Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

afatinib 20mg, 30mg, 40mg, 50mg film-coated tablets (Giotrif®)

SMC No. (920/13)

Boehringer Ingelheim International GmbH

08 November 2013 *(Issued 07 February 2014)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

afatinib (Giotrif®) is accepted for use within NHS Scotland.

Indication under review: As monotherapy, for the treatment of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

In two phase III studies, in patients with EGFR mutation positive adenocarcinoma of the lung, afatinib was significantly superior to the chemotherapy regimen comparators for the primary endpoint of progression free survival. Overall survival data are immature. A mixed treatment comparison provides indirect comparative data versus other tyrosine kinase inhibitors.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

Dosing Information

Treatment with afatinib should be initiated and supervised by a physician experienced in the use of anticancer therapies.

EGFR mutation status should be established prior to initiation of afatinib therapy.

The recommended dose is 40mg once daily continuously until disease progression or until no longer tolerated by the patient.

A dose escalation to a maximum of 50mg daily may be considered in patients who tolerate a 40mg daily dose (i.e. absence of diarrhoea, skin rash, stomatitis and other adverse reactions with NCI common terminology criteria for adverse events [CTCAE] grade >1) in the first three weeks. The dose should not be escalated in any patients with a prior dose reduction. The maximum daily dose is 50mg.

Symptomatic adverse reactions (e.g. severe persistent diarrhoea or skin related adverse reactions) may be managed by treatment interruption and dose reductions as outlines in the summary of product characteristics.[1]

It should not be taken with food. Food should not be consumed for at least three hours before and at least one hour after administration.

Product availability date

20 January 2014

Summary of evidence on comparative efficacy

Epidermal growth factor receptor (EGFR) gene mutations are found in a minority of lung adenocarcinomas which require EGFR pathway signalling for tumour cell survival. Afatinib is the third oral tyroine kinase inhibitor (TKI) licensed for NSCLC, and is indicated in patients who are EGFR-TKI-naïve.

Two similarly designed phase III, open-label, randomised studies have compared afatinib with intravenous (iv) platinum based chemotherapy regimens.[2,3] The studies recruited patients aged ≥18 years who had treatment-naïve advanced (stage IIIb with pleural effusion or stage IV) lung adenocarcinoma with proven EGFR mutations; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate end-organ function; and measurable disease using response evaluation criteria is solid tumours (RECIST) version 1.1.

In study LUX-lung 3, 345 patients were randomised in a ratio of 2:1 to oral afatinib 40mg once daily (increased to 50mg after the first cycle if no rash, diarrhoea, mucositis or any other

adverse events >grade 1 severity occurred) or pemetrexed 500mg/m^2 iv plus cisplatin 75mg/m^2 iv on day one of a 21-day cycle. In study LUX-lung 6, conducted in an Asian population, 364 patients were randomised in a ratio of 2:1 to oral afatinib 40mg once daily (dose increase as in LUX-lung 3) or gemcitabine 1,000mg/m^2 iv on day one and eight plus cisplatin 75mg/m^2 iv on day one of a 21-day cycle. In both studies, patients were stratified according to EGFR mutation (L858R, exon 19 deletion or other) and additionally, in LUX-lung 3, according to race (Asian or non-Asian). Study treatment was continued until disease progression, and up to six cycles of chemotherapy were administered.

The primary endpoint in the intent-to-treat population, which included all randomised patients, was progression free survival (PFS), defined as the time from randomisation to progression (as determined by independent blinded review) or death. PFS was significantly longer in the afatinib group versus the chemotherapy group for both studies. The table below includes results of primary and some secondary endpoints.

Table: results of primary and some secondary endpoints of phase III studies[2,3]

	LUX-lung 3		**LUX-lung 6**	
	afatinib	**pemetrexed plus cisplatin**	**afatinib**	**gemcitabine plus cisplatin**
N	230	115	242	122
Primary endpoint; progression free survival (PFS)				
PFS; % of events	66% (152/230)	60% (69/115)	65% (157/242)	53% (64/122)
PFS; months	11.1	6.9	11.0	5.6
PFS; hazard ratio, 95% CI, p-value	0.58, 95% CI 0.43 to 0.78 p=0.001		0.28, 95% CI 0.20 to 0.39 p<0.0001	
Secondary endpoints				
Objective response; % * (CR + PR)	56%	23%	67%	23%
Median duration of objective response; months	11.1	5.5	9.7	4.3
Disease control; % (CR + PR + SD)**	90%	81%	93%	76%
Median duration of disease control; months	13.6	8.1	11.1	5.7

*p=0.001 for LUX-lung 3 and p<0.0001 for LUX-lung 6. **p<0.0001 for LUX-lung 6.
CI= confidence interval, CR=complete response, PR=partial response, SD=stable disease

Overall survival data are immature; the primary overall survival analysis will be undertaken when approximately 209 deaths have been observed. For LUX-lung 3, in an updated analysis (January 2013) where approximately half of deaths had occurred, the median overall survival was 28.1 months for afatinib and 28.2 months for pemetrexed/cisplatin (hazard ratio 0.91, 95% CI 0.66 to 1.25, p=0.55).[4,5] In the LUX-lung 6 study, where the proportion of patients who had died overall was 43% (October 2012), the median overall survival was 22.1 months for afatinib versus 22.2 months for gemcitabine/cisplatin, hazard ratio 0.95, p=0.76.[3]

Patient reported outcomes, included the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and the Lung cancer-specific module QLQ-LC13. A change of at least 10 points in an item or domain is considered clinically meaningful.[7] The pre-specified items of interest were cough, dyspnoea and pain. For LUX-lung 3, in the afatinib group (compared to pemetrexed/cisplatin group) there were numerically but not significantly higher proportions of patients with ≥10 point improvements in cough (67% versus 60%) and pain (59% versus 48%) and a significantly higher proportion for dyspnoea (64% versus 50%).[5,7] Compared to pemetrexed/cisplatin, afatinib significantly delayed the time to deterioration of cough and dyspnoea but not pain. For LUX-lung 6, in the afatinib group (compared to gemcitabine/cisplatin group) there were significantly higher proportions of patients with ≥10 point improvements in cough (76% versus 55%), dyspnoea (71% versus 48%) and pain (64% versus 47%). Compared to gemcitabine/cisplatin, afatinib significantly delayed the time to deterioration of cough, dyspnoea and pain.[8]

LUX-lung 2 was a phase II, open-label, non-comparative study that included 129 patients with stage IIIb with pleural effusion or stage IV adenocarcinoma of the lung with EGFR mutations.[9] Patients were required to have received ≤1 previous chemotherapy regimen for advanced disease, an ECOG PS of 0 to 2 and no previous treatment with EGFR-TKI. All patients received afatinib 50mg (reduced to 40mg after a protocol amendment) orally once daily until disease progression, intolerable adverse events, or patient withdrawal. The primary endpoint was the proportion of patients with a confirmed objective response (complete response or partial response), as determined by RECIST 1.0, by independent review of imaging and was achieved in 61% (79/129) of patients. The study included 68 patients receiving afatinib as second-line treatment, and in this sub-group, the median PFS was 8.0 months (95% CI 4.6 to 13.8) and the median overall survival (updated analysis, date unknown) was 23.6 months[5].

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

Summary of evidence on comparative safety

In LUX-lung 3, study treatment-related adverse events of ≥grade 3 severity occurred in 49% (112/230) of afatinib patients and 48% (53/115) of pemetrexed/cisplatin patients. Treatment was discontinued (due to treatment-related adverse events) in 8% and 12% of patients receiving afatinib and pemetrexed/cisplatin respectively. The following adverse events of ≥grade 3 severity occurred in >10% of patients (afatinib and pemetrexed/cisplatin groups respectively): diarrhoea (14% and 0%), rash/acne (16% and 0%), paronychia (11% and 0%), fatigue (1.3% and 13%) and neutropenia (0.4% and 18%). Four deaths in the afatinib group were considered to be potentially treatment related by the investigator (two respiratory decompensations, one sepsis, and one unknown). There were no treatment-related deaths in the pemetrexed/cisplatin group.[2]

In LUX-lung 6, study treatment-related adverse events of ≥grade 3 severity occurred in 36% of afatinib patients and 60% of gemcitabine/cisplatin patients. Treatment related adverse events leading to discontinuation occurred in 5.9% and 40% of patients receiving afatinib and gemcitabine/cisplatin respectively. The following grade 3/4 adverse events occurred in >5% of patients (afatinib and gemcitabine/cisplatin groups respectively): diarrhoea (5.4% and 0%), rash/acne (14% and 0%), stomatitis/mucositis (5.4% and 0%), vomiting (0.8% and 19%), nausea (0% and 8.0%), neutropenia (0.4% and 26%), leucopenia (0.4% and 15.1%), anaemia (0.4% and 8.9%), neutrophil count decreased (0% and 9.8%) and decreased white cell count

(0% and 6.2%). There were two treatment-related deaths; one in the afatinib group (sudden death) and one in the gemcitabine/cisplatin group (cardiac failure).[3]

Summary of clinical effectiveness issues

Two other tyrosine kinase inhibitors (TKI's) are licensed for the treatment of advanced NSCLC with activating EGFR mutations: erlotinib and gefitinib. SMC has accepted erlotinib but did not recommend gefitinib for use in NHS Scotland. Clinical experts consulted by SMC report the use of erlotinib for first-line treatment.

Efficacy results from the phase III studies (one of which is published in poster form only) showed significant improvements in PFS for afatinib compared to chemotherapy in a population of treatment-naïve EGFR mutation positive adenocarcinoma patients, corresponding to additional PFS of around five months. This was supported by sensitivity and subgroup analyses of PFS. However, no conclusions regarding overall survival can be made, as the data are immature. In LUX-lung 6, patients were recruited from Asia only and 76% of patients recruited to LUX-lung 3 were Asian. The EGFR mutation is more prevalent in the Asian (30%) than Caucasian (10% to 15%) population. The studies compared afatinib with doublet chemotherapy regimens; however, TKI are now considered more relevant comparators and there are no direct comparative efficacy data with these.

Comparative data for afatinib versus other TKI inhibitors come from a mixed treatment comparison (MTC) which compared afatinib with erlotinib, gefitinib and chemotherapy regimens in the first-line treatment of NSCLC. The MTC was conducted using WinBUGS version 1.4.3 and results for random and fixed effects models were reported. For the PFS endpoint, 14 studies were included and the results indicated that afatinib was similar to gefitinib and erlotinib but significantly superior to gemcitabine/cisplatin and pemetrexed/cisplatin. For the overall survival endpoint, 19 studies were included and the results indicated that afatinib was similar to all comparators. The MTC has some limitations. A number of the studies were conducted in the NSCLC population (rather than the EGFR-mutation-positive NSCLC population). However, for the TKI studies, data from the EGFR-mutation-positive NSCLC population (either entire population or a subgroup analysis) were used in the MTC. The rationale for exclusion of an erlotinib study (OPTIMAL[11]) was not considered to be robust. Furthermore, there was some heterogeneity in baseline characteristics of patients across studies and adverse event results are uncertain. In spite of these limitations, the MTC was considered to be acceptable.

A subgroup of the LUX-lung 2 single-arm study (n=68) provides uncontrolled efficacy data for patients who had received one previous chemotherapy regimen. However, it is unlikely afatinib will be used in second-line treatment as, in practice, most patients will have already received a TKI first-line and therefore will be ineligible for afatinib.

The availability of afatinib will provide clinicians and patients with an additional TKI for use in the treatment of EGFR mutation positive NSCLC. However, clinical experts consulted by SMC did not consider that there was unmet need in first-line use, the setting in which afatinib is most likely to be used. Afatinib is administered orally and food should not be consumed for three hours before or one hour after its administration. It may be swallowed whole or dispersed in non-carbonated drinking water, and swallowed or administered via a gastric tube.[5] Erlotinib is taken orally at least one hour before or two hours after the ingestion of food.[12]

Before initiating afatinib the EGFR mutation status of the patient needs to be confirmed and a well-validated and robust methodology should be used to avoid false negative or false positive determinations.[5] The National Institute for Health and Care Excellence (NICE) has published a diagnostics guideline which recommends tests and test strategies for detecting EGFR TK mutations in the tumours of adults with previously untreated, locally advanced or metastatic NSCLC.[14]

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis (CMA) comparing afatinib with erlotinib for the treatment of tyrosine kinase inhibitor-naive adult patients with locally advanced or metastatic NSCLC with activating EGFR mutation(s). The company indicated that the analysis was relevant to both first and second line uses of afatinib, with erlotinib being the relevant comparator in both cases. The results were presented on a per day and one year time horizon. SMC clinical experts confirmed the appropriateness of erlotinib as current first line treatment.

The efficacy data to support the CMA came from the MTC. On the basis of no significant differences in PFS or OS, the company asserted that a CMA was appropriate.

No adverse events were considered in the analysis and the only costs in the model related to drug acquisition costs. Treatment was assumed to continue until progression, and its duration was assumed to be the same in both treatment arms at 11.1 months. Administration, monitoring and EGFR testing costs were common to both arms and thus excluded. A patient access scheme (PAS) is in place in NHS Scotland for erlotinib and was incorporated into the analysis as the relevant price for erlotinib.

The results indicated that afatinib costs £72.26 per day compared to £54.38 per day for erlotinib without the erlotinib PAS. On this basis, afatinib would not be the preferred treatment on cost-effectiveness grounds. A PAS was also submitted for afatinib and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a confidential discount was given on the price of the medicine. When both the afatinib and erlotinb PAS were taken into account, afatinib became a cost-effective treatment option.

The company provided sensitivity analysis to test the impact of using the PFS hazard ratio point estimates and credible intervals from the MTC. The impact of this was to vary the duration of PFS and hence the duration of treatment/cost in each arm of the model. This showed that as the hazard ratio for afatinib decreased, afatinib was associated with incremental costs as treatment duration was longer due to PFS being longer.

There were a number of issues with the analysis:

- The company indicated that the results apply for first and second line use, but the data in the MTC was only in first line use. As such, relative benefits in the second line setting are unclear.
- The analysis took as its starting point that PFS was not significantly different and hence a CMA was appropriate. From this, treatment with both agents was assumed until treatment progression and thus in the analysis treatment duration would be the same in

each arm. As the analysis testing the hazard ratios shows, any movement away from assuming a common duration of treatment may alter the relative cost differences between treatments in practice.

- There are weaknesses in the MTC which mean the assumption of comparable efficacy and safety needed for a cost-minimisation analysis is associated with some uncertainty.

Despite these weaknesses, the economic case has been demonstrated.

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

Summary of patient and public involvement

A Patient Interest Group Submission was received from Roy Castle Lung Cancer Foundation.

Additional information: guidelines and protocols

NICE published clinical guideline 121; lung cancer; the diagnosis and treatment of lung cancer, in April 2011.[13] It includes the following recommendations:

- Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80 to 100), to improve survival, disease control and quality of life.
    - Chemotherapy for advanced NSCLC should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience.
    - Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug.
    - Docetaxel monotherapy should be considered if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy.

- The guideline refers to the technology appraisals for advice on gefitinib, pemetrexed and erlotinib.

NICE published diagnostics guideline 9; EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer, in August 2013.[14] The guideline includes the following recommendations:

- The tests and test strategies listed below are recommended as options for detecting EGFR-TK mutations in the tumours of adults with previously untreated, locally advanced or metastatic non-small-cell lung cancer (NSCLC), when used in accredited laboratories participating in an external quality assurance scheme. The laboratory-developed tests should be designed to detect the mutations that can be detected by one of the CE-marked tests as a minimum.
    - therascreen EGFR RGQ PCR Kit (CE-marked, Qiagen)

- cobas EGFR Mutation Test (CE-marked, Roche Molecular Systems)
- Sanger sequencing of samples with more than 30% tumour cells and therascreen EGFR RGQ PCR Kit for samples with lower tumour cell contents
- Sanger sequencing of samples with more than 30% tumour cells and cobas EGFR Mutation Test for samples with lower tumour cell contents
- Sanger sequencing followed by fragment length analysis and polymerase chain reaction (PCR) of negative samples.

- There was insufficient evidence for the Committee to make recommendations on the following methods:

  - high-resolution melt analysis
  - pyrosequencing combined with fragment length analysis
  - single-strand conformation polymorphism analysis
  - next-generation sequencing
  - therascreen EGFR Pyro Kit (CE-marked, Qiagen).

The Scottish intercollegiate Guideline Network published guideline 80; management of patients with lung cancer, in February 2005.[15] In patients with stage IIIB and IV NSCLC the guideline includes the following recommendations:

- Chemotherapy with a platinum-based combination doublet regimen should be considered in all patients who are not suitable for curative resection or radical radiotherapy and are fit enough to receive it.
- Selected older patients with stage III/IV NSCLC should be offered chemotherapy.
- For patients with advanced NSCLC the number of chemotherapy cycles should not exceed four.
- Second line chemotherapy with docetaxel 75 mg/m^2 (three weekly) should be considered for stage IIIB/IV NSCLC patients with good performance status.

The following good practice point is included:

- Chemotherapy is not generally recommended for NSCLC patients who are PS3 or 4.

The guideline includes the following statement on targeted therapies:

Newer approaches to chemotherapy have involved blocking specific tumour growth factor receptors. Current evidence does not support the routine use of targeted therapies in patients with stage IIIB/IV NSCLC outwith a clinical trial.

NB: an update to incorporate new evidence on chemotherapy, surgery, radiotherapy is in progress and is expected in autumn 2013.

Additional information: comparators

Erlotinib and gefitinib (which is not recommended by SMC for treatment of advanced or metastatic NSCLC with activating mutations of EGFR-TK).

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Afatinib	**40mg orally once daily**	**26,303**
Erlotinib	150mg orally once daily	19,796
Gefitinib*	250mg orally once daily	26,302

Doses are for general comparison and do not imply therapeutic equivalence. Cost of erlotinib from www.mims.co.uk on 22 August 2013 and cost of afatinib from company's submission. Costs do not take any patient access schemes into consideration.
*not recommended by SMC

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 314 patients per year with an estimated uptake rate of 0% in year 1, 3% in year 2 and 35% by year 5.

Without PAS: The gross impact on the medicines budget was estimated to be £0 in year 1 rising to £2.68m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £0 in year 1 rising to £663k in year 5.

Note that these figures do not include the PAS for afatinib or erlotinib.

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

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. European Medicines Agency. European Public Assessment Report for erlotinib (Tarveca). 21 July 2011
2. Sequist L, Yang, Yamamoto N et al Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung adenocarcinoma With EGFR Mutations J Clin Oncol 31.2013
3. Wu YL, Zhou C, Hu CP, et al. LUX-Lung 6: A randomized, open-label, phase III study of afatinib versus gemcitabine/cisplatin as first-line treatment for Asian patients with EGFR mutation-positive advanced adenocarcinoma of the lung. Poster presentation. 2013 American Society of Clinical Oncology (ASCO) Annual Meeting Proceedings, Chicago, 31 May - 4 Jun 2013
4. Food and Drug Administration (Center for drug evaluation and research). Medical review for afatinib (application number 201292Orig1s000)
5. Boehringer Ingelheim International GmbH. Draft summary of product characteristics for afatinib (Giotrif®).
6. Clinical Trial Report LUX-Lung 6 (2013) LUX-Lung 6: A randomised, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR-activating mutation (April 2013)
7. Yang CH Vera Hirsh, Martin Schuler et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations J Clin Oncol 31.2013
8. Geater SL, Zhou C, Hu CP, et al. LUX-Lung 6: Patient-reported outcomes from a randomized open-label, phase iii study in first-line advanced NSCLC patients harboring EGFR mutations. Poster presentation. 2013 American Society of Clinical Oncology (ASCO) Annual Meeting Proceedings, Chicago, 31 May - 4 Jun 2013.
9. Yang CH, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. Lancet Oncol 2012; 13(5):539-548.
10. Scottish Intercollegiate Guidelines Network. SIGN 80; management of patients with lung cancer (draft update)
11. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncology 2011 Aug;12(8):735-42
12. Roche Products Ltd. Summary of product characteristics for erlotinib (Tarceva®). Last updated September 2010.
13. National Institute for Care and Clinical Excellence (NICE). Clinical guideline 121: lung cancer; the diagnosis and treatment of lung cancer. April 2011
14. NICE diagnostics guideline 9; EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer. August 2013
15. Scottish Intercollegiate Guidelines Network. SIGN 80; management of patients with lung cancer. February 2005.

This assessment is based on data submitted by the applicant company up to and including 21 January 2014.

**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_Statements/Policy_Statements

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

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.