Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

retigabine, 50mg, 100mg, 200mg, 300mg and 400mg film-coated tablets (Trobalt®) SMC No. (712/11)

GlaxoSmithKline

10 June 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

retigabine (Trobalt®) is accepted for restricted use within NHS Scotland.

Indication under review: Adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy.

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

In two placebo-controlled studies in patients with refractory epilepsy retigabine was superior to placebo in terms of the proportion of patients experiencing ≥ 50% reduction in partial seizure frequency per 28 days. An indirect comparison indicates that retigabine has similar efficacy to two other antiepileptic drugs used as adjunctive therapy.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 11 July 2011

Indication

Adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy.

Dosing Information

The maximum total daily starting dose is 300mg (100mg three times daily). Thereafter, the total daily dose is increased by a maximum of 150mg every week, according to the individual patient response and tolerability. An effective maintenance dose is expected to be between 600mg/day and 1,200mg/day [given as three divided doses].

The maximum total maintenance dose is 1,200mg/day. The safety and efficacy of doses higher than 1,200mg/day have not been established.

Product availability date

05 May 2011

Summary of evidence on comparative efficacy

Retigabine is the first of a new class of antiepileptic drug (AED) that acts on potassium ion channels.

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers the use of this product when positioned for use as an adjunctive treatment in patients with refractory partial onset epilepsy i.e. patients who have been trialled adequately on two drug schedules (monotherapies or combination) and at least one further combination therapy before treatment with retigabine is considered.

Two pivotal phase III double-blind placebo-controlled studies with similar design have been conducted in patients with refractory epilepsy and simple partial or complex partial seizures with or without secondary generalisation. Refractory epilepsy was defined as diagnosis of epilepsy for two years or longer, with partial seizures despite having been treated in the past with at least two approved anti-epileptic drugs (AEDs) either alone or together at adequate doses for sufficient length of time in the opinion of the investigator. Patients were aged 18 to 75 years and had a 28-day partial seizure frequency of ≥4 seizures over an eight-week baseline period, and did not have a consecutive period of 21 days without seizures. Patients must have been treated with one to three established AEDs at a stable dose for at least one month prior to the screening evaluation and remained on these throughout the study. In one study patients were randomised equally to retigabine 1,200mg/day or placebo and in the other study to retigabine 600mg/day, 900mg/day or placebo. Patients underwent a forced titration with retigabine according to a pre-specified dosing schedule (lasting six weeks in the higher dose study and four weeks in the lower doses study) up to the final dose, administered three times daily for a maintenance phase of 12 weeks.

For the European Medicines Agency (EMA) review the primary endpoint was the proportion of responders (defined as patients experiencing a ≥ 50% reduction in partial seizure frequency per 28 days) from baseline to maintenance phase with retigabine versus placebo. In the lower doses study the primary endpoint related to retigabine 900mg/day and efficacy in the retigabine 600mg/day group was considered a secondary endpoint, analysed if the retigabine 900mg/day group was statistically superior to placebo on the specific endpoint. Patients recorded seizure frequency in a daily diary. The EMA intent to treat population (ITT) was defined as all randomised patients who received at least one dose of study drug in the maintenance phase and had at least one seizure measurement (whether or not they had a seizure) recorded in the maintenance phase. Results for the primary endpoint are included in the table below.

Table 1: Primary endpoint (European Medicines Agency), proportion of responders for the pivotal studies

Treatment	n ITT (EMA)	Median baseline seizure frequency	Proportion of responders	P value versus placebo
Study 1				
Retigabine 1,200mg/day	119	12.4	56% (66/119)	p<0.001
Placebo	137	11.3	23% (31/137)	
Study 2				
Retigabine 600mg/day	158	9.8	39% (61/158)	p<0.001
Retigabine 900mg/day	149	10.1	47% (70/149)	p<0.001
Placebo	164	9.2	19% (31/164)	

Secondary endpoints included the % reduction in the 28-day total partial seizure frequency from baseline to the maintenance phase and the proportion of patients who were seizure free. Results for the ITT (EMA) populations are presented. There was a significant difference in median % reduction during the maintenance phase in 28-day total partial seizure frequency for retigabine 1,200mg/day (55%) versus placebo (19%). There was also a significant difference between treatment groups with respect to the proportion of patients who were seizure-free during the maintenance phase (7.6% [9/119] versus 1.5% [2/137]; p=0.027). The median % reductions during the maintenance phase in 28-day total partial seizure frequency were 25%, 31% and 5.1% for retigabine 600mg/day, 900mg/day and placebo respectively and were significant for both retigabine doses versus placebo. However there was no significant difference between treatment groups and placebo in the proportion of patients who were seizure free during the maintenance phase (3.2% [5/158] versus 4.7% [7/149] versus 1.2% [2/164] in the respective groups).

In both studies there was a significant difference in favour of retigabine for Clinical Global Impression of Improvement scores at the end of the maintenance period. Patient Global Impression scores were significantly improved for retigabine in the lower doses study only. The Quality of Life in Epilepsy-Problems Questionnaire (QOLIE-31-P, version 2.0) was used to assess quality of life (QoL). In the higher dose study the overall mean score in groups were comparable at weeks 6 and 10 and at week 18 was slightly higher, indicating improved QoL, for placebo compared to retigabine at week 18 (57.3 versus 53.8 versus). In the lower doses study

there was a small general improvement in mean scores from baseline to weeks 4, 8, 16, and 20 for all groups.

Both studies included open-label extensions in which patients who successfully completed the maintenance phase were invited to participate. Patients entered a six- or four-week transition phase, respectively and were titrated where applicable to the target dose (1,200mg/day or 900mg/day in the respective studies). Following the transition phase, doses could be individualised within the range 600mg/day to 1,200mg/day, administered as monotherapy or in combination with up to three approved AEDs and vagal nerve stimulation. Results for the extension studies are available at an interim cut-off on 30 June 2008. In the extension to the higher dose study the responder rate was 57% (102/179) and there was a 57% median reduction in partial seizure frequency. In the extension to the lower doses study the responder rate was 54% (201/373) and there was a 53% median reduction in partial seizure frequency. In patients treated for at least six months the % of patients who were seizure free for any continuous six-month period was 8% to 10% across the two extension studies.

Summary of evidence on comparative safety

Adverse events (AE) were experienced by 92% and 85% of patients in retigabine 1,200mg/day and placebo groups respectively. A greater proportion of patients in the retigabine 1,200mg/day group versus placebo had serious AE (12% versus 5.3%) or AE possibly related to study drug (86% versus 55%). The number of patients who discontinued study drug due to AE were 47 (31%) versus 18 (12%) respectively. AE were experienced by 73%, 79% and 66% on retigabine 600mg/day, 900mg/day and placebo respectively. Most AE were mild to moderate in severity. The percentage of patients who discontinued study drug due to AE was 17%, 26% and 8% respectively.

The most common AE in both studies were dizziness, somnolence, headache and fatigue. During the double-blind phase of the studies there were four deaths reported overall; two whilst on retigabine treatment, with one death (due to ketoacidosis) considered as possibly related to study drug.

Safety data from the extension studies reflected those observed during the double-blind phases.

The summary of product characteristics (SPC) notes that adverse reactions related to voiding dysfunction, including urinary retention, were reported in 5% of retigabine-treated patients in the pooled safety dataset. The majority of events occurred in the first eight weeks of treatment, and there was no apparent dose-relationship. The SPC warns that retigabine must be used with caution in patients at risk of urinary retention, and it is recommended that patients are advised about the risk of these possible effects.

Summary of clinical effectiveness issues

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers the use of this product when positioned for use as an adjunctive treatment in patients with refractory partial onset epilepsy i.e. patients who have been trialled adequately on two drug schedules (monotherapies or combination) and at least one further combination therapy before

treatment with retigabine is considered. The pivotal studies provide efficacy data for retigabine in the patient population proposed by the submitting company.

The pivotal studies have some limitations. They included patient populations that were highly selected and the forced titration and maintenance dose regimens were fixed, which may explain the higher drop out rates for retigabine groups relative to placebo (25% to 37% for retigabine and 15% to 17% for placebo). In addition discontinuations due to AE were higher in the retigabine groups than placebo groups. Patients were required to be taking one to three AEDs concurrently during the study period. In the higher dose study the percentage of patients on one AED was 21% versus 14%, two AEDs; 52% versus 46% and three AEDs; 28% versus 40% in the retigabine and placebo groups respectively. Therefore it appears that retigabine treated patients were more likely to be on one or two concomitant AEDs and placebo treated patients on two or three AEDs. In the study of lower doses the percentage of patients on one AED was 27%, 20% and 22%, two AEDs was 42%, 56% and 49%, and three AEDs was 31%, 25% and 29% in the retigabine 600mg/day, 900mg/day and placebo groups respectively, and appeared to be approximately matched across treatment groups. However it is unclear whether this level of concurrent AED administration observed in the pivotal studies reflects current Scottish practice.

There are no direct comparative data other than versus placebo. The submitting company in their submission to SMC included a network meta-analysis that allowed an indirect comparison of retigabine, eslicarbazepine and lacosamide. Although there was some heterogeneity in the studies included, it can be reasonably concluded that retigabine has similar efficacy to eslicarbazepine and lacosamide.

Retigabine is administered three times daily; this compares to a once daily dosing administration regimen for eslicarbazepine and zonisamide and twice daily for lacosamide. A less frequent dosing regimen may be favoured by patients although it is acknowledged that patients are likely to be concurrently receiving other AEDs which may require twice or thrice daily administration.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing retigabine with lacosamide and eslicarbazepine in patients with refractory partial onset epilepsy i.e. patients who have been trialled adequately on two drug schedules (monotherapy or combination) and at least one further combination therapy before treatment with retigabine is considered. A decision tree model was used over a two year time horizon. Patients were categorised at 26 weeks as seizure free, responders, non-responders or discontinued treatment due to adverse events and were assumed to remain in these health states for the remainder of the model.

The source of the clinical data used in the economic analysis was an indirect comparison in the form of a network meta-analysis comparing retigabine with lacosamide and eslicarbazepine. The utility values in the model were adapted from a study where quality of life of patients with partial onset epilepsy was measured using EQ-5D. Resource use estimates were based on those used in the economic model in the draft National Institute for Health and Clinical Excellence (NICE) clinical guideline on the management of epilepsy.

The results of the analysis showed that retigabine was dominant versus both eslicarbazepine and lacosamide. For the comparison with lacosamide, retigabine was estimated to result in savings of £90 and a QALY gain of 0.0078. For the comparison with eslicarbazepine, retigabine was estimated to result in modest cost savings and a QALY gain of 0.0083. The analysis used the confidential cost of eslicarbazepine that is effective in NHS Scotland under the patient access scheme on which SMC advice is contingent.

The key limitations of the analysis were:

- The indirect comparison showed that the three treatments have comparable efficacy, but the non-significant differences in efficacy outcomes were included in the model. The manufacturer subsequently provided a cost-minimisation analysis which assumed no difference in efficacy between the treatments. In this analysis retigabine was estimated to result in modest savings versus both lacosamide and eslicarbazepine.
- The model does not allow for sequencing of treatments following failure of initial therapy. This is a simplifying assumption as it seems likely that patients who do not respond to retigabine would move on to another treatment. However, it is recognised that in clinical practice epilepsy is not typically treated with a defined sequence of treatments.
- There was some heterogeneity between the studies included in the indirect comparison. However, this is unlikely to alter the conclusion that the treatments have comparable efficacy.

When the non-significant differences in efficacy outcomes were excluded, retigabine would still be considered cost-effective due to the lower drug acquisition cost. As such, the economic case has been demonstrated.

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

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 70; diagnosis and management of epilepsy in adults in April 2003. This recommends that carbamazepine, sodium valproate, lamotrigine and oxcarbazepine can all be regarded as first line treatments for partial and secondary generalised seizure. Combination therapy should be considered when treatment with two first line AEDs has failed or when the first well tolerated drug substantially improves seizure control but fails to produce seizure-freedom at maximal dosage. The choice of drugs in combination should be matched to the patient's seizure type(s) and should be limited to two or at most three AEDs. In relation to drug-resistant focal epilepsy, the guideline notes that seven AEDs have been licensed in the last decade [at the time of publication of the guideline]. These are in chronological order, vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine and levetiracetam. Systematic reviews have confirmed the efficacy and tolerability of all of these agents as adjunctive therapy for patients with drug-resistant focal epilepsy. The development of concentric visual field effects with vigabatrin has substantially limited its clinical use. In 2007 a review consultation report

indicated that the entire guideline or elements of it should be reviewed. No date is available for publication of the updated guideline.

In March 2004 NICE published technology appraisal number 76; newer drugs for epilepsy in adults in March 2004. NICE also published clinical guideline number 20; the diagnosis and management of the epilepsies in adults and children in primary and secondary care in October 2004. Both of these recommend that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with anti-epileptic drugs have not resulted in seizure freedom. The newer antiepileptic drugs, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin are recommended for patients who have not benefited from or are unsuitable for treatment with older anti-epileptics such as carbamazepine or sodium valproate. The clinical guideline is currently being reviewed; the publication date is January 2012.

Additional information: comparators

The majority of AEDs can be used within their licensed indications as adjunctive treatment for partial seizures with or without secondary generalisation. In practice the older drugs (e.g. carbamazepine and sodium valproate) tend to be used as first-line treatments, with the newer AEDs used as adjunctive therapy in patients not controlled with monotherapy.

Comparators relevant to the licensed indication under review have been included in the table below.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Retigabine	**600mg to 1,200mg daily**	**1,012 to 1660**
Eslicarbazepine	800mg to 1,200mg daily	1,871 to 2,806
Zonisamide	300mg to 500mg daily	1,223 to 2,038
Lacosamide	200mg to 400mg daily	1,124 to 1,874
Levetiracetam	1,000mg to 3,000mg daily	635 to 1,840
Tiagabine	15mg to 45mg daily*	447 to 1,340
Pregabalin	150mg to 600mg daily	1,256
Oxcarbazepine	600mg to 2,400mg daily	247 to 990
Gabapentin	900mg to 3,600mg daily	122 to 518
Topiramate	200mg to 800mg daily	76 to 240
Lamotrigine	100mg to 400mg daily*	39 to 93

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis on 30 March 2011, except for cost of retigabine (which has been taken from company's submission and is to be confirmed). The above total daily doses are taken as two or three divided doses, except for eslicarbazepine and zonisamide, which may be taken once daily.
* maximum dose dependent upon concomitant use of enzyme inducing drugs.

Additional information: budget impact

The manufacturer estimated the net drug budget impact with retigabine would be savings of £25k in year 1 rising to £49k in year 5. The number of refractory partial epilepsy patients assumed to be eligible for treatment was 4,787. Assuming a market share of 2.6% rising to 9.7% the manufacturer estimated 123 patients would be treated with retigabine in year 1 rising to 472 in year 5. It was assumed that market share would be taken from eslicarbazepine and lacosamide equally.

References

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

GlaxoSmithKline Group. A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Phase 3 Study to Determine the Efficacy and Safety of Retigabine (1200 mg/day) Used as Adjunctive Therapy in Refractory Epilepsy Patients with Partial-Onset Seizures. Published 2009

French JA, Abou-Khalil B, Leroy RF. Retigabine (ezogabine) Efficacy and safety trial for partial onset epilepsy (RESTORE 1): Double-blind, randomised, placebo-controlled trial of retigabine 1200mg/day as adjunctive therapy in adults with partial onset seizures. Neurology. Published online ahead of print (30 March 2011).

GlaxoSmithKline Group. A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Phase 3 Study to Determine the Efficacy and Safety of Two Doses of Retigabine (900 mg/day and 600 mg/day) Used as Adjunctive Therapy in Refractory Epilepsy Patients with Partial-Onset Seizures. Published 2009

Brodie MJ, Lerche H, Gil-Nagel A, Elger C, Hall S, Shin P, et al. Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. Neurology 2010 Nov 16;75(20):1817-24.

GlaxoSmithKline Group. Interim Report: A Multicenter, Open-Label, Long-Term, Safety, Tolerability and Efficacy Study of Retigabine in Adult Epilepsy Patients with Partial-Onset Seizures (Extension of Study VRX-RET-E22-301). Published 2009

GlaxoSmithKline Group. Interim Report: A Multicenter, Open-Label, Long-Term, Safety, Tolerability and Efficacy Study of Retigabine in Adult Epilepsy Patients with Partial-Onset Seizures (Extension of Study VRX-RET-E22-302). Published 2009

European Medicines Agency. CHMP Assessment Report; retigabine. Procedure No. EMEA/H/C/001245. 20 January 2011

Leroy R, Rosenfield W, Hall S et al. Long-term maintenance of efficacy with regitagine 600mg - 1200mg/day in adult patients with refractor epilepsy; extension study of RESTORE 1. Epilepsia 2010; 51 (suppl. 4): 1-189 (p258).

Lerche H, Leroy R, Hall S et al. Long-term maintenance of efficacy with regitagine 600mg - 1200mg/day in adult patients with refractor epilepsy; extension study of RESTORE 2. Epilepsia 2010; 51 (suppl. 4): 1-189 (p259).

*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/

This assessment is based on data submitted by the applicant company up to and including 13 May 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.