

Resubmission

reslizumab 10mg/mL concentrate for solution for infusion (Cinqaero®)
SMC No 1233/17

Teva UK Ltd

4 August 2017 (*Issued November 2017*)

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 resubmission

reslizumab (Cinqaero®) is not recommended for use within NHS Scotland.

Indication under review: as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

Reslizumab, compared with placebo, decreased the incidence of asthma exacerbations and improved lung function in adult patients with severe eosinophilic asthma.

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

As add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.¹

Dosing Information

Reslizumab is given as an intravenous (IV) infusion once every four weeks.

Patients below 35kg or above 199kg

The recommended dose is 3mg/kg body weight. The volume (in mL) required from the vial(s) should be calculated as follows: $0.3 \times \text{patient body weight (in kg)}$.

For patients between 35kg and 199kg

The recommended dose is achieved using the vial-based dosing scheme detailed in the summary of product characteristics (SPC). This dosing scheme is based on a maximum recommended dose of 3mg/kg.

Reslizumab is intended for long-term treatment. A decision to continue therapy should be made at least annually based on disease severity and level of exacerbation control. Reslizumab should be prescribed by physicians experienced in the diagnosis and treatment of the indication.¹

Product availability date

3 October 2016 - 100mg vial / 12 October 2017 - 25mg vial.

Summary of evidence on comparative efficacy

Reslizumab is a monoclonal antibody against interleukin-5 (IL-5), a cytokine involved in the differentiation, maturation, recruitment and activation of eosinophils. Inhibiting IL-5 reduces the activity and survival of eosinophils. Reslizumab is licensed for treatment of adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment¹, i.e. in patients at British Thoracic Society (BTS) / Scottish Intercollegiate Guidelines Network (SIGN) and Global Initiative for Asthma (GINA) step 4 or 5. The submitting company requested that SMC considers reslizumab for use in patients who had at least four asthma exacerbations in the preceding year or are receiving maintenance treatment with oral corticosteroids.

Two pivotal double-blind phase III studies (3082 and 3083) recruited patients aged 12 to 75 years with asthma characterised by at least 12% reversibility after beta-agonist administration that was inadequately controlled, defined by asthma control questionnaire (ACQ) score at least 1.5, on at least medium dose inhaled corticosteroid (i.e. at least GINA step 3), equivalent to fluticasone 440micrograms daily, with or without another controller medication (e.g. oral corticosteroids at daily doses not exceeding prednisolone 10mg were permitted). Patients had blood eosinophil concentration of at least 400 per microlitre and at least one asthma exacerbation requiring corticosteroid treatment in the preceding year. Randomisation was stratified by use of regular

corticosteroid (yes or no) and region (USA or outside USA). Patients were equally assigned to reslizumab 3mg/kg intravenous (IV) infusions every four weeks or placebo for 13 doses. The primary outcome was annual frequency of asthma exacerbations, defined as a worsening of asthma requiring systemic corticosteroid or an increase in use of inhaled corticosteroid for at least three days or asthma-related emergency treatment, which was corroborated by a decrease in forced expiratory volume in one second (FEV₁) of at least 20%, a decrease in peak expiratory flow rate of at least 30% or worsening of symptoms identified by the treating physician. This was assessed in the intention-to-treat (ITT) population, which comprised all randomised patients, using a negative binomial regression model.^{2,3}

In both studies reslizumab, compared with placebo, significantly reduced the annual rate of asthma exacerbations, the primary outcome, as detailed in table 1. The difference was significant for exacerbations defined by corticosteroid use, but not in the small numbers of exacerbations requiring hospital admission or emergency treatment.^{2,3} Reslizumab was licensed for use in the subgroup of patients, comprising around 80% of the study populations, who were at GINA step 4 or 5 (i.e. severe asthma) and results in this subgroup are detailed in table 2.

Table 1: Primary outcome in studies 3082 and 3083 in total study population.^{2,3}

	Study 3082		Study 3083		Pooled data	
	Placebo	Reslizumab	Placebo	Reslizumab	Placebo	Reslizumab
	N=244	N=245	N=232	N=232	N=476	N=477
Clinical asthma exacerbations (primary outcome)						
Rate/year	1.80	0.90	2.11	0.86	1.81	0.84
Rate ratio (95% CI)	0.50 (0.37 to 0.67)		0.41 (0.28 to 0.59)		0.46 (0.37 to 0.58)	
p-value	<0.0001		<0.0001		<0.0001	

CI = confidence interval

Table 2: Results in studies 3082 and 3083 in subgroup at GINA step 4 or 5 asthma.^{2,4}

	Study 3082		Study 3083		Pooled data	
	Placebo	Reslizumab	Placebo	Reslizumab	Placebo	Reslizumab
Clinical asthma exacerbations (primary outcome)						
Rate/year	*	*	*	*	1.81	0.84
Rate ratio (95% CI)	0.50 (0.37 to 0.69)		0.34 (0.23 to 0.52)		0.44 (0.34 to 0.56)	
Change in forced expiratory volume in one second (FEV ₁) at week 52 (litres)						
Difference in LS mean (95% CI)	0.159 (0.092 to 0.227)		0.092 (0.019 to 0.166)		0.129 (0.080 to 0.179)	
Change in Asthma Control Questionnaire (ACQ-7) at week 52 (scale 0 to 6)						
Difference (95% CI)	-0.348 (-0.496 to -0.200)		-0.301 (-0.448 to -0.153)		-0.330 (-0.433 to -0.226)	
Change in Asthma Quality of Life Questionnaire (AQLQ) at week 52 (scale 1 to 7)						
Difference in LS mean (95% CI)	0.34 (0.160 to 0.519)		0.339 (0.157 to 0.521)		0.346 (0.219 to 0.473)	

Change in Asthma Symptom Utility Index (ASUI) at week 52 (scale 0 to 1)			
Difference in LS mean (95% CI)	0.073 (0.047 to 0.098)	0.053 (0.029 to 0.078)	0.064 (0.046 to 0.082)

LS = least square; CI = confidence interval. *Commercial in Confidence**

Using pooled (study 3082 and 3083) data from total study populations, rate ratios for clinical asthma exacerbation in the subgroups who had one, two, three or at least four clinical asthma exacerbations in the year before study entry were 0.68 (95% CI: 0.49 to 0.95), 0.44 (95% CI: 0.28 to 0.69), 0.39 (95% CI: 0.21 to 0.70) and 0.36 (95% CI: 0.22 to 0.58), respectively.^{2,3}

A double-blind phase III study (3081) recruited 315 patients similar to those in pivotal studies 3082 and 3083, except that there was no requirement for an asthma exacerbation in the preceding year and use of oral corticosteroids was prohibited. They were stratified by age (12 to 17 years or ≥18 years) and asthma exacerbation in preceding year (yes or no) and randomised equally to IV infusions every four weeks of reslizumab 3mg/kg, 0.3mg/kg or placebo for four doses. The primary outcome, change from baseline to week 16 in FEV₁, was assessed in the full analysis set, which comprised all randomised patients who received at least one dose of study drug, using a mixed effect model for repeated measures. The primary outcome was significantly greater in reslizumab 3mg/kg and 0.3mg/kg groups compared with placebo, with least squares (LS) mean of 286mL, 242mL and 126mL, respectively. The difference versus placebo was 160mL (95% CI: 60 to 259mL) in the 3mg/kg group and 115mL (95% CI: 16 to 215mL) in the 0.3mg/kg group. Reslizumab 3mg/kg group, compared with placebo, was associated with significant improvements in key secondary outcomes similar to those in the pivotal studies, with LS mean between treatment difference of -0.359 (95% CI: -0.577 to -0.140) for ACQ, 0.359 (95% CI: 0.047 to 0.670) for AQLQ and 0.047 (95% CI: 0.009 to 0.085) for Asthma Symptom Utility Index (ASUI).^{2,5}

A double-blind phase III study (3084) recruited 496 adults (18 to 65 years) to similar criteria as in study 3081, except that there was no requirement for a specific blood eosinophil concentration. Subjects were randomised in a 4:1 ratio, with stratification for asthma exacerbations in preceding year, to reslizumab 3mg/kg IV or placebo every four weeks for four doses. The primary analysis was a linear regression of change from baseline in FEV₁ at week 16 with model effects including treatment, baseline blood eosinophil concentration and interaction of treatment and eosinophils. There was no significant interaction between blood eosinophil concentration and change from baseline in FEV₁ at week 16. In patients with baseline eosinophils less than 400 per microlitre, the difference in change in FEV₁ from baseline to week 16 between reslizumab (n=275) and placebo (n=68) was 33mL (p=0.54); and in those with eosinophils of at least 400 per microlitre, the difference between reslizumab (n=69) and placebo (n=13) was 270mL (p=0.04). Between treatment difference in the latter subgroup was attributed to a near complete lack of change in the placebo arm. Mean change from baseline to week 16 in FEV₁ in the respective reslizumab and placebo groups was 243mL and 219mL in patients with eosinophils less than 400 per microlitre and was 253mL and -0.72mL in patients with eosinophils at least 400 per microlitre.^{2,6}

An open-label extension safety study, 3085, included 1052 patients who completed studies 3082 or 3083 or received at least two doses of study medicine in study 3081. They were given reslizumab 3mg/kg IV every four weeks for up to two years, with 488 (46%) receiving reslizumab for the first time. In reslizumab-experienced patients lung function was maintained and in reslizumab-naïve patients lung function, asthma symptoms and quality of life scores improved.²

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

Summary of evidence on comparative safety

In pooled data from placebo-controlled studies 3081, 3082, 3083, 3084 and a phase II study, Res-5-001, adverse event rates with reslizumab 3mg/kg and placebo were 67% (690/1028) and 81% (589/730), respectively. Across the groups there were similar rates of treatment-related adverse events, 12% (122/1028) and 13% (95/730) and withdrawals due to adverse events, 4.7% (48/1028) and 5.4% (40/730), respectively. Serious adverse events were reported by 6.3% (65/1028) and 9.0% (66/730) of patients in the respective groups. It was noted that there were no differences in rates of adverse events, serious adverse events, treatment-related adverse events and discontinuations due to adverse events in this pooled population compared with the “targeted” pooled cohort, which only included patients with blood eosinophil concentration of at least 400 cells per microlitre who received reslizumab 3mg/kg.²

As specified in the protocol, asthma worsening was reported as an adverse event. This was the most common adverse event, occurring within the pooled cohort in 23% (232/1028) and 40% (289/730) of patients in the reslizumab 3mg/kg and placebo groups, respectively. The next most frequent adverse events were nasopharyngitis (10% and 14%), upper respiratory tract infection (9.3% and 9.5%), headache (7.6% and 8.5%), sinusitis (5.5% and 7.0%), bronchitis (3.3% and 7.1%), urinary tract infection (3.3% and 3.4%), back pain (3.2% and 3.4%), influenza (3.2% and 5.1%), allergic rhinitis (2.7% and 3.0%), oropharyngeal pain (2.6% and 2.2%), pharyngitis (2.2% and 3.4%), cough (2.1% and 3.2%) and dyspnoea (2.1% and 2.7%). For common adverse events occurring in at least 2% of patients the incidence in the reslizumab group was the same or lower than the placebo group, except for oropharyngeal pain.²

There have been literature reports suggesting eosinophils may play an immunomodulatory role in some tumours. However, there is no definitive biological evidence that neutralisation of IL-5 or reduction of eosinophil number or function is associated with malignancy. In the pooled cohort of placebo-controlled studies malignancy was reported in the reslizumab 3mg/kg and placebo groups by 0.6% (3/1028) and 0.3% (2/730) of patients, respectively. Other adverse events of special interest include hypersensitivity reactions and myalgia. In the pooled placebo-controlled studies five patients in the reslizumab group had an anaphylactic reaction (versus none in the placebo group). Three were reported as serious treatment-related adverse events, had a temporal link to the infusion and lead to discontinuation of study treatment. Myalgia occurred in 1.0% (10/1028) and 0.55% (4/730) of patients in the reslizumab 3mg/kg and placebo groups, respectively. Elevations of creatinine phosphokinase were reported more frequently in the reslizumab group compared with placebo.²

Summary of clinical effectiveness issues

Reslizumab is the second monoclonal antibody against IL-5 licensed for the treatment of severe eosinophilic asthma in adults.¹ The first, mepolizumab,⁷ has been accepted by SMC for restricted use in patients who have eosinophils of at least 150 cells per microlitre ($0.15 \times 10^9/L$) at initiation of treatment and have had at least four asthma exacerbations in the preceding year or are receiving maintenance treatment with oral corticosteroids (SMC advice number 1149/16). Another monoclonal antibody, omalizumab,⁸ may also be a treatment option for the subgroup of patients with eosinophilic asthma who also have allergic asthma, as this medicine is licensed for use in allergic asthma. Healthcare Improvement Scotland (HIS) has endorsed the National Institute of Health and Care Excellence (NICE) multiple technology assessment number 278, which

recommends omalizumab as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged six years and older: who need continuous or frequent treatment with oral corticosteroids (defined as four or more courses in the previous year) contingent upon continuing availability of a patient access scheme.

In the two pivotal studies (3082 and 3083), reslizumab compared with placebo, significantly reduced clinical asthma exacerbation rates and improved lung function (FEV₁), asthma control (ACQ) and quality of life (AQLQ and ASUI) outcomes in the overall population and the subgroup of approximately 80% of patients at GINA step 4 or 5 (i.e. severe asthma). In the latter group, which is representative of the licensed population, rate ratio for clinical asthma exacerbations was 0.44.

The dose of reslizumab used in the pivotal studies (3mg/kg) differed slightly from the licensed dose, which is a vial-based dosing scheme for patients weighing between 35kg and 199kg. This is based on a maximum dose of 3mg/kg, using nominal vial sizes (10mL or 2.5mL). Data demonstrate no clinically meaningful difference between vial-based dosing and the 3mg/kg regimen.

There is a lack of clarity around the criteria defining eosinophilic asthma, which is characterised by a pattern of inflammatory cells in the airway. The best indicator is induced sputum eosinophil count.⁹ In the pivotal reslizumab studies asthma was defined as eosinophilic by a blood eosinophil count of at least 400 cells per microlitre. The correlation between blood eosinophilia and sputum eosinophilia is poor. However, the European Medicines Agency (EMA) regarded this as acceptable as the measurement of sputum eosinophils is not standardised or routinely available in practice.²

There are no direct comparative data relative to alternative treatment options, mepolizumab, or in the subgroup of patients who also have severe allergic asthma, omalizumab. Reslizumab was compared with these medicines in patients with severe asthma within Bayesian network meta-analyses for the outcomes of clinical asthma exacerbation rate, mean change from baseline to week 52 in FEV₁, ACQ and AQLQ, rate of serious adverse events and discontinuations due to adverse events at week 52. These suggested no differences between treatments. The analyses were limited by heterogeneity across the studies in study design, disease severity, eosinophilic phenotype, blood eosinophil concentration, concomitant asthma medications, definitions of clinically significant asthma exacerbation and adverse events. There was variation in outcomes in the common control, placebo, groups and in the inclusion of unlicensed doses. There were issues with external validity, as there were no analyses in the patient group in which reslizumab is positioned for use. Analyses of FEV₁, ACQ, AQLQ and of rates of serious adverse events and discontinuation due to adverse events were based on small numbers of studies, typically three to five. Upon request additional sensitivity analyses of clinical asthma exacerbation rates were provided, which included data from up to eight studies. These mitigate to some extent concerns relating to differences in study design, definition of clinical asthma exacerbations, variations in outcomes across the placebo control groups and use of unlicensed doses. They provide support to the assumption of similar clinical effect.

The introduction of reslizumab would provide another treatment option for patients with severe eosinophilic asthma. It is administered intravenously, whereas alternatives (mepolizumab and omalizumab) are given subcutaneously. Therefore, it may impact the service through increased time requirements for administration of an IV infusion.

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

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing reslizumab to treatment with either omalizumab or mepolizumab in adult patients with severe eosinophilic asthma at BTS/ SIGN and GINA step 4/5 who have had at least four asthma exacerbations in the preceding year or are receiving maintenance treatment with oral corticosteroids. The time horizon for the analysis was one year.

The evidence to support the equivalence between treatments, as necessary for a cost-minimisation analysis, was taken from the network meta- analyses described above. Treatments were assumed to be equally effective in terms of controlling exacerbations and also in terms of adverse events.

Costs in the analysis related to medicines acquisition costs and the costs associated with administering treatment and any associated monitoring. Omalizumab was estimated using a weighted average dose of 511mg per 4 weekly dose. Resource use related to the time taken to administer and monitor treatment was estimated using a combination of expert opinion, summary of product characteristic documents and other health technology appraisals. This resulted in 55 minutes, 40 minutes and 10 minutes of specialist nurse time being assumed for reslizumab, omalizumab and mepolizumab respectively.

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. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented and are shown in table 3.

However, PAS discounts are in place for mepolizumab and omalizumab and when estimates of these PAS were included and used for decision-making, reslizumab became less cost-effective. SMC is unable to present the results provided by the company which used an estimate of the PAS prices for omalizumab and mepolizumab, due to commercial confidentiality and competition law issues.

Table 3: Cost-minimisation analysis results without PAS

Analysis	Incremental cost versus omalizumab at list price	Incremental cost versus mepolizumab at list price
Base case- vial based dosing	£2,657 without reslizumab PAS	£3,632 without reslizumab PAS

Given the simplicity of the analysis, no sensitivity analysis was presented, other than to account for estimates of the comparator PAS discounts.

On the basis of the cost-effectiveness evidence presented, the economic case was not demonstrated.

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

Summary of patient and public involvement

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

- We received a patient group submission from Asthma UK, which is a registered charity.
- Asthma UK has received 2% pharmaceutical company funding in the past two years, including from the submitting company.
- People with severe asthma require intensive therapies to control symptoms to prevent attacks, hospitalisations and death. Symptoms include difficulty breathing and limited mobility, leaving many people housebound. Repeated hospital admissions may lead to further social isolation and economic disadvantage. Persistent symptoms may also lead to sleep deprivation, feelings of despair and depression, low activity levels, weight gain and increased dependence on family and carers.
- The side effects of medicines used in severe asthma, especially long-term oral corticosteroids, may be significant, potentially causing concern and distress to patients. There is a need for more effective therapies, particularly steroid sparing medicines for severe asthma.
- Reslizumab would provide another treatment option for this group of patients with severe asthma that has an eosinophilic phenotype. It may allow these patients to better control their symptoms and avoid some of the side-effects associated with currently available treatments.

Additional information: guidelines and protocols

In September 2016 the BTS and SIGN issued publication number 153, British guideline on the management of asthma. This recommends that omalizumab given by subcutaneous injection may be considered in patients with a high steroid burden. The good practice point is noted that omalizumab treatment should only be initiated in specialist centres with experience of evaluation and management of patients with severe and difficult asthma.¹⁰

Additional information: comparators

The relevant comparators in practice are mepolizumab or, in patients with severe allergic asthma, omalizumab.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Reslizumab	Vial-based dosing scheme based on a maximum recommended dose of 3mg/kg by IV infusion every four weeks	13,000*
Mepolizumab	100mg SC every four weeks	10,920
Omalizumab	150mg to 600mg SC every four weeks or 375mg to 600mg SC every two weeks**	3,330 to 26,640

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 03 May 2017 for mepolizumab and omalizumab; from the eMIMS on 01 June 2017 for reslizumab. Costs are based on 70kg body weight: *the SPC for reslizumab recommends using two 100mg vials for patients weighing 67 to 74 kg; ** doses vary according to IgE level. Costs calculated using the full cost of vials assuming wastage. These costs do not take account of patient access schemes. IV: intravenous, SC: subcutaneous.

Additional information: budget impact

The submitting company estimated there would be 3,699 patients eligible for treatment with reslizumab in year 1 increasing to 3,804 patients in year 5 to which confidential estimates of treatment uptake were applied.

The submitting company requested that the budget impact estimates remain in confidence.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission.

1. Teva Pharmaceuticals Ltd. Summary of product characteristics for reslizumab (Cinqaero®), last updated 11 May 2017
2. European Medicines Agency. European public assessment report for reslizumab (Cinqaero®), Committee for Medicinal Products for Human Use (CHMP) assessment report, EMA/CHMP/481610/2016, 23 June 2016.
3. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; 3(5): 355-66.
4. Commercial in Confidence*
5. Bjermer L, Lemiere C, Maspero J, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomised phase 3 study. *Chest* 2016; 150: 789-98.
6. Corren J, Weinstein S, Janka L, et al. Phase 3 study of reslizumab in patients with poorly controlled asthma. Effects across a broad range of eosinophil counts. *Chest* 2016; 150: 799-810.
7. GlaxoSmithKline. Summary of product characteristics for mepolizumab (Nucala®), last updated 21 November 2016.
8. Novartis Pharmaceuticals. Summary of product characteristics for omalizumab (Xolair®), last updated 21 September 2016.
9. European Medicines Agency. European public assessment report for mepolizumab (Nucala®), Committee for Medicinal Products for Human Use (CHMP) assessment report, EMA/CHMP/672504/2015 rev. 1, 24 September 2015.
10. British Thoracic Society and Scottish Intercollegiate Guidelines Network. SIGN publication number 153: British Guideline on the Management of Asthma, September 2016.

This assessment is based on data submitted by the applicant company up to and including 12 October 2017.

**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.