Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Re-Submission

stiripentol 250mg and 500mg hard capsule, 250mg and 500mg powder for oral suspension in sachet (Diacomit®) SMC No 524/08

Biocodex

4 August 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 considered under the orphan equivalent process

stiripentol (Diacomit®) is accepted for use within NHS Scotland.

Indication under review: in conjunction with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI; Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate.

Adjunctive treatment with stiripentol, compared with placebo, significantly reduced seizure frequency in children aged at least three years with SMEI who had at least four seizures per month despite treatment with clobazam and valproate.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

In conjunction with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI; Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate.[1]

Dosing Information

In the paediatric population, starting at stiripentol 20mg/kg/day in week one the dose should be increased gradually to the recommended dose of 50mg/kg/day and should be administered orally in two to three divided doses. The capsule should be swallowed whole with a glass of water during a meal. Stiripentol must be taken with food as it degrades rapidly in an acidic environment. However, it should not be taken with milk or dairy products, carbonated drinks, fruit juice or food and drinks that contain caffeine or theophylline. The sachet formulation and capsules are not bioequivalent and any switch of formulations should be done under medical supervision.[1]

The clinical decision to use stiripentol in children with SMEI less than 3 years of age should be made on an individual patient basis taking into consideration the potential clinical benefits and risks. In this younger group of patients, adjunctive therapy with stiripentol should only be started when the diagnosis of SMEI has been clinically confirmed. Data are limited about the use of stiripentol under 12 months of age. For these children the use of stiripentol will be done under the close supervision of the doctor. Long-term data has not been collected in a sufficient number of adults to confirm maintenance of effect in this population. Treatment should be continued for as long as efficacy is observed. See summary of product characteristics (SPC) for further information.[1]

Stiripentol should only be administered under the supervision of a paediatrician / paediatric neurologist experienced in the diagnosis and management of epilepsy in infants and children.[1]

Product availability date

18 February 2008

Stiripentol meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Stiripentol is an anticonvulsant with a mechanism of action that is not fully characterised. It may increase levels of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the brain by inhibiting synapse uptake or by inhibition of GABA transaminase. It may act by potentiating the efficacy of other anti-epileptic medicines, such as clobazam and to a lesser extent valproate, through pharmacokinetic interactions, mainly by inhibition of cytochrome P450 isoenzymes.[1,2]

Two identical protocol double-blind studies (STICLO-FR and STICLO-IT) recruited children aged 3 to 18 years with severe myoclonic epilepsy in infancy (SMEI) who had at least four clonic or tonic-clonic seizures per month despite treatment with clobazam (up to 20mg daily) and valproic acid (up to 30mg/kg daily). After a 28-day baseline observation they were equally randomised to add-on oral stiripentol 50mg/kg/day or placebo for eight weeks. The primary outcome was proportion of patients achieving a response, defined as at least a 50% reduction in the number of clonic or tonic-clonic seizures during the second month of the treatment period compared with baseline and not having any of the following: status epilepticus; increase versus baseline in seizures of more than 50% during first 20 days of double-blind treatment; or increase versus pre-study in seizures of more than 50% during baseline if the number of

seizures did not return to pre-study number during month one of double-blind treatment. This was assessed in the intention-to-treat (ITT) population, which comprised all randomised patients (except one non-evaluable patient in STICLO-FR).[2-4]

In STICLO-FR stiripentol significantly increased the proportion of responders, compared with placebo, 71% (15/21) versus 5.0% (1/20), respectively, p<0.0001, with a difference of 66% (95% confidence intervals [CI]: 42.2% to 85.7%). As the lower limit of the CI was greater than the pre-specified clinically relevant difference of 25%, enrolment in the study was stopped. In STICLO-IT stiripentol significantly increased the proportion of responders, compared with placebo, 67% (8/12) versus 9.1% (1/11), respectively, p=0.009, with a difference of 58%. Some secondary outcomes are detailed in table 1.[2-5]

Table 1: Percent change in seizure frequency in STICLO-FR and STICLO-IT.[2-6]

	STICLO-FR			STICLO-IT		
	Stiripentol	**Placebo**	**p-value**	**Stiripentol**	**Placebo**	**p-value**
Decrease ≥50% in seizures during month two*						
	n=21	n=20		n=11	n=9	
≥50% decrease n (%)	15 (71%)	1 (5.0%)	p<0.0002	8 (73%)	1 (11%)	p<0.01
Decrease in seizures during month two in those completing treatment						
	n=20	n=16		n=11	n=9	
100% decrease n (%)	9 (45%)	0	p<0.01	3 (27%)	0	p=0.05
>50%, <100% decrease n (%)	6 (30%)	1 (6.2%)		5 (45%)	1 (11%)	
<50% decrease n (%)	3 (15%)	5 (31%)		3 (27%)	7 (78%)	
<50% increase n (%)	2 (10%)	8 (50%)		0	0	
>50% increase n (%)	0	2 (13%)		0	1 (11%)	

*assessed in intention-to-treat population in STICLO-FR and in per protocol population in STICLO-IT

Mean seizure frequency and mean percent change from baseline were significantly different in the stiripentol groups compared with placebo at month one in both studies and month two in STICLO-FR study as detailed in table 2. The proportion of patients who were seizure free in month two was greater with stiripentol compared with placebo.[2]

Table 2: Monthly seizure frequency in STICLO-FR and STICLO-IT studies.[2,5,6]

	STICLO-FR			STICLO-IT		
	Stiripentol	**Placebo**	**p-value**	**Stiripentol**	**Placebo**	**p-value**
Baseline month						
	n=21	n=20		n=12	n=11	
Mean	17.9	18.5		33.6	27.4	
Month one						
	n=21	n=20		n=12	n=11	
Mean	2.72	23.82	p<0.001	4.7	29.0	p=0.003
Change from baseline	-83%	+11%	p<0.001	-90%	+5.5%	p<0.05
Month two						
	n=20	n=16		n=11	n=9	
Mean	5.15	13.8	p<0.002	9.8	16.7	NS
Change from baseline	-69%	+7.4%	p<0.002	-74%	-13%	NS
Seizure free % (n/N)	45% (9/20)	(0/16)	p=0.0013	27% (3/11)	(0/9)	p=0.05

* In month two seizure frequency, change from baseline and proportion of seizure-free patients were assessed only in patients who completed the study

Two open-label studies (Inoue 2009 and STP-1) conducted in Japan recruited 23 and 24 patients, respectively, with SMEI aged at least one year who had at least four clonic or tonic-clonic seizures per month despite treatment with at least one anti-epileptic drug in the study by Inoue 2009 and with clobazam (up to 0.5mg/kg daily) plus valproate (up to 30mg/kg daily) in the STP-1 study. (In the Inoue 2009 study 22 patients were receiving valproate and 11 patients were receiving clobazam). After a 28-day baseline observation they received stiripentol 50mg/kg daily, with some titration and adjustment of concomitant anti-epileptic doses. Doses were then fixed for 8 and 12 weeks in the respective studies. The primary outcome, proportion of patients achieving at least 50% reduction in monthly seizure frequency during the last four weeks of the fixed dose period compared with baseline was 61% (14/23) and 67% (16/24) in the respective studies. Both studies continued after this time point. In the Inoue 2009 study the dose of stiripentol could be increased to 100mg/kg daily if necessary and dose of other anti-epileptics adjusted, then fixed for 8 weeks. The primary outcome was achieved by 48% (11/23) of patients in this late phase. In the STP-1 study 21 patients benefiting from stiripentol continued treatment for up to an additional 40 weeks, with 19 patients completing this phase. Over this period the number of responders in each month ranged from eight to 14, with response rates of at least 50% (12/24) in nine of the 11 months. At the end of this period the response rate was 54% (13/24) or when expressed as proportion of patients remaining in the study, 68% (13/19).[7-9]

An open-label study (STILON) included 45 patients with SMEI who benefited from stiripentol in previous clinical studies. The study continued from July 1999 until January 2003. Efficacy was assessed by comparing 30-day seizure frequency at the end of the study with that at inclusion (i.e. while patients were receiving stiripentol in their previous study). Efficacy of stiripentol was generally maintained at the end of the STILON study.[10]

Summary of evidence on comparative safety

The European Medicines Agency (EMA) review of safety in 2007 included the pivotal double-blind and open-label studies and post-marketing data. It concluded that despite the relatively small exposure and suboptimal quality of reporting methods, the overall adverse event profile of stiripentol did not give rise to any major concerns. Adverse events were common, most frequently affecting the central nervous system (CNS) and gastrointestinal (GI) tract, and could often be severe. However, they were mostly reversible, particularly with dosage adjustments of concomitant medication.[2]

The DIAVEY post-marketing surveillance study in the EU from 2007 to 2012 found no effect of stiripentol of patient's growth in height or weight or in mental development or behaviour. Observed effects on blood (e.g. neutropenia, thrombocytopenia) and liver function tests were known and there were no adverse reactions identified which would raise major safety concerns.[11]

In the pivotal studies adverse events most frequently reported within the stiripentol and placebo groups were in the CNS, 37 versus 6 events in STICLO-FR and 17 versus 8 in STICLO-IT, and in the GI tract, 22 versus 8 event in STICLO-FR and 14 versus 1 in STICLO-IT. The most commonly reported CNS events were sleepiness or drowsiness, hyperexcitability, agitation or aggressiveness, ataxia and hypotonia. The most common GI events were loss of appetite, weight loss, weight gain, nausea and vomiting. Haematological events were reported in the STICLO-FR study, with neutropenia in three patients, thrombocytopenia in two patients and eosinophilia in one patient. Some increases in transaminases were also noted in the stiripentol studies.[2]

Stiripentol is an inhibitor of cytochrome P450 isoenzymes CYP3A4 and CYP2C19 and may increase the serum concentration of concomitantly administered anti-epileptics drugs.[2]

Summary of clinical effectiveness issues

Stiripentol is the only medicine licensed for the treatment of SMEI (Dravet syndrome).[1] The marketing authorisation is no longer subject to the conditional requirements specified at first approval. It was designated by the European Commission as an orphan medicinal product for the treatment of SMEI in December 2001. This designation expired in January 2017 at the end of the period of market exclusivity.[12] Stiripentol meets SMC orphan equivalent criteria.

SMEI (Dravet syndrome) is characterised by general or unilateral seizures beginning in the first year of life, with secondary development of myoclonic jerks and partial seizures. Psychomotor and cognitive development can be retarded from the second year of life. A genetic mutation in the SCN1A gene has been identified in many patients with SMEI. It is usually not possible to adequately control this severe form of epilepsy with available treatments.[2] National Institute of Health and Clinical Excellence (NICE) guideline recommends initial treatment with sodium valproate or topiramate and in patients not adequately controlled on first-line therapy clobazam or stiripentol may be added as adjunctive treatment.[13] Clinical experts consulted by SMC also recommend this treatment pathway and note that anti-epileptic medicines which block sodium channels can exacerbate the condition. They note that there are limited treatment options for patients who have inadequate seizure control with initial anti-epileptic medicines. The experts advised that stiripentol is currently used within NHS Scotland and fulfils an unmet need for an effective treatment option for patients with this condition who have who have inadequate seizure control with anti-epileptic medicines such as valproate and clobazam.

In the STICLO-FR and STICLO-IT studies stiripentol was associated with a significant increase over placebo of about 60% of patients achieving a response, defined by at least 50% reduction in monthly seizure frequency. In the stiripentol groups mean monthly seizure frequency decreased from baseline values of 18 and 34 in the respective studies to means of 2.7 in month one and 5.2 in month two of the STICLO-FR study and to 4.7 in month one and 9.8 in month two of the STICLO-IT study. The reduction in seizure frequency with stiripentol was statistically significant and clinically relevant.[2]

The primary outcome of the STICLO studies only assessed frequency of clonic or tonic-clonic seizures, it did not assess any treatment effects on other types of seizure. The pivotal studies assessed efficacy over two months in a small number of patients and did not provide evidence of longer-term treatment effects on seizures.[2] However, open-label studies provide reassurance with respect to maintenance of effect, with STP-1 having data up to one year and STILON providing evidence over several years.[2,8,9] There were no data on the effect of stiripentol on psychomotor and cognitive development.

The pivotal studies included children aged 3 to 18 years with SMEI.[2] This limits application of the results to adults or children aged less than 3 years. The SPC provides guidance for use in these groups as described above in dosing information section.

Stiripentol is an inhibitor of cytochrome P450 isoenzymes CYP3A4 and CYP2C19 and may increase the serum concentration of concomitantly administered anti-epileptics medicines, such as clobazam (and its active metabolite norclobazam). In clinical studies there were two to three fold increases in clobazam and five-fold increases in norclobazam plasma concentrations with concomitant stiripentol administration in children with SMEI. The potential for a metabolic interaction between stiripentol and valproate is noted to be modest in the SPC.[1,2]

Clinical experts consulted by SMC considered that stiripentol is a therapeutic advancement due to its therapeutic effects. They advised that the place in therapy of stiripentol is as adjunctive therapy for patients with SMEI who have inadequate seizure control despite treatment with valproate and clobazam. They note that stiripentol is currently used within NHS Scotland.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with a patient group representative and clinical specialists was held to consider the added value of stiripentol, as an orphan-equivalent medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Dravet's syndrome is a very rare severe form of childhood epilepsy that has been associated with a genetic mutation in the SCN1A gene (in the vast majority of patients). Patients experience prolonged seizures (including status epilepticus where seizure duration exceeds 30 minutes) and serial seizures. These children also experience significant developmental delay, including in learning, speech and language. Patients walking can also be affected, with ataxia present.
- This is a treatment-resistant form of epilepsy and there is an unmet need for effective medications. Other options are limited as many anti-epileptic medications are not suitable for patients with Dravet's syndrome. Some patients in Scotland are currently receiving stiripentol.
- Dravet's syndrome has a huge impact on family as patients will need to be cared for throughout their life. There is an extra family burden and one family member is unlikely to be able to work. There is a high impact on siblings, including the psychological distress of witnessing seizures.
- Reducing seizure frequency is key to improving quality of life and health benefits. Treatment with stiripentol could lead to a reduction in seizure-related injuries, and in post-seizure effects including fatigue. Treatment could also lead to a reduction in mortality from status epilepticus, seizure-related injury and Sudden Unexpected Death in Epilepsy (SUDEP).
- A reduction in seizure burden could lead to fewer unplanned hospital admissions and less contact with health care professionals. Side effects of stiripentol are manageable and specialists are familiar with this medicine.

Addition of Patient and Carer Involvement

We received a patient group submission from Epilepsy Action, which is a registered charity. Epilepsy Action has received less than 3% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from Epilepsy Action participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost utility analysis comparing stiripentol, in addition to clobazam and valproate to clobazam and valproate alone, for the treatment of refractory generalised tonic-clonic seizures in patients with SMEI (Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate. Based on SMC clinical expert responses the comparators appear to be appropriate and are currently used in Scotland for treatment of Dravet syndrome.

A Markov model was used which contained four health states defined by the level of reduction in seizure frequency i.e. seizure free (patients have no seizures after treatment), not seizure free (patients have between ≥50% to <100% reduction in seizure frequency), not adequately controlled (patients have less than 50% reduction in seizure frequency) and maintenance (patients discontinue due to adverse events and receive maintenance therapy). After one cycle (3 months) of treatment patients were distributed into one of the four health states and subsequently moved through the model according to a set of transition probabilities. The time horizon used in the analysis was 15 years.

The clinical data used in the economic model were derived from the pooled pivotal studies.[5-6] The distribution of patients within each health state at the end of cycle one was a key efficacy parameter and is outlined in table 3 below. Transition probabilities from cycle 2 onwards were taken from the long term study post marketing study.[11] Due to a lack of long term comparative efficacy data, the company assumed that both treatment arms would have the same transition probabilities from cycle 2 onwards.

Table 3: Distribution of patients in each health state (at the end of the pivotal studies)

	Seizure free	Not seizure free	Not adequately controlled	Maintenance
Stiripentol arm	36.36%	33.33%	30.30%	0%
Comparator arm	0%	6.45%	93.55%	0%

Utility values were taken from a conference poster[14] whereby preferences for health states associated with Lennox-Gastaut syndrome were recorded. Preferences were elicited using the time trade off method, from 119 members of the UK public (of which 48% were caregivers/ parents of children aged 4-18 years). Utility values were 0.699, 0.605, 0.427 and 0.516 for seizure free, not seizure free, not adequately controlled and maintenance health states respectively.

Medicine costs, including the cost of maintenance therapy were incorporated within the analysis. The dose for each treatment was dependent on patient weight and age. For children aged 0-10 years, patient weights were taken from the World Health Organisation (WHO) child growth standards and WHO growth reference data, while patient weight for patients aged 10-19 years was estimated as the multiplication of squared height and the BMI for each age. Hospitalisation and monitoring costs were captured in the model and included inpatient costs, outpatient visits, emergency room visits and epilepsy nurse phone calls. Resource use estimates were taken from a NICE model of treatments for focal epilepsies (CG137) and were based on expert opinion. The costs of adverse events were also captured in the model.

The base case results indicated stiripentol in addition to clobazam and valproate resulted in an incremental cost effectiveness ratio (ICER) of £14,261 per quality adjusted life year (QALY) versus clobazam and valproate alone, based on an incremental cost of £3,055 and an incremental QALY gain of 0.214. The incremental cost associated with the addition of stiripentol (£14,193), was largely offset by a reduction in monitoring costs, associated with more patients being in less severe health states (-£11,126). In relation to QALYs, a higher proportion of patients in the stiripentol treatment arm finished the first cycle of the model in the seizure free (SF) health state 36.36% vs. 0% respectively, which is associated with a utility value of 0.69. The company provided one-way and scenario analyses and the key results are presented in table 4 below:

Table 4: Key sensitivity analysis results

One-way sensitivity/scenario analysis	ICER
Cost of maintenance therapy per kg per cycle decreased in comparator arm to £0.153 (from £0.191)	£37,493
Cost of maintenance therapy per kg per cycle increased in stiripentol arm to £0.229 (from £0.191)	£34,284
Probability of remaining in the 'not seizure free' health state increased to 100% in the comparator arm (from 91.5%)	£35,646
Cost of inpatient stay increased by 20% in the 'not seizure free' health state	£31,194
Weight factor (increased from 1 to 1.2)	£21,260
Alternative source for utilities[15]	£30, 585

10% of patients remain on stiripentol at 18 years old	£41,976
30% of patients remain on stiripentol at 18 years old	£62,733

The following limitations were noted;

- Treatment with stiripentol is likely to continue beyond the age of 18 and into adulthood if patients are responding to treatment. However, due to the small proportion of patients predicted to remain on stiripentol by the end of the 15 year time horizon i.e. 4%, the economic model may not adequately capture the appropriate costs and effects of stiripentol treatment. To address this uncertainty the company provided sensitivity analyses where 10% and 30% of patients were assumed to remain on stiripentol at 18 years old and the results are presented in Table 4 above.
- The data used to estimate health state utility values have some important limitations. For example members of the UK general public (adults), were used to elicit preferences for health states associated with Lennox-Gastaut syndrome and therefore quality of life data were not measured directly from children with Dravet syndrome. SMC clinical experts have indicated that quality of life is likely to be similar for patients with these conditions, but the generalisability of adult values to children remains unclear. In addition, other published literature sources have generally revealed utility values higher than those used in the base case. The company provided a sensitivity analysis using values from an alternative literature source[15] According to this source responders who were seizure free at the end of 6 months had a utility weight of 0.94, who experienced less than one seizure per month had a utility of 0.88, more than one seizure per month had a utility of 0.93 and no response had a utility of 0.84. These alternative values were considered to have less face validity for application to Dravet syndrome than base case values, but provide an additional evidence source for an uncertain parameter set. The ICER using the alternative utility values in the economic model is available in Table 4 above.

The Committee also considered the benefits of stiripentol in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as stiripentol is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted stiripentol for use in NHS Scotland

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

Additional information: guidelines and protocols

In January 2012 the National Institute for Health and Care Excellence (NICE) published clinical guideline number 137, Epilepsies: diagnosis and management. This recommends that when a child presents with suspected Dravet syndrome they should be discussed with or referred to a tertiary paediatric epilepsy specialist. Sodium valproate or topiramate should be considered as first-line treatment in children with Dravet syndrome. If first-line treatments in children, young people and adults with Dravet syndrome are ineffective or not tolerated, clobazam or stiripentol should be considered as adjunctive treatment. Treatment should not be offered with carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.[13]

In May 2015 the Scottish Intercollegiate Guidelines Network published a guideline number 143, Diagnosis and management of epilepsy in adults. This makes no recommendation about the treatment of Dravet syndrome.[16]

Additional information: comparators

Stiripentol is added on to standard therapy with anti-epileptic medicines.

Cost of relevant comparators

Medicine	Dose regimen	Cost per year (£)
Stiripentol	**50mg/kg orally daily in two to three divided doses**	**3,446 to 20,936**

Costs from eVadis on 03 March 2017 and based on a dose range for a 10kg child to a 70kg adult.

Additional information: budget impact

The submitting company estimated there would be 11 patients eligible for treatment with stiripentol in year 1 rising to 13 patients in year 5, with an estimated uptake rate of 60% and 100% in years 1 and 5 respectively. The gross impact on the medicines budget was estimated to be £53k in year 1 rising to £102k in year 5. As no other medicines were assumed to be displaced, the net medicines budget impact was estimated to be the same as the gross budget impact.

References

The undernoted references were supplied with the submission.

1. Biocodex. Summary of product characteristics for Diacomit, last updated 8 January 2014.

2. European Medicines Agency. European public assessment report of stiripentol (Diacomit®), scientific discussion.

3. Canadian Agency for Drug and Technologies in Health. Common Drug Review, CDEC final recommendation for stiripentol, indication: severe myoclonic epilepsy in infancy (Dravet syndrome)

4. Chiron C, Marchand MC, Tran A, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. Lancet 2000; 356: 1638-42.

5. *Commercial in Confidence**

6. *Commercial in Confidence**

7. Inoue Y, Ohtsuka Y, Oguni H, et al. Stiripentol open study in Japanese patients with Dravet syndrome. Epilepsia 2009; 50(11): 2362-8

8. Inoue Y, Ohtsuka Y. Effectiveness of add-on stiripentol to clobazam and valproate in Japanese patients with Dravet syndrome: additional supportive evidence. Epilepsy Res 2014; 108: 725-31.

9. Inoue Y, Ohtsuka Y. Long-term safety and efficacy of stiripentol for the treatment of Dravet syndrome: A multicenter, open-label study in Japan. Epilepsy Res 2015; 113: 90-7.

10. *Commercial in Confidence**

11. *Commercial in Confidence**

12. European Medicines Agency. Orphan designation for stiripentol (EU/3/01/17), last updated 08 February 2017.

13. National Institute for Health and Care Excellence (NICE) published clinical guideline number 137, Epilepsies: diagnosis and management, January 2012.

14. Lachaine J, Lambert-Obry V. Cost-effectiveness of stiripentol in the treatment of severe myoclonic epilepsy in infancy in Canada. Value in Health Conference: ISPOR 19th Annual International Meeting Montreal, QC Canada Conference Start: 20140531 Conference End: 20140604 Conference Publication: 2014; 17: May.

15. Selai CE, Trimble MR, Price MJ, Remak E. Evaluation of health status in epilepsy using the EQ-5D questionnaire: a prospective, observational, 6-month study of adjunctive therapy with anti-epileptic drugs. Curr Med Res Opin 2005; 21: 733-9.

16. Scottish Intercollegiate Guidelines Network. Guideline number 143, Diagnosis and management of epilepsy in adults, May 2015.

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

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.