Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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fampridine 10mg prolonged-release tablets (Fampyra®) SMC No. (789/12)

Biogen Idec Ltd

07 October 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

fampridine (Fampyra®) is not recommended for use within NHS Scotland.

Indication under review: For the improvement of walking in adult patients with multiple sclerosis (MS) with walking disability (EDSS [expanded disability status scale] 4 to 7).

In two short-term, randomised, double-blind, phase III studies, significantly higher proportions of patients in the fampridine than placebo groups were considered responders, as assessed using the timed 25 foot walk test.

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

The submitting company has indicated its intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Improvement of walking in adult patients with multiple sclerosis (MS) with walking disability (EDSS [expanded disability status scale] 4 to 7).

Dosing Information

Fampridine 10mg, twice daily, taken 12 hours apart (one tablet in the morning and one tablet in the evening), without food.

Starting and evaluating fampridine treatment

- Initial prescription should be limited to two weeks of therapy as clinical benefits should generally be identified within two weeks after starting fampridine
- A timed walking test, eg, the timed 25 foot walk (T25FW), is recommended to evaluate improvement after two weeks. If no improvement is observed, fampridine should be discontinued
- Fampridine should be discontinued if benefit is not reported by patients.

Re-evaluating fampridine treatment

If decline in walking ability is observed physicians should consider an interruption to treatment in order to reassess the benefits of fampridine. The re-evaluation should include withdrawal of fampridine and performing the walking test. Fampridine should be discontinued if patients no longer receive walking benefit.

Treatment with fampridine is restricted to prescription and supervision by physicians experienced in the management of MS.

Product availability date

20 July 2011

Summary of evidence on comparative efficacy

Multiple sclerosis (MS) is an inflammatory condition that damages the myelin of the central nervous system and causes neurologic impairment and often severe disability. Fampridine is a selective potassium channel blocker which readily crosses the blood-brain barrier due to its lipid solubility. It acts on damaged nerves, where it prevents charged potassium particles from leaving the nerve cells, which is believed to allow electrical impulses to continue travelling along the nerves to stimulate the muscles, making it easier to walk. Fampridine is available as a prolonged-release tablet which reduces peak plasma concentration-associated adverse events and is the first treatment licensed to improve walking in patients with MS.[1]

Evidence of efficacy comes from two similar, double-blind, randomised, placebo-controlled, phase III studies, MS-F203 and MS-F204, and their open-label extensions. Patients aged 18 to 70 years were recruited to the studies if they had confirmed MS (as defined by McDonald criteria) and were able to complete two trials of the timed 25 foot walk (T25FW) in an average time of 8 to 45 seconds at screening. Exclusion criteria included onset of MS exacerbation within 60 days of screening and a history of seizures.[1-5]

Following a two-week, single-blind, placebo run-in phase, patients were randomised (in a ratio of 3:1 in MS-F203 and 1:1 in MS-F204) to fampridine 10mg prolonged-release tablets orally twice daily or

placebo for 14 weeks in MS-F203 and nine weeks in MS-F204, followed by a two to four week period of no treatment. Restrictions on changes in concomitant medications were specified to avoid related changes in MS symptoms during the studies.

The primary efficacy outcome for both studies was the proportion of timed walk responders, measured using T25FW. A responder was defined as a patient with a faster walking speed for at least three of the four visits during the double-blind treatment period than the maximum speed for any of first five off-drug visits (four before double-blind treatment and one at two weeks after discontinuation of treatment). Results for the primary outcome for studies MS-F203, MS-F204 and pooled analysis are included in table 1, below.[2, 3]

Table 1: primary outcome from MS-F203, MS-F204 and the pooled analysis[2-4]

	MS-F203		**MS-F204**		**Pooled analysis**	
	fampridine (n=224)	placebo (n=72)	fampridine (n=119)	placebo (n=118)	fampridine (n=343)	placebo (n=190)
Timed walk responder, % (n/N)	35% (78/224)	8.3% (6/72)	43% (51/119)	9.3% (11/118)	38% (129/343)	8.9% (17/190)
Odds ratio, (95% CI), p-value	4.8 (2.1 to 10.9) p<0.0001		8.1 (3.7 to 17.7) p<0.0001		NR p<0.0001	

CI=confidence interval, NR=not reported

In study MS-F203, two outcomes were pre-specified as primary measures to validate the clinical significance of the T25FW responder results. Firstly, the MS walking scale (12 item) (MSWS-12) was compared between the timed walk responders and timed walk non-responders, regardless of study treatment. MSWS-12 captured patients' perspectives on their ambulatory disability over 12 domains: function (walking, running, climbing stairs, standing and balancing) and quality (distance, effort, need for support outdoors/indoors, speed, smoothness and required mental concentration). The results indicated that self-assessed ambulation-related disability was reduced in patients considered to be timed walk responders (regardless of study treatment). Secondly, change in walking speed from baseline to the last observed visit was compared for fampridine timed walk responders (0.51 feet/second) versus placebo-treated patients (0.10 feet/second) and was statistically significant.[1,2] These outcomes were analysed post hoc for study MS-F204 and were similar to those reported for MS-F203.[3]

In MS-F204, the only pre-specified secondary endpoint was lower extremity manual muscle testing (LEMMT). This measured strength in four muscle groups bilaterally (hip flexors, knee flexors and extensors, and ankle dorsiflexors) with the modified British Medical Research Council scale. In MS-F204, the mean change in LEMMT score from baseline (of around 3.9 units) was 0.145 for fampridine-treated timed walk responders versus 0.042 for placebo (nominal p=0.028). In MS-F203, the mean change in LEMMT score from baseline (of around 4.0 units) was 0.18 for fampridine-treated timed walk responders versus 0.04 for placebo (nominal p=0.0002).

Subject global impression (SGI) and a clinician global impression (CGI) (secondary validation variables for study MS-F203) were reported for timed walk responders versus timed walk non-responders, regardless of study treatment. For SGI, patients rated their perception of the effects of the study medication on their physical wellbeing during the preceding week with a seven point scale (1=terrible to 7=delighted). For CGI, the supervising clinician judged the patient's neurological condition on a seven point scale (1=very much improved to 7=very much worse) relative to the screening visit. Timed walk responders had more positive SGI scores and were rated more improved

on CGI score than were timed-walk non-responders. These outcomes were analysed post hoc for study MS-F204 and were similar to those reported for MS-F203.[2,3]

In post hoc analyses, treatment with fampridine compared with placebo generally resulted in statistically significant improvements in walking speed, MSWS-12 score, LEMMT score and Ashworth score (spasticity examination which assessed muscle tone) in both studies.[1-3]

Patients who had not discontinued the pivotal studies prematurely entered the extension studies, MS-F203EXT (n=269) and MS-F204EXT (n=214). Following the two to four week off-treatment period, all patients commenced fampridine 10mg prolonged-release tablets twice daily for up to 36 months. The mean treatment exposure was 39 months and 26 months in MS-F203EXT and MS-F204EXT respectively. The mean improvement from baseline in walking speed in patients considered fampridine-treated timed walk responders in the double-blind studies was lost when patients entered the extension study (due to the two to four week off-treatment period). By eight weeks, the mean improvement in walking speed was 0.24 feet/second (from a baseline of 2.11 feet/second) in MS-F203EXT and 0.27 feet/second (from a baseline of 2.33 feet/second) in MS-F204EXT. However, at the end of the extension studies, the mean walking speed was similar to or slightly below baseline levels.[5]

In a randomised, multicentre, double-blind, exploratory phase II study (MOBILE) conducted in patients with MS and a EDSS score of 4 to 7, patients (following a two-week screening period) were randomised equally to fampridine 10mg prolonged-release tablets orally twice daily (n=68) or placebo (n=64) for 24 weeks. There were no pre-specified primary or secondary endpoints. There were greater median improvements in MSWS-12 score for fampridine over placebo during the 24-week treatment period. The 29-item MS impact scale (MSIS-29) physical subscale assessed the impact of MS on quality of life and there were greater improvements from baseline for fampridine than placebo. However there were no differences between the two groups in utility and visual analogue scale scores derived from the EuroQoL-5 Dimensions 5-level (EQ-5D-5L).[6] In a post hoc analysis, fampridine-treated responders (MSWS-12 score of ≥8 points over 24 weeks [n=27]) had an improvement in EQ-5D-5L utility score compared with fampridine-treated non-responders (MSWS-12 score of <8 points over 24 weeks [n=29]) where there was a decline.[7]

An open-label, 48-week, phase IV non-comparative study (ENABLE) provided quality of life data in 835 patients treated with fampridine prolonged-release 10mg twice daily. The primary outcome was change from baseline in the Short-Form Health Survey (SF-36) physical component summary (PCS) (range 0 to 100, where an increase in score indicates improvement). There were significant and clinically (at least two points) meaningful improvements in SF-36 PCS scores from baseline to week 12 (4.30 units), 24 (3.75 units), 36 (3.46 units) and 48 (3.24 units). There were also significant improvements from baseline in secondary health measures in patients on treatment.[8]

Summary of evidence on comparative safety

In pooled analysis of the pivotal studies (MS-F203 and MS-F204), any treatment-emergent adverse event was reported by 84% (294/348) and 72% (137/191) of patients in the fampridine and placebo groups respectively and serious treatment-emergent adverse events were reported in 6.3% (22/348) and 1.6% (3/191) of patients respectively. Treatment-related adverse events occurred in 26% (89/348) and 18% (34/191) of patients in the respective groups. The proportion of patients who discontinued treatment due to adverse events was 3.2% (11/348) in the fampridine group and 2.1% (4/191) in the placebo group.[4]

The most common adverse events in the fampridine and placebo groups respectively were: fall (16% versus 18%), urinary tract infection (15% versus 10%), insomnia (9.2% versus 2.6%), dizziness (8.3% versus 2.6%), headache (6.9% versus 3.1%), asthenia (6.6% versus 4.7%), nausea (6.6% versus 2.1%), upper respiratory tract infection (6.0% versus 7.9%), balance disorder (5.7% versus 1.6%), back pain (5.5% versus 1.6%), MS relapse (5.5% versus 3.7%), fatigue (5.2% versus 3.1%) and arthralgia (2.9% versus 5.2%). There were two reports of seizures, one in the fampridine group (a focal seizure involving the right extremity in the context of severe sepsis associated with community-acquired pneumonia) and one in the placebo group (presumed complex partial seizure).[4]

In the extension studies (MS-F203EXT and MS-F204EXT), the most common adverse events were urinary tract infections, falls, MS relapses, arthralgia and peripheral oedema and no new safety signals were identified. Four patients had seizure-related adverse events and all had previously received fampridine in the double-blind studies.[5]

Summary of clinical effectiveness issues

Current treatments for MS include symptom control (mainly of complications), modification of acute relapses (corticosteroids) and modification of the course of the disease (eg, immunomodulators [beta-interferons, glatiramer and natalizumab] and immunosuppressants [mitoxantrone, azathioprine]). Fampridine has conditional marketing authorisation from the European Medicines Agency (EMA) and is the first treatment licensed to improve walking in patients with MS. The EMA considered that the availability of fampridine addressed unmet need; this was also noted by clinical experts consulted by SMC. The National Institute for Health and Care Excellence (NICE) guideline on management of MS in adults recommends that patients with mobility problems should have access to an assessment to establish individual goals and discuss ways in which to achieve them. This would usually involve rehabilitation specialists and physiotherapists with expertise in MS. This was confirmed by clinical experts consulted by SMC.[1,9]

In the pivotal studies, significantly higher proportions of patients treated with fampridine than placebo were considered responders when assessed using the T25FW. Around 70% of patients received concomitant immunomodulating therapy.[2,3] In both studies (pre-specified in MS-F203 only), results of the MSWS-12 outcome indicated that self-assessed ambulation-related disability was reduced in patients considered to be timed walk responders (regardless of study treatment). The EMA considered that clinical validation of the primary endpoint had been shown.[1] Analysis of all other endpoints for patients randomised to the fampridine and placebo groups was performed post hoc.

Approximately one third of patients treated with fampridine were classed as responders showing improvement in walking speed. The EMA considered that the efficacy data allowed a population who will benefit from fampridine to be defined. Consequently, criteria for selecting responders and discontinuing treatment were included in the summary of product characteristics (SPC) for fampridine. This requires assessment after two weeks treatment using a timed walked test such as the T25FW. Fampridine should be discontinued if no benefit is reported by patients.[1,10]

The EMA acknowledged that there is a relationship between walking speed and walking distance. However, in the pivotal studies, the range of walking speeds was lower than those from the published studies that support the relationship. Furthermore, the EMA noted that other aspects of walking (eg, balance, endurance as well as walking distance) are relevant and additional data from a clinical study were required. These are to be obtained from a double-blind, placebo-controlled, long-term efficacy and safety study (ENHANCE) as part of the conditional marketing authorisation. Results are expected to be available in the near future.[1,11]

Increased risk of seizures whilst on fampridine treatment is expected given its mode of action. However, patients were excluded from the pivotal studies if they had a history of seizures or evidence of epileptiform activity at screening. The EMA noted that the safety of fampridine in seizure-susceptible patients (applicable to MS patients who have a higher risk of seizures) might be different.[1] Fampridine is contraindicated in patients with prior history or current presentation of seizure; it should be administered with caution in the presence of any factors which may lower seizure threshold and discontinued in patients who experience a seizure while on treatment.[10]

The EMA considered that there were sufficient long-term safety data from the extension studies as toxicity would be unlikely to increase over time. However, the proportions of patients who withdrew were high; 43% (115/269) in MS-F203EXT and 32% (68/214) in MS-F204EXT. Furthermore, it was unclear whether the decline in walking speed over time in these studies was due to progression of disease or lack of maintenance of effect. The SPC includes guidance on re-evaluating efficacy when physicians observe a decline in walking ability, by stopping treatment and performing the walking test.[1,10]

Fampridine has a narrow therapeutic index. The proportion of patients aged ≥65 years who were recruited to the pivotal phase III studies and a dose-finding phase II study was small. The SPC recommends checking renal function before commencing treatment and fampridine is contra-indicated in patients with mild, moderate or severe renal impairment.[1, 10]

The supportive, exploratory study (MOBILE) had some imbalances between groups in terms of baseline characteristics. Furthermore, no difference between groups was shown in quality of life when the generic EQ-5D-5L tool was used.[6]

Clinical experts consulted by SMC considered that fampridine is a therapeutic advancement. They noted that use, following a thorough assessment, may be considered in patients able to walk with aids, with ongoing assessment required to assess response.

Summary of comparative health economic evidence

A cost-utility analysis was presented comparing prolonged-release fampridine with best supportive care in patients with MS with walking disability. A health care perspective was taken in the base case and a societal perspective was explored in a sensitivity analysis. A relatively short time horizon of 5 years was used as this was considered sufficient to capture most of the relevant costs and outcomes. The results were not sensitive to alternative longer time horizons.

A simple decision tree, determining responder and non-responder status, followed by a cohort Markov model, was used to simulate outcomes with and without fampridine treatment. The Markov model contained four health states: responding to treatment, withdrawn from treatment, continuing with best supportive care and death.

The key clinical data used in the model were taken from the MOBILE study and a pooled analysis of MS-F203 and MS-F204 studies. Important model parameters estimated from these data are the responder rates, definition of response, and health state utility values.

The responder rates used in the base case analysis used the definition of response from the MOBILE study (improvement of ≥8 points on the MSWS-12 over 24 weeks) applied to the data from the pooled analysis of the MS-F203 and MS-F204 studies. Alternative responder rates using the definition of response and clinical data from the pooled analysis of MS-F203 and MS-F204 studies were used in a sensitivity analysis. Alternative responder definitions were also explored in sensitivity analyses.

Treatment discontinuation rates used in the model were based on data from the pooled analysis of MS-F203EXT and MS-F204EXT.

Health-related quality-of-life data collected using the EQ-5D survey questionnaire from the MOBILE study provided the key utility weights in the model. Declines in mobility for the BSC and non-responders were estimated based on the ENABLE study.

Medicines costs for fampridine were included. No administration costs were applied. Monitoring costs included a single GP visit at 4 weeks. It was assumed that there were no additional monitoring costs. Additional resource use by patients including outpatient visits in various specialties and primary care were estimated for each treatment group. This was based on data from a German disease registry. Treatment group resource use was estimated by taking the average resource use one year before and one year after initiation of fampridine treatment.

A Patient Access Scheme (PAS) was proposed by the submitting company for fampridine and has been assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount is offered on the price of fampridine. 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.

The base case analysis presented by the submitting company produces an incremental cost-effectiveness ratio (ICER) of £52,710 without PAS.

One-way sensitivity analysis, probabilistic sensitivity analysis and scenario analysis were presented. Using alternative responder rates from the pooled analysis of MS-F203EXT and MS-F204EXT studies, the ICER was £48,516. If response rates and utility weights from the ENABLE study (EQ-5D) are used, the ICER is £135,406. Using the alternative SF-36 derived utility weights from the ENABLE study, the ICER is £121,281. It should be noted that the analysis of ENABLE data was based on a comparison of fampridine responders and non-responders (there was no placebo control group). This may be biased as an estimate of treatment effect by the selection into the two groups based on treatment response at week 4, ie, the responders may be expected to do better in the long term compared to the non-responders even in the absence of subsequent treatment.

The key weaknesses with the analysis are:

- In several analyses informing key model parameters it was assumed that non-responders and control group patients had the same outcomes and could therefore be pooled in the analysis of EQ-5D and other data. This may be inappropriate. Most importantly, this is an issue in the base case analysis health state utility weights which are derived from EQ-5D data from the MOBILE study. Two utility weights are estimated; a weight for responders and a weight for 'withdrawn from treatment'/best supportive care. The 'withdrawn from treatment'/best supportive care weight is estimated by pooling non-responder and control group patients' EQ-5D data. Pooling placebo control and non-responder groups creates a potential selection bias. Non-responder status, determined by short-term mobility outcomes, may be an independent (ie irrespective of treatment status) predictor of other outcomes such as EQ-5D at 24 weeks. These patients may therefore have systematically worse outcomes than placebo control patients. This creates a large bias in favour of fampridine treatment. This weakness has been addressed in the case of the EQ-5D data in a revised analysis in which separate utility weights are estimated for responders, withdrawn from treatment, and best supportive care. The revised analysis produces an ICER for the base case scenario of £88,660 without PAS. With the revised utility weights, in the scenario analysis using alternative responder rates from the pooled analysis of the MS-F203 and MS-F204 studies, the ICER increased to £145,088. For

the reasons mentioned above, these results may be more appropriate than the base case estimates.

- Resource use data are taken from a German patient registry which may not reflect Scottish practice. A simple before and after comparison is made to estimate resource use with and without fampridine. This analysis may be subject to bias from confounding factors associated with starting fampridine treatment.
- Results are sensitive to the use of alternative sources of health related utility data such as the ENABLE study. This suggests that there is some uncertainty around the generalisability of any one estimate to the Scottish population.
- There is some structural uncertainty around how responder status would be measured. The SPC specifies assessment at 2 weeks, the model base case assumes assessment at 4 weeks and the evidence of treatment effects is based on studies which used longer assessment periods (24 weeks in the case of MOBILE). Clinical expert responses indicate that the measurement of responder status in current and potential future Scottish practice might not match with that used in model so treatment effects and discontinuation rates may differ from those used in the model.
- In the key source for the base case utility weights (MOBILE study) there is some imbalance in the treatment and control groups at baseline. The mean time since diagnosis was 12.4 years in the control group and 10.9 years in the treatment group.

Due to the weaknesses in the analysis noted above the economic case has not been demonstrated.

Summary of patient and public involvement

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

- We received patient group submissions from MS Society Scotland and the MS Trust.

- The MS Society Scotland has received <0.5% pharmaceutical company funding in the past two years, including from the submitting company. The MS Trust has received 2.7% pharmaceutical company funding in the past two years, including from the submitting company.

- Multiple Sclerosis (MS) is an incurable, degenerative neurological condition and people are typically diagnosed in their 30s. It can result in a wide range of symptoms including reduced mobility, a decline in cognitive function and bladder weakness. Walking problems affect a large proportion of people with MS.

- There are no medicines currently available to improve mobility in people with MS. Some people may use non-medicine treatments such as functional electrical stimulation or physiotherapy.

- Fampridine is the only licensed medicine for the treatment of mobility problems in people with MS. It can improve walking speed and steadiness, resulting in less dependence on others for care and support. A significant proportion of people with MS do not respond to this treatment; however, the effectiveness of the medicine can be established within a few weeks.

- Fampridine can cause a variety of side-effects, although most people view them as an acceptable risk.

Additional information: guidelines and protocols

In October 2014 NICE published Clinical Guideline 186 *Multiple sclerosis in adults: management*.[9] Reduced mobility is a common consequence of the gradual decline in function associated with MS. This can arise from multiple causes such as visual deficit, disordered balance, co-ordination problems, spasticity and muscle weakness. Walking problems suffered by people living with MS can have a significant impact on all aspects of their life, whether recreational activities, usual activities of daily living or in the workplace. Non-pharmacological methods to improve mobility are recommended in the guidance, eg supervised exercise programmes involving resistance and cardiovascular training. The guideline noted that fampridine has beneficial effects on subjective improvement in muscle strength and walking speed; however it recommended that fampridine should not be used to treat lack of mobility in people with MS because it was found not to be a cost effective treatment.

Additional information: comparators

There are no comparator treatments for this indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Fampridine prolonged-release tablets	**10mg orally twice daily**	**4,706**

Costs from eVadis on 3 August 2016. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 9,724 patients eligible for treatment with fampridine in year 1, rising to 10,027 in year 5.

Without the PAS, the gross impact on the medicines budget was estimated to be £327k in year 1 rising to £1.7m in year 5. As no medicines were assumed to be displaced, the net medicines budget impact is the same as the gross.

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

References

The undernoted references were supplied with the submission.

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9. National Institute for Health and Care Excellence. Multiple sclerosis in adults: management. Clinical guideline 186. 2014.

10. Biogen Idec Ltd. Summary of product characteristics for fampridine (Fampyra) 10mg prolonged-release tablets. Last updated May 2016.

11. www.clinicaltrials.gov [NCT02219932].

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

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.