up to and including 12 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.