Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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brivaracetam 10mg, 25mg, 75mg, 100mg film-coated tablets; 10mg/mL oral solution; 10mg/mL solution for injection/infusion (Briviact®)

SMC No. (1160/16)

UCB Pharma Ltd

10 June 2016

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

brivaracetam (Briviact®) is accepted for restricted use within NHS Scotland.

Indication under review: Adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy.

SMC restriction: for use in patients with refractory epilepsy and treatment should be initiated by physicians who have appropriate experience in the treatment of epilepsy.

In a pooled analysis of three fixed-dose, placebo-controlled, phase III studies there were statistically significant reductions in the frequency of partial-onset seizures with brivaracetam versus placebo.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 11 July 2016

Indication

Adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy.

Dosing Information

The recommended starting dose is brivaracetam 50mg/day or 100mg/day based on physician assessment of required seizure reduction versus potential side effects. The dose should be administered in two equally divided doses, once in the morning and once in the evening. Based on individual patient response and tolerability, the dose may be adjusted in the dose range of 50mg/day to 200mg/day.

Brivaracetam may be initiated with either intravenous or oral administration. When converting from oral to intravenous administration or *vice versa*, the total daily dose and frequency of administration should be maintained. Brivaracetam solution for injection/infusion is an alternative for patients when oral administration is temporarily not feasible. There is no experience with twice daily intravenous administration of brivaracetam for a period longer than four days.

Film-coated tablets must be taken orally swallowed in whole with liquid and may be taken with or without food.

Product availability date

18 January 2016

Summary of evidence on comparative efficacy

Brivaracetam is a new anti-epileptic drug (AED) and binding to synaptic vesicle protein 2A (SV2A) in the brain is believed to be the primary mechanism of action for its anticonvulsant activity. The primary treatment of epilepsy is with AEDs, with an aim to prevent or reduce seizures as quickly as possible, resulting in reduced morbidity and mortality.[1] Recent guidance includes a number of AED for adjunctive treatment, where choice is guided by a number of factors including sex, reproductive potential, age, concomitant medications, pre-existing or co-morbid conditions, other medical or psychiatric conditions and adverse effect profiles.[2]

Evidence of efficacy comes from three, fixed-dose, placebo-controlled, double-blind, phase III studies, N01252, N01253 and N01358.[1, 3-5] These were conducted in patients aged 16 to 70 years (16 to 80 years in N01358) with well-characterised focal epilepsy or epileptic syndromes according to International League against Epilepsy (ILAE) criteria, with a history of partial-onset seizures with or without secondary generalisation. Patients were required to have ≥ two focal seizures per month for three months prior to screening and ≥ eight focal seizures during an eight-week prospective baseline period. At screening, patients were receiving one or two concomitant AEDs at a stable and optimal dosage for at least one month previously, and these were continued throughout the study. Following the baseline period, eligible patients were randomised equally to 12 weeks treatment with placebo or brivaracetam; N01252 (20mg/day, 50mg/day or 100mg/day), N01253 (5mg/day, 20mg/day or 50mg/day) and N01358 (100mg/day or 200mg/day). Brivaracetam was given orally twice daily as a fixed dose with no dose titration, and one dose reduction was permitted. Patients were stratified by concomitant use of levetiracetam in studies N01252 and N01253 (limited to 20% of the study population) and geographical region. Following completion of the 12-week treatment period, patients entered a long-term follow-up study or underwent a down-titration period.

The primary endpoint for N01252 and N01253 was percent reduction over placebo in the focal seizure frequency per week over the treatment period. This analysis used a predefined sequential procedure to control for multiplicity, starting with brivaracetam 50mg/day. The co-primary endpoints for N01358 were the percent reduction over placebo in the focal seizure frequency per 28 days over the treatment period and ≥50% responder rate (proportion of patients with ≥50% reduction in seizure frequency), which was a secondary endpoint in N01252 and N01253. Analyses were conducted in the intention to treat (ITT) population in studies N01252 and N01358 and in the modified ITT population in N01253.[1,3-5]

Only results for licensed doses of brivaracetam (50mg/day to 200mg/day) are reported in this document. There was no significant difference for brivaracetam 50mg/day versus placebo in the primary endpoint for N01252 and the study was not considered positive. In N01253 and N01358, the primary endpoints were met. Results for primary and some secondary endpoints for N01252 and N01253 are included in table 1 and for N01358 in table 2.[1, 3-5]

Table 1: results of primary and secondary endpoints for licensed doses of brivaracetam in studies N01252 and N01253. [1, 3, 4]

	Study N01252			**Study N01253**	
	Brivaracetam 50mg/day (n=99)	**Brivaracetam 100mg/day (n=100)**	**Placebo (n=100)**	**Brivaracetam 50mg/day (n=101)**	**Placebo (n=96)**
Primary endpoint					
Median POS frequency/week at baseline	1.80	2.0	2.1	2.9	2.6
Median reduction in focal seizure frequency/week over placebo, %	6.5%	12%	-	13%	-
p-value	p=0.261	p=0.037 (nominal)	-	p=0.025	-
Secondary endpoints					
≥50% responder rate, % (n/N)	27% (27/99)	36% (36/100)	20% (20/100)	33% (33/101)	17% (16/96)
Proportion of patients seizure free, % (n/N)	0%	4.0% (4/100)	0%	4.0% (4/101)	0%
p-value	p=0.339	p=0.023	-	p=0.008	

POS=partial-onset seizure

Table 2: results of co-primary and secondary endpoint for licensed doses of brivaracetam in study N01358. [1, 5]

	Brivaracetam 100mg/day (n=252)	**Brivaracetam 200mg/day (n=249)**	**Placebo (n=259)**
Co-primary endpoints			
Median POS frequency/28 days at baseline	9.5	9.3	10.0
Median reduction in focal seizure frequency/28 days over placebo, %	23%	23%	-
p-value	p<0.001	p<0.001	-
≥50% responder rate, % (n/N)	39% (98/252)	38% 94/249)	22% (26/259)
p-value	p<0.001	p<0.001	-
Secondary endpoint			
Proportion of patients seizure free, % (n/N)	5.2% (13/252)	4.0% (10/249)	0.8% (2/259)

POS=partial-onset seizure

In studies N01252 and N01253, health related quality of life was assessed using a number of tools including the Hospital Anxiety and Depression Scale (HADS) score, Patient's Global Evaluation Scale (P-GES) and the Investigator's Global Evaluation Scale (I-GES) (where improvement in disease was defined as slight, moderate, or marked improvement). For the HADS subscales of anxiety and depression, there was no clinically significant difference for any brivaracetam dose over placebo. Results of the P-GES and I-GES for study N01252 indicated that both patients and investigators considered that more patients treated with brivaracetam improved compared with placebo and this was statistically significant for the brivaracetam 100mg/day group. In N01253, similar proportions of patients in the brivaracetam and placebo groups considered that their disease improved after treatment and a larger proportion of patients was considered by the investigator to have improved after treatment with brivaracetam compared with placebo, although the difference was not statistically significant. [1]

A pooled analysis of studies N01252, N01253 and N01358, excluding patients on concomitant levetiracetam (around 19% of patients in studies N01252 and N01253), has been reported and is of relevance to the licensed indication. There were statistically significant reductions over placebo in partial-onset seizure frequency per 28 days for brivaracetam 50mg/day (20%), brivaracetam 100mg/day (24%) and brivaracetam 200mg/day (24%). The ≥50% responder rates were 34% (55/161) for brivaracetam 50mg/day, 39% (131/332) for brivaracetam 100mg/day, 38% (94/249) for brivaracetam 200mg/day and 20% (85/418) for placebo (all p≤0.001 versus placebo). The proportions of patients who were seizure-free during the entire treatment period were 2.5% (4/161) for brivaracetam 50mg/day, 5.1% (17/332) for brivaracetam 100mg/day, 4.0% (10/249) for brivaracetam 200mg/day and 0.5% (2/418) for placebo.[1]

Two long-term open-label studies are on-going, where patients were treated with brivaracetam at a starting dose from the previous study and the dose was adjusted up to 200mg/day. Interim analyses of these studies are available. In study N01125, 853 patients were recruited, and at the clinical cut-off (17 January 2014), where there was up to 96 months exposure to brivaracetam, 293 patients were still on treatment. The median reduction from baseline in seizure frequency per 28 days was 42% in patients with partial-onset seizures on treatment. The proportion of patients with partial-onset seizures on treatment who were ≥50% responders was 43%. In study N01199, 668 patients were recruited, and at the clinical cut-off (when there was up to 90 months exposure to brivaracetam), 239 patients were still on treatment. The median reduction from baseline in seizure frequency per 28 days was 55% for patients on treatment. The proportion of patients on treatment who were ≥50% responders was 54%.[1]

Summary of evidence on comparative safety

There are no safety data versus an active comparator. Overall, the European Medicines Agency (EMA) noted that the safety profile of brivaracetam was acceptable and as expected based on experience with levetiracetam. Pooled safety data from the pivotal studies described previously have been reported. Investigator determined drug related adverse events occurred in 47% (94/200), 40% (141/353), 44% (109/250) and 30% (139/459) of patients in the brivaracetam 50mg/day, brivaracetam 100mg/day, brivaracetam 200mg/day and placebo groups respectively. Investigator determined drug-related serious adverse events occurred in 0.5% (1/200), 0.8% (3/353), 0.8% (2/250) and 0.4% (2/459) of patients in the brivaracetam 50mg/day, brivaracetam 100mg/day, brivaracetam 200mg/day and placebo groups respectively.[1]

The most common treatment-emergent adverse events (occurring in ≥5% of patients in any group) were somnolence (14% [all doses of brivaracetam] versus 8.5% [placebo]), dizziness (11% versus 7.2%), headache (10.0% versus 10.2%) and fatigue (8.2% versus 3.7%).[1]

Psychosis is considered to be more prevalent in patients with epilepsy and AEDs can induce psychotic disorders. Given the reports of psychosis from the brivaracetam clinical studies, and that a causal relationship with brivaracetam could not be excluded, psychotic disorder has been included in the undesirable effects section of the summary of product characteristics (SPC). Patients treated with brivaracetam have reported suicidal ideation/behaviour, and suicidal ideation has also been included as an AED class warning uncommon adverse drug reaction in the SPC.[1,6]

Summary of clinical effectiveness issues

Brivaracetam is licensed as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy.[6] Scottish Intercollegiate Guidelines Network (SIGN) guidance advises consideration of combination therapy when monotherapy with two, first-line AEDs has failed or when improved control occurs during the process of phased substitution. It recommends the use of carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide in the adjunctive treatment of focal epilepsy.[2] Around 20% to 30% of newly diagnosed patients will have drug resistant epilepsy. The International League against Epilepsy (ILAE) defines drug-resistant epilepsy as failure of adequate trials of two tolerated and appropriately chosen AED schedules, whether as monotherapies or in combination, to achieve sustained seizure freedom.[1] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area in patients with treatment resistant/refractory epilepsy.

In two of the pivotal studies, the primary endpoint of median reduction over placebo for focal seizures per week (per 28 days for study N01358) was significantly superior for brivaracetam versus placebo. However, there was no significant difference in study N01252. The median reduction over placebo for focal seizures per 28 days was superior for brivaracetam in the pooled analysis, which excluded patients who were on concomitant levetiracetam. Subgroup analyses of studies N01252 and N01253 showed no benefit for brivaracetam in patients taking concomitant levetiracetam.[1] This is noted in the SPC for brivaracetam.[6] The preferred outcome for the EMA is 50% responder rate, which was a co-primary outcome for study N01358 and a secondary outcome for the other studies. Brivaracetam was significantly superior to placebo for ≥50% responder rates only in studies N01253 and N01358 and the pooled analysis.[1] The studies were initiated before the ILAE definition of drug-resistant epilepsy was agreed. Therefore, patients recruited to the studies were not required to have failed on two adequate trials of AED regimens. However, the EMA considered the study populations to be drug-resistant based on their high baseline seizure frequency and inadequate seizure control with at least one AED trial.[1]

In the interim analyses of the long-term studies, the proportions of patients who discontinued due to lack of efficacy were high. The EMA noted that a selection bias may be present as patients who entered these studies may have responded better compared to those who discontinued from the initial double-blind studies. Therefore, limited conclusions can be drawn from the long-term studies.[1]

Clinical experts consulted by SMC reported a range of AEDs used as adjunctive treatment, which included levetiracetam, eslicarbazepine, lacosamide, zonisamide, retigabine and perampanel. This is supported by treatment guidelines. The submitting company considers the key comparator to be lacosamide, which SMC has accepted, restricted for use in refractory epilepsy. The company chose this comparator based on lacosamide having the highest market share of the AEDs only licensed for adjunctive treatment. However, the validity of this approach is in question given the range of AEDs described by clinical experts. Comparative efficacy data to support the cost minimisation analysis in the economic case come from a matching adjusted indirect comparison (MAIC). This included three studies each for brivaracetam and lacosamide. The efficacy outcomes reported were percentage reduction in partial-onset seizure frequency, 50% responder rate and proportion of patients who were seizure free. Two safety outcomes, rate of discontinuation due to adverse events and rate of serious adverse events, were reported. Following propensity score matching, undertaken to adjust for remaining differences in baseline characteristics, there was no significant difference between treatments for the efficacy and safety outcomes analysed. The key limitation of the MAIC is the focus on one comparator, lacosamide.

The submitting company noted that a network meta-analysis (NMA) has been undertaken comparing brivaracetam with eslicarbazepine, lacosamide, perampanel and retigabine for adjunctive treatment of partial-onset seizures. However, while data from the NMA were not presented in the company's submission, the NMA report was supplied in the reference pack provided by the company.[7] A total of 21 studies were identified which met the inclusion criteria and included brivaracetam or comparator. For each intervention, doses (within the licensed range) were pooled. Four efficacy, five safety and two tolerability outcomes were reported and were synthesised in separate NMAs. The 50% responder rate was assessed although percent reduction over placebo in partial onset seizures frequency was not. Results showed no significant differences between any adjunctive anti-epileptic drugs for partial-onset seizures. The search strategy has not been appraised which is a limitation. Furthermore levetiracetam was not included in the NMA.

Clinical experts consulted by SMC considered that the place in therapy of brivaracetam is as add-on treatment of refractory epilepsy. The availability of brivaracetam will offer another AED for clinicians to consider when adjunctive treatment is required.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing brivaracetam as adjunctive therapy with lacosamide for the treatment of partial-onset seizures with or without secondary generalisation in adults and adolescent patients from 16 years of age with epilepsy. SMC clinical experts highlighted that a number of therapies may be displaced.

The efficacy and safety data to support the cost-minimisation analysis came from findings of the MAIC, described above. On the basis of no significant differences between the treatments, the company asserted that a cost-minimisation analysis was appropriate. The results were presented over a two year time horizon.

Costs in the model related to medicine acquisition costs for both treatments for the maintenance phase of treatment only. Lacosamide was associated with lower medicine acquisition costs in the titration phase; however, the submitting company indicated that, as titration would be associated with other health care costs for monitoring, it was reasonable to assume that any cost difference in the titration phase would be considered negligible and thus to focus the analysis only on maintenance phase costs. No adverse events were considered in the base case analysis on the basis of no significant differences in rates between treatments.

The results indicated that brivaracetam costs £3,080 over the two year time horizon compared to £3,082 for lacosamide. Thus brivaracetam costs £2 less per patient than lacosamide.

The company have performed two sensitivity analyses; including serious adverse events and applying different discount rates. The analysis with the inclusion of adverse events was based on lacosamide being associated with numerically higher adverse events rates in the indirect treatment comparison. The results were not sensitive to these scenarios and resulted in greater cost savings.

The main weaknesses of the analyses are;

- The company excluded the costs of the titration phase from the analysis on the basis that if monitoring costs of the titration phase were included along with the medicines costs in the phase, the overall costs would be similar and thus focused only on the maintenance phase. On request, the company subsequently provided formal analysis to support this statement, and this demonstrated that including medicines and other costs associated with titration resulted in brivaracetam remaining cost-saving.
- There is some uncertainty over the most appropriate comparator. SMC experts highlighted that there are a number of comparators currently used in clinical practice but the base case analysis only compared to lacosamide. However, the company provided some additional analysis to indicate that brivaracetam could also be considered a cost-effective treatment option versus eslicarbazapine or perampanel.

Despite these issues, the economic case has been demonstrated.

Summary of patient and public involvement

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

- A submission was received from Epilepsy Scotland, which is a registered charity.
- The patient group has received 3.4% pharmaceutical company funding in the past two years, but none from the submitting company.
- Epilepsy varies widely in its severity and impact and can be a profoundly disabling condition for those who are unable to control their seizures. Difficulties include unpredictability of seizures and injuries caused, side effects of medications, loss of employment, stigma/discrimination, inability to drive and restrictions on other activities, poor self-esteem, tiredness, anxiety and depression, poor memory and loss of motor skills, reliance on carers, social isolation, cognitive impairment, feeling unable to go out in public or carry out tasks alone, seizure activity or medication triggering anger/rage episodes.
- Currently available medicines reduce seizure frequency and severity for the majority of patients. However, debilitating side effects are commonly experienced, which can also have a psychological impact. This leads to some patients to stop taking their medication.

- A new clinically effective drug for epilepsy would offer more individuals the opportunity to control or reduce seizures. Controlling individuals' seizures may in turn reduce their risk of epilepsy-related death, seizure-related injury, cognitive impairment and loss of brain function. Rates of anxiety, depression, suicide and unemployment are higher among people with epilepsy. Better seizure control could also help to address these issues.

Additional information: guidelines and protocols

SIGN published guideline number 143 Diagnosis and management of epilepsy in adults, in May 2015. This document states that once two AEDs have failed as monotherapy the chance of seizure freedom with further monotherapy is low and that combining AEDs may help to improve seizure control. The patient should be established on the best combination at the optimal dose, ie one that produces best efficacy with fewest adverse effects. Choice of adjunctive AED will depend on a number of factors including sex, reproductive potential, age, concomitant medications, pre-existing or co-morbid conditions, other medical or psychiatric conditions and adverse effect profiles. The guideline recommends that for adjunctive treatment of focal epilepsy, carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used. Lamotrigine, levetiracetam, ethosuximide, sodium valproate and topiramate may be used in the adjunctive treatment of generalised epilepsy. The choice of drugs in combination should be matched to the patient's seizure type(s) and should, where possible, be limited to two, or at most three, antiepileptic drugs.[2]

The National Institute for Health and Care Excellence (NICE) published clinical guideline number 137 Epilepsy, in January 2012. This recommends that adjunctive or 'add-on' therapy should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. The choice of AED should be based on the presenting epilepsy syndrome, or, if this is not clear at the time of presentation, on the presenting seizure type. The guidance recommends carbamazepine or lamotrigine as the first-line therapy for focal seizures; if the first AED tried is ineffective then an alternative may be tried from among these five AEDs: lamotrigine, carbamazepine, levetiracetam, oxcarbazepine or sodium valproate. In patients with refractory focal seizures, adjunctive treatment may be offered with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate. If adjunctive treatment is unsuccessful, then a tertiary epilepsy specialist may consider treatment with eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.[8]

The guidelines predate the availability of brivaracetam.

Additional information: comparators

The majority of AEDs can be used within their licensed indications as adjunctive treatment for partial-onset seizures with or without secondary generalisation. The newer AEDs are used as adjunctive therapy in patients not controlled with monotherapy.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
brivaracetam	**25mg to 100mg orally twice daily**	**1,685**
lacosamide	100mg to 200mg orally twice daily	1,126 to 1,874
perampanel	4mg to 12mg orally once daily	1,820
eslicarbazepine acetate	800mg to 1,200mg orally once daily	1,650 to 2,475
pregabalin	50mg to 200mg orally three times daily	1,193
zonisamide	300mg to 500mg orally daily in one or two divided doses	1,162 to 1,936
retigabine	200mg to 400mg orally three times daily	1,012 to 1,660
tiagabine	5mg to 15mg orally three times daily	568 to 1,705
lamotrigine	50mg to 200mg orally twice daily	520 to 1,526
oxcarbazepine	300mg to 1,200mg orally twice daily	100 to 1,127
topiramate	100mg to 200mg orally twice daily	61 to 187
levetiracetam	500mg to 1,500mg orally twice daily	58 to 167
gabapentin	300mg to 1,200mg orally three times daily	51 to 222

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis, on 30 March 2016. Costs are for oral solid dosage forms and dosing regimens are for adults. Costs do not take any patient access schemes into consideration. This is not an exhaustive list of AED licensed for adjunctive treatment.

Additional information: budget impact

The gross impact on the medicines budget was estimated to be £35k in year 1 and £714k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be cost neutral in year 1 and a saving of around £500 in year 5. These estimates were based on confidential estimates of patient numbers and treatment uptake.

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

References

The undernoted references were supplied with the submission.

1. European Medicines Agency. Assessment report for brivaracetam (Briviact). 2015.

2. Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults; SIGN 143. 2015.

3. Ryvlin P, Werhahn KJ, Blaszczyk B et al. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: Results from a double-blind, randomized, placebo-controlled trial. Epilepsia. 2014;55(1):47-56.

4. Biton V, Berkovic SF, Abou-Khalil B et al. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: A phase III randomized, double-blind, placebo-controlled trial. Epilepsia. 2014;55(1):57-66.

5. Klein P, Schiemann J, Sperling MR et al. A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. Epilepsia. 2015;56(12):1890-8.

6. Brivaracetam film-coated tablets (Briviact). Summary of product characteristics. UCB Pharma Ltd.Last updated 14 January 2016.

7. UCB Data on File (NMA of adjunctive AEDs for POS). 2015

8. National Institute for Health and Care Excellence. Epilepsy, clinical guideline number 37. 2012.

This assessment is based on data submitted by the applicant company up to and including 13 May 2016.

**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.

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.