Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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erlotinib 25, 100 and 150mg film-coated tablets (Tarceva®)

SMC No. (749/11)

Roche Products Ltd

09 December 2011

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

erlotinib (Tarceva®) is accepted for use within NHS Scotland.

Indication under review: first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations.

In patients with advanced or metastatic NSCLC with EGFR mutations, erlotinib was associated with significantly improved progression-free survival compared with platinum-based doublet chemotherapy regimens. There are no mature overall survival data.

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Published 16 January 2012

Indication

First-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations.

Dosing Information

The recommended dose is 150mg daily taken at least one hour before or two hours after the ingestion of food.

EGFR mutation testing should be performed prior to initiation of erlotinib therapy in chemo-naïve patients with advanced or metastatic NSCLC.

Erlotinib treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Product availability date

24 August 2011

Summary of evidence on comparative efficacy

Erlotinib is an epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitor which blocks EGFR downstream signalling processes that activate cell proliferation, cell migration, angiogenesis and cell survival. SMC has previously accepted erlotinib for restricted use for the treatment of locally advanced or metastatic NSCLC, after failure of at least one prior chemotherapy regimen in patients who would otherwise be eligible for treatment with docetaxel monotherapy. This submission relates to a licence extension allowing erlotinib to be used as a first-line treatment in patients whose tumours harbour an activating EGFR mutation. Around 11% of patients with metastatic NSCLC will have an EGFR activating mutation (EGFR M+).

The key evidence to support the indication under review comes from one phase III, open-label study (EURTAC) in European patients with advanced or metastatic NSCLC with activating mutations of EGFR. Eligible patients were aged ≥ 18 years, with stage IIIB or IV NSCLC, who had EGFR mutations (exon 19 deletion or exon 21 mutation). Patients were randomised in a ratio of 1:1 to receive erlotinib 150mg daily (n=77) or platinum-based doublet chemotherapy (n=76) (cisplatin plus docetaxel, cisplatin plus gemcitabine, docetaxel plus carboplatin or gemcitabine plus carboplatin), stratified according to Eastern Co-operative Oncology Group performance status (0 or 1 or 2) and EGFR mutation (exon 19 deletion or exon 21 L858R mutation). Erlotinib was continued until disease progression and platinum-based doublet chemotherapy combinations for up to four cycles.[1,2]

The primary endpoint was investigator-assessed progression-free survival (PFS) in the full analysis set. At the planned interim analysis (2 August 2010), the primary endpoint of PFS (n=153) was a median of 9.4 months in the erlotinib group and 5.2 months in the doublet chemotherapy group, corresponding to a hazard ratio (HR) of 0.42 (95% confidence interval [CI]: 0.27 to 0.64), p<0.0001.[1] At this point, the median duration of follow-up was 14.3 months in the erlotinib group and 10.7 months in the doublet chemotherapy group. There had been 27

and 28 deaths in each treatment group respectively and PFS had been reported in 45 and 47 patients respectively. [2]

Sensitivity analysis of PFS results, as assessed by the independent review committee (n=129), reported median PFS of 10.4 and 5.4 months respectively (HR: 0.47 [95% CI: 0.27 to 0.78]), p=0.003. There was an overall concordance rate of 70% between the investigator and independent review committee assessments of PFS. A further exploratory updated analysis (26 January 2011) (n=173), reported median PFS of 9.7 months in the erlotinib group and 5.2 months in the doublet chemotherapy group (HR: 0.37 [95% CI: 0.27 to 0.54]), p<0.0001.[1]

At the planned interim analysis, median overall survival was 22.9 months in the erlotinib group and 18.8 months in the doublet chemotherapy group (HR: 0.80 [95% CI: 0.47 to 1.37], p=0.42.[3] At the time of the exploratory updated analysis, the reported result for overall survival was HR 1.04 [95% CI: 0.65 to 1.68], p=0.87 but 77% of doublet chemotherapy patients had received further therapy on disease progression, with 65 of these crossing over to erlotinib.[2] Best overall response rates (complete or partial response) were significantly higher in the erlotinib than the doublet chemotherapy group; 54% versus 10% respectively at the interim analysis and 58% versus 15% at the exploratory updated analysis. [1]

Another phase III, open-label study (OPTIMAL) compared first-line erlotinib monotherapy with gemcitabine plus carboplatin in Chinese patients with advanced or metastatic NSCLC with activating mutations of EGFR. Eligible patients were centrally randomised in a ratio of 1:1 to receive erlotinib 150mg daily orally (n=83) or gemcitabine plus carboplatin for up to four cycles (n=72) stratified by mutation type (exon 19 mutation or exon 21 mutation), histological subtype (adenocarcinoma or non- adenocarcinoma) and smoking status (present/former smoker or never smoker). The primary endpoint of median PFS, as assessed by the investigator, was significantly longer in the erlotinib than the gemcitabine/carboplatin group (13.1 months versus 4.6 months: HR 0.16 [95% CI: 0.10 to 0.26], p<0.0001). An updated analysis, reported median PFS of 13.7 months versus 4.6 months for erlotinib and gemcitabine/carboplatin respectively (HR: 0.164, p<0.0001). Subgroup analyses suggest that the benefit seen in PFS is consistent across clinical subgroups (age, sex, performance status, disease stage, tumour histology or smoking status). The most important factor in PFS benefit was activating EGFR mutations: in patients with exon 19 mutation (n=82) the HR was 0.13 (95% CI: 0.07 to 0.25) and in patients with exon 21 mutation (n=72) the HR was 0.26 (95% CI: 0.14 to 0.49).[4]

Patients in the erlotinib group achieved significant improvements in quality of life as measured by Functional assessment of cancer therapy-lung (FACT-L), Trial outcome index (TOI) and Lung cancer symptom scale (LCSS) compared with the gemcitabine/carboplatin group". [5]

Data on overall survival are not mature with 16 deaths (20%) in the erlotinib group and 12 (17%) deaths in the gemcitabine/carboplatin group. Objective response rate (complete or partial response) was reported in significantly more erlotinib than gemcitabine/carboplatin patients: 83% (68/82) versus 36% (26/72) respectively, p<0.0001. [4]

Summary of evidence on comparative safety

The use of erlotinib as first-line therapy did not raise any new safety concerns over the established safety profile for erlotinib. The most frequently reported adverse events in the erlotinib group in both studies were rash and diarrhoea. In the EURTAC study, 80% of erlotinib patients had at least one EGFR-related rash (which included other skin adverse events e.g. acne, folliculitis, dermatitis) and 73% of erlotinib patients in the OPTIMAL study reported rash. Diarrhoea was reported in 57% and 25% of erlotinib-treated patients in the EURTAC and OPTIMAL studies respectively.

In the key EURTAC study, the following adverse events were reported in the erlotinib and doublet chemotherapy groups respectively: diarrhoea (57% versus 19%), nausea (23% versus 41%), vomiting (13% versus 22%), constipation (8.0% versus 22%), rash (49% versus 1.4%), paronychia (16% versus 0), folliculitis (8.0% versus 0), anaemia (11% versus 46%), neutropenia (0 versus 36%), leukopenia (2.7% versus 14%), thrombocytopenia (1.3% versus 12%), asthenia (53% versus 69%) and mucosal inflammation (17% versus 5.4%). [2]

Summary of clinical effectiveness issues

The results of both studies indicate that erlotinib is more effective than platinum-based doublet chemotherapy in terms of PFS as first-line treatment for advanced or metastatic NSCLC with EGFR mutations. However both studies were open-label and the primary outcome was assessed by the investigator without blinding. In the EURTAC study the primary endpoint was also assessed by the independent review committee which served to support the results.

Overall survival was a secondary endpoint in both studies and available data are not yet mature. On the basis of 54 events in the EURTAC study, there was no significant difference between erlotinib and platinum-based doublet chemotherapy. Patients were permitted to cross-over from platinum-based doublet chemotherapy to erlotinib on disease progression thus confounding reported and future results on overall survival.

The OPTIMAL study was performed in patients from China and the results of this study may be less generalisable to the Scottish population. Furthermore there was a difference between the PFS results obtained with erlotinib between the two studies (9.4 months in EURTAC and 13.1 months in OPTIMAL) and the reason for this is not clear.

There is no direct clinical evidence comparing erlotinib with pemetrexed plus cisplatin and the submitting company has performed an indirect comparison using a study which compared pemetrexed/cisplatin with gemcitabine/cisplatin. Descriptive methods and assumptions were used to allow the PFS HR to be applied to the PFS results for the doublet chemotherapy arm of the EURTAC study. There is also no direct clinical evidence comparing erlotinib with gefitinib in the first-line treatment of NSCLC.

EGFR-TK mutation testing will be necessary to identify patients eligible for treatment with erlotinib in this licensed indication. Around 11% of patients with metastatic NSCLC will have an EGFR activating mutation. There are variations in the availability of EGFR testing within

Scotland and the introduction of first-line erlotinib treatment may have service implications in relation to the genetic testing.

The oral formulation of erlotinib offers an advantage in ease of administration for the patient and the service.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of a sequence of first line erlotinib therapy followed by second line pemetrexed/cisplatin, pemetrexed monotherapy or docetaxel in patients who are EGFR mutation- positive, compared to first line pemetrexed/cisplatin followed by second line erlotinib. A standard 3 health state semi-Markov model was used consisting of PFS, progressive disease (PD) and death health states. The comparator is appropriate if it is assumed that patients with non-squamous histology (those eligible for pemetrexed/cisplatin treatment), correspond to those with an EGFR M+ status. Gefitinib is also licensed for use in patients with EGFR M+ status, but SMC clinical experts did not indicate that it is used in Scottish clinical practice and it is not recommended for use by SMC.

The clinical data for the economic analysis was the EURTAC trial. However, as this contained standard doublet platinum chemotherapy as the comparator an indirect comparison was performed in order to assess the relative effectiveness of erlotinib with pemetrexed/cisplatin. Based on published meta analysis and clinical opinion an assumption of similar efficacy between the standard chemotherapy regimens in the EURTAC trial was made. This assumption was used to justify applying the PFS hazard ratio for pemetrexed versus standard doublet chemotherapy of 0.9 to adjust the PFS efficacy of the comparator arm in the EURTAC trial. The relative PFS curves for erlotinib and pemetrexed/cisplatin were derived by fitting a Weibull function to the end of the observed K-M data for PFS data from the EURTAC trial. An estimate was made of the monthly probability of death post progression. As there was cross-over of 66% of the comparator arm patients to receive erlotinib post progression in the EURTAC trial, the submitting company adjusted the comparator mortality rate associated with this to reflect an estimate that 35% of EGFR M+ patients in clinical practice in Scotland will receive second line treatment. This adjustment was based on a simple linear association between use of erlotinib and mortality rate, and had the impact of reducing the relative probability of mortality in the PD health state for the erlotinib versus pemetrexed/cisplatin treatment sequences.

Utility values for the health states were derived from a survey using the standard gamble approach in 100 members of the UK public. These utilities are published and have been applied in other National Institute for Health and Clinical Excellence (NICE) and SMC technology assessments of NSCLC products. The acquisition costs of erlotinib were based on a 'time to complete cessation' analysis which is based on a K-M analysis of data from the EURTAC trial and takes into account dose adjustment and drug discontinuation. This approach has been used before, and appears reasonable. The costs for the comparator were derived from a recent NICE appraisal of 1st line pemetrexed/cisplatin, and was based on 4 cycles of treatment as per Scottish Intercollegiate Guidelines Network (SIGN) guidance and clinical practice. Costs for drug administration, which are higher for the comparator, for AE management and for best supportive care in PFS and PD states were included and appear reasonable. The cost of EGFR M+ testing was included, based on an assumption of a cost of £140 per test and incidence of EGFR M+ patients of 10.2% of NSCLC patients in Scotland.

This was based on a review of posters on EGFR testing presented at the 2011 British Thoracic Oncology Group meeting.

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 of erlotinib. Based on the PAS, the cost per QALY was estimated at £21,491, based on incremental costs of £4,572 with PAS and a QALY gain of 0.21.

The mean life years gained were driven by greater time in PFS for the erlotinib sequence at 1.02 years compared to 0.57 years for the pemetrexed/cisplatin sequence, whereas time post progression to death was 0.83 years and 1.02 years for the erlotinib and pemetrexed/cisplatin sequences respectively. The difference in costs was associated with higher drug costs for erlotinib, the costs of EGFR testing, and costs of best supportive care (BSC) whilst in PFS, and partly offset by the higher costs of pemetrexed/cisplatin administration and costs of BSC provided after disease progression. The gain in life years and QALYs was driven by longer time spent in PFS, as less time was spent in PD for the first line erlotinib patients.

Deterministic sensitivity analysis was performed on utilities, cost assumptions, and efficacy estimates. The incremental cost effectiveness ratios (ICERs) when alternative PFS functions were applied were £15.7K/QALY to £25K/QALY with PAS. Probabilistic sensitivity analysis indicated a probability of erlotinib being cost-effective at a threshold of £20/QALY and £30K/QALY as 37% and 94% respectively based on the PAS.

The key limitations were:

- The estimate of incremental life years gained for erlotinib over pemetrexed/cisplatin is uncertain and is based on an unproven assumption of a linear association between post progression mortality rate and erlotinib use. There was some sensitivity to the estimates of post disease progression mortality associated with pemetrexed/cisplatin, with a 20% reduction resulting in an ICER of £24K/QALY with PAS. However, an improvement in overall survival for erlotinib has not been demonstrated in the EURTAC trial. Assuming no difference in overall survival between erlotinib and pemetrexed/cisplatin resulted in an ICER of £24,251 with PAS. The company explained it was not possible to robustly fit a survival function to estimate overall survival for erlotinib and pemetrexed/cisplatin and apply statistical adjustment methods to address bias associated with patient cross-over. It is uncertain what impact this analysis would have on the relative life years gained and ICER estimates for the erlotinib versus pemetrexed/cisplatin sequences.

- When exploring the use of alternative PFS curves, applying a Weibull function from the start of the trial rather than the end of the K-M plot resulted in a slightly higher ICER of £22.3K/QALY with PAS.

- The indirect comparison was limited, which increases the uncertainty around the relative PFS efficacy for pemetrexed/cisplatin used in the economic analysis. However, the pemetrexed/cisplatin HR for PFS of 0.9 was non-significant, and applying a HR of 1 in sensitivity analysis, resulted in an improved ICER of £19.3K/QALY with PAS.

- A relevant consideration is the feasibility and cost of introducing routine EGFR M+ testing, which is not current practice in Scotland. The unit cost of £140 is based on a

single Scottish treatment centre and may be too low, and does not account for the costs of setting up an EGFR testing service with appropriate capacity across treatment centres in Scotland. In sensitivity analysis a cost of £180 per test increased the ICER to £23.2K/QALY (with PAS).

Despite some limitations and uncertainties in the analysis the economic case for first line erlotinib use in patients who are EGFR M+ 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 The Roy Castle Lung Foundation.

Additional information: guidelines and protocols

SIGN published guideline number 80 "management of patients with lung cancer" in February 2005. This recommends 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. Chemotherapy is not generally recommended for NSCLC patients who are WHO performance status 3 or 4. This guideline is currently being updated and is expected to be published in autumn 2012.

NICE published clinical guideline 121 "Lung cancer. The diagnosis and treatment of lung cancer" in April 2011. This guideline states that chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0 or 1 or Karnofsky score of 80-100) 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.

The European Society of Medical Oncology published "Metastatic non-small cell lung cancer: consensus on pathology and molecular tests, first-line, second-line and third-line therapy. 1st ESMO consensus conference in lung cancer, Lugano 2010" in May 2011. This guideline recommends that EGFR somatic mutation testing should be carried out to identify patients eligible for first-line treatment with EGFR-TKIs and that patients harbouring sensitising EGFR mutations should be treated with an EGFR-TKI regardless of genotype of the sensitising mutation (del 19 versus L858R in exon 21).

The American Society of Clinical Oncology published a provisional clinical opinion "Epidermal growth factor receptor (EGFR) mutation testing for patients with advanced or non-small cell lung cancer considering first-line (EGFR) tyrosine kinase inhibitor therapy" in May 2011. This states that in the basis of results from five phase III randomised controlled trials, patients with NSCLC who are being considered for first-line therapy with an EGFR TKI (patients who have not previously received chemotherapy or an EGFR TKI) should have their tumour tested for EGFR mutations to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy.

Additional information: comparators

The current standard first-line treatment in patients with advanced disease consists of four cycles of platinum-based doublet regimens (combination of gemcitabine, vinorelbine, docetaxel, paclitaxel or pemetrexed with cisplatin or carboplatin). The EGFR-TK inhibitors, erlotinib and gefitinib, are administered continuously until disease progression or toxicity. SMC has not recommended gefitinib for use in NHS Scotland.

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)	Cost per course (£)
Erlotinib*	**150mg orally daily**	**1,523**	**6,091**
Gefitinib*	250mg orally daily	2,023	8,093
Pemetrexed Cisplatin	500mg/m^2 iv infusion day 1 75mg/m^2 iv infusion day 1	1,491	5,964
Gemcitabine plus platinum			
Gemcitabine Carboplatin	1,200mg/m^2 iv infusion day 1 and 8 575mg/m^2 iv infusion day 1	1,141	4,563
Gemcitabine Cisplatin	1,000mg/m^2 iv infusion day 1, 8 and 15 100mg/m^2 iv infusion day 1 (4-week cycle)	938	3,752
Gemcitabine Cisplatin	1,250mg/m^2 iv infusion day 1 and 8 75mg/m^2 iv infusion day 1 (3-week cycle)	827	3,308
Paclitaxel plus platinum			
Paclitaxel Carboplatin	200mg/m^2 iv infusion day 1 690mg iv infusion day 1	1,039	4,155
Paclitaxel Cisplatin	175mg/m^2 iv infusion day 1 80 mg/m^2 iv infusion day 2	719	2,876
Docetaxel plus platinum			
Docetaxel Cisplatin	75mg/m^2 iv infusion on day 1 75mg/m^2 iv infusion on day 1	1,074	4,296
Vinorelbine plus platinum			
Vinorelbine cap Cisplatin	60 to 80mg/m^2 orally day 1 and 8 75mg/m^2 iv infusion on day 1	535 to 667	2,139 to 2,667
Vinorelbine iv Cisplatin	25 to 30mg/m^2 iv infusion day 1 and 8 75mg/m^2 iv infusion on day 1	331 to 390	1,324 to 1,562

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 29 September 2011, BNF edition 61 (March 2011) or MIMs (August 2011). A body surface area of 1.8m^2 was used for dose calculations and one course comprises four cycles. *Costs for erlotinib and gefitinib were calculated on a 28 day cycle to allow comparison but erlotinib and gefitinib treatment will be continuous. At the time of the interim analysis in the EURTAC study, the median duration of erlotinib treatment was 8.2 months equating to a cost of £12,489. Costs for additional vitamin supplements for pemetrexed and corticosteroids for pemetrexed, paclitaxel and docetaxel have not been included. iv = intravenous.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 104 stage 3 or 4 NSCLC patients who are EGFR mutation positive in year 1 and 106 patients in year 5. This represents 3.8% of the estimated number of patients with NSCLC in Scotland. Based on a forecast uptake of first line erlotinib of 50% in year 1 (52 patients), and 90% in year 5 (90 patients), the impact on the medicines budget was estimated at £561K in year 1 and £1.16 million in year 5 with PAS. The net impact after displacement of first line pemetrexed/cisplatin and second line erlotinib was estimated to be £274K in year 1 and £304K in year 5 with PAS.

EGFR-TK mutation testing will be necessary and this may have additional service implications.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. Roche Registration Ltd. Tarceva summary of product characterstics, 24 August 2011

2. The European Medicines Agency (EMA). European Public Assessment Report for erlotinib (Tarceva®), www.ema.europa.eu Procedure No : EMEA/H/C/000618/II/0020

3. Rosell et al (2011). Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomised trial. Abstract 7503. ASCO 2011 Annual Meeting. Chicago. USA

4. Zhou C, Wu Y-L, 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;12:735-42.

5. Zhou et al (2011a). Updated efficacy and quality-of-life (QoL) analyses in OPTIMAL, a phase III, randomised, open-label study of first-line erlotinib versus gemcitabine/carboplatin in patients with EGFR-activating mutation-positive (EGFR Act Mut+) advanced non-small cell lung cancer (NSCLC). Abstract 7520. ASCO Annual Meeting, Chicago. USA.

This assessment is based on data submitted by the applicant company up to and including 14 November 2011.

**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. These have been confirmed from the eVadis drug database. 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.