

# Partial-onset seizures in epilepsy: zonisamide as monotherapy

## Evidence summary

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[nice.org.uk/guidance/esnm17](https://www.nice.org.uk/guidance/esnm17)

## Overview

The content of this evidence summary was up-to-date in April 2013. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Key points from the evidence

In June 2012, the approved licence for zonisamide (Zonegran; adjunctive treatment of partial seizures, with or without secondary generalisation, in adults) was extended to include monotherapy for treating partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy.

One randomised, double blind, non-inferiority trial assessed the efficacy and tolerability of zonisamide in 583 patients with newly diagnosed partial seizures. The response rates were consistently lower with zonisamide compared with carbamazepine controlled release. In the per-protocol population, 79.4% of patients taking zonisamide were seizure free for at least 26 weeks (the primary outcome) compared with 83.7% of patients taking carbamazepine, an absolute difference of 4.5% in favour of carbamazepine. Zonisamide was not shown to be non-inferior to carbamazepine because the lower confidence interval of 12.2% was outside the pre-defined absolute non-inferiority margin of 12%. However, in its assessment of zonisamide, the European Medicines Agency concluded that a lower level of efficacy was acceptable because, overall, the

response rates were high in both study groups (around 80%); the difference in absolute and relative point estimates was less than 5%; and retention rates were similar in both groups.

The incidence of adverse events that were considered to be treatment related was similar for zonisamide and carbamazepine (36% compared with 38% respectively). The most frequently reported treatment-emergent adverse events (5% or more in either group) were headache, decreased appetite, somnolence, dizziness and weight loss. The adverse events reported for each drug were consistent with their established safety profiles.

The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (NICE clinical guideline 137) advises that people with newly diagnosed partial-onset seizures (also known as 'focal' seizures) should be offered monotherapy with carbamazepine or lamotrigine as first-line treatment. If carbamazepine and lamotrigine are unsuitable or not tolerated, levetiracetam, oxcarbazepine or sodium valproate is the next treatment option. If the first anti-epileptic drug tried is ineffective, an alternative from these 5 anti-epileptic drugs should be offered.

Zonisamide could offer an alternative to other anti-epileptic drugs in some people because of its different mechanism of action, once-daily dosing, and adverse event and interaction profiles (unlike some other anti-epileptic drugs, zonisamide is not thought to affect the pharmacokinetics of other medicines, such as oral contraceptives, through cytochrome P450-mediated mechanisms).

When making decisions about using zonisamide, localities will need to consider the available evidence suggesting similar efficacy and tolerability to carbamazepine alongside its less well established safety profile compared with other treatment options. Furthermore, the acquisition cost of zonisamide is generally, considerably higher than the other potential treatment options.

#### **Key evidence**

Baulac M, Brodie MJ, Patten A et al. (2012) Efficacy and tolerability of zonisamide versus controlled-release carbamazepine for newly diagnosed partial epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. *The Lancet Neurology* 11: 579–88

### *About this evidence summary*

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically

reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

## Relevance to NICE guidance programmes

Zonisamide as monotherapy for treating partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy was not considered appropriate for a NICE technology appraisal and is not currently planned into any other NICE work programme.

Zonisamide as adjunctive therapy for partial-onset seizures in epilepsy was considered during the development of [The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care](#) (NICE clinical guideline 137). The Guideline Development Group found that zonisamide was one of several anti-epileptic drugs that were more costly and less effective than other cost-effective treatment alternatives. The Guideline Development Group concluded that eslicarbazepine acetate, lacosamide, pregabalin, tiagabine and zonisamide should be considered only when initial adjunctive therapy options are contraindicated, ineffective or not tolerated. See the [introduction](#) for more details.

A [NICE Pathway on epilepsy](#) brings together all NICE guidance and associated products on epilepsy.

## Introduction

Epilepsy is a common neurological condition characterised by recurring seizures. Epileptic seizures can be broadly categorised into 2 main types: partial and generalised. Partial-onset seizures (also known as 'focal' seizures) are epileptic seizures in which the neuronal discharge begins in, or is restricted to, a localised part of the brain. Generalised seizures are characterised by more diffuse neuronal discharges involving both hemispheres of the brain at the same time (see the NICE clinical guideline on [epilepsy](#) and the final scope for the NICE technology appraisal on [retigabine for the adjunctive treatment of partial onset seizures in epilepsy](#)).

Epilepsy has been estimated to affect 260,000 to 416,000 people in England and Wales, 55% of whom have partial-onset seizures. It has been estimated that recurrent seizures could be controlled with anti-epileptic drugs in approximately 70% of people with active epilepsy, but only 52% of people are seizure free in clinical practice (see the final scope for the NICE technology appraisal on [retigabine](#)).

The NICE clinical guideline on [epilepsy](#) advises that people with newly diagnosed partial-onset seizures should be offered monotherapy with carbamazepine or lamotrigine as first-line treatment. If carbamazepine and lamotrigine are unsuitable or not tolerated, levetiracetam, oxcarbazepine or sodium valproate is the next treatment option. If the first anti-epileptic drug tried is ineffective, an alternative from these 5 anti-epileptic drugs should be offered.

According to the NICE clinical guideline on [epilepsy](#), if first-line treatments are ineffective or not tolerated, adjunctive treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate should be offered.

If adjunctive treatment is ineffective or not tolerated, the NICE clinical guideline on [epilepsy](#) recommends that advice should be sought from a tertiary epilepsy specialist. Anti-epileptic drugs that may be considered are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. The NICE technology appraisal on [retigabine for the adjunctive treatment of partial onset seizures in epilepsy](#) (NICE technology appraisal guidance 232) recommends retigabine as an option at this point.

## Product overview

### *Drug action*

Zonisamide is a benzisoxazole derivative that is chemically unrelated to other anti-epileptic drugs (see the [summary of product characteristics](#)). The mechanism of action of zonisamide is not fully understood. It appears to act on voltage-sensitive sodium and calcium channels, disrupting synchronised neuronal firing and reducing the spread of abnormal electrical activity in the brain and disrupting subsequent epileptic activity. Zonisamide also has a modulatory effect on gamma-aminobutyric acid (GABA)-mediated neuronal inhibition (see the [European public assessment report for Zonogran](#)).

### *New licensed therapeutic indication*

In June 2012, the approved licence for zonisamide (Zonogran; adjunctive treatment of partial-onset seizures, with or without secondary generalisation, in adults) was extended to include monotherapy for treating partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy (see the [European public assessment report for Zonogran](#)).

## Course and cost

When used as monotherapy, the [summary of product characteristics](#) advises that zonisamide should be initiated at a dose of 100 mg once daily, titrated upwards according to clinical response in increments of 100 mg at 2-weekly intervals. The usual maintenance dose is 300 mg once daily, although some people may respond to lower doses. The maximum dose is 500 mg once daily.

The current NHS cost of zonisamide (excluding VAT; costs taken from [Drug Tariff](#), March 2013) is:

- £8.82 for 14×25 mg capsules
- £47.04 for 56×50 mg capsules
- £62.72 for 56×100 mg capsules.

Based on this, the cost per patient per year for a 300 mg maintenance dose is estimated to be £1226.40. Costs may vary in different settings because of negotiated procurement discounts.

## Evidence review

This evidence review is based on a randomised controlled non-inferiority trial that compared the efficacy and tolerability of zonisamide with controlled-release carbamazepine in people with newly diagnosed partial epilepsy ([Baulac et al. 2012](#); see table 1).

- Design: phase III, [randomised](#), [double-blind](#), non-inferiority trial.
- Population: 583 adults (aged 18 to 75 years, mean 36 years) from 120 centres in 22 countries in Asia, Australia and Europe newly diagnosed (mean time since diagnosis 2.8 months) with unprovoked partial-onset seizures in epilepsy. Patients were eligible if they had had at least 2 partial-onset seizures (with or without secondary generalisation) or generalised tonic-clonic seizures without a clear focal origin (58% secondarily generalised tonic-clonic, 39% complex partial, 14% simple partial without motor signs, 13% generalised tonic-clonic, 10% simple partial with motor signs) in the past 12 months (mean 4.7 to 4.8) and at least 1 in the past 3 months (mean 2.9). Of all patients, 82% had not previously taken anti-epileptic drugs or had been treated with 1 anti-epileptic drug only for no more than 2 weeks. At study entry, 15% of patients were using concomitant anti-epileptic drugs. Anti-epileptic drug treatment was discontinued before randomisation or, if this was considered unsafe, treatment was down-titrated in the 2 weeks after randomisation.

- **Intervention and comparison:** after a 2-week screening period, patients were randomised to receive zonisamide 100 mg daily or carbamazepine controlled release 200 mg daily. Over 4 weeks, the doses were up-titrated to zonisamide 300 mg daily or carbamazepine 600 mg daily before patients entered a 26 to 78 week flexible-dosing period (zonisamide 200–500 mg once daily or carbamazepine 400–1200 mg daily in 2 divided doses). During this period the dose was up-titrated in patients who had seizures and down-titrated if necessary because of intolerance. All patients took the same number of identical capsules each day. Allocation was concealed. Once patients were seizure free for 26 weeks they entered a 26-week maintenance phase. Patients were withdrawn from the study if they needed a dose outside the permitted range or had seizures during the maintenance phase of the study. After the maintenance phase, patients could continue to an extension study or have their treatment down-titrated and withdrawn.
- **Outcome:** the primary end point was the proportion of patients who achieved seizure freedom (irrespective of seizure type) for 26 weeks or more, while receiving a stable dose of study medication. Seizure freedom was assessed using patient seizure diaries. Secondary end points included the proportion of patients who had no seizures for at least 52 weeks and the median times to the start of 26-week and 52-week seizure-free periods. Adverse events were also assessed. Analyses were primarily performed in the per-protocol population, with sensitivity analyses performed in the intention-to-treat population.

**Table 1 Summary of the trial:**[Baulac et al. \(2012\)](#)

		Zonisamide	Carbamazepine	Analysis <sup>a</sup>
Randomised		n=282	n=301	
Efficacy		ITT n=281 <sup>b</sup> PP n=223 <sup>c</sup>	ITT n=300 <sup>b</sup> PP n=233 <sup>c</sup>	

Primary outcome: proportion of patients seizure free for 26 weeks or more <sup>d</sup>	PP population	79.4% (177/223)	83.7% (195/233)	<p><u>Absolute</u> difference –4.5%; 95% CI –12.2% to 3.1%</p> <p>The lower limit of the CI is outside the –12% margin pre-specified in the study <u>protocol</u> to show zonisamide is non-inferior to carbamazepine; <u>p value</u> not reported</p> <p><u>Relative</u> difference –5.4%; 95% CI –14.7% to 3.7%</p> <p>The lower limit of the CI is inside the –20% margin required by guidelines to show non-inferiority in monotherapy studies in epilepsy; p value not reported</p>
	ITT population	69.4% (195/281)	74.7% (224/300)	<p>Absolute difference –6.1%; 95% CI –13.6% to 1.4%</p> <p>p value not reported</p>
Selected secondary outcomes				
Proportion of patients seizure free for at least 52 weeks <sup>d</sup>	PP population	67.6% (146/216)	74.7% (171/229)	<p>Absolute difference –7.9%; 95% CI –17.2% to 1.5%</p> <p>p value not reported</p> <p>Non-inferiority margins not pre-specified</p>
	ITT population	55.9% (157/281)	62.3% (187/300)	<p>Absolute difference –7.7%; 95% CI –16.1% to 0.7%</p> <p>p value not reported</p>
Median time to seizure freedom for 26 weeks	PP population	204 days	204 days	<p>HR 0.92; 95% CI 0.75 to 1.14</p> <p>p value not reported</p>
	ITT population	205 days	204 days	<p>HR 0.91; 95% CI 0.75 to 1.11</p> <p>p value not reported</p>

Median time to seizure freedom for 52 weeks	PP population	381 days	381 days	HR 0.88; 95% CI 0.70 to 1.11 p value not reported
	ITT population	382 days	381 days	HR 0.83; 95% CI 0.67 to 1.04 p value not reported
Safety		n=281 <sup>b</sup>	n=300 <sup>b</sup>	
Patients with treatment-related adverse events	ITT population	36% (102/281)	38% (115/300)	Significance not reported
Patients with serious treatment-related adverse events		1% (3/281)	2% (7/300)	Significance not reported
Patients with treatment-emergent adverse events leading to withdrawal		11% (31/281)	12% (35/300)	Significance not reported

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PP, per-protocol.

<sup>a</sup> Analyses for the primary and secondary outcomes were done using the PP population and sensitivity analyses were done using the ITT population.

<sup>b</sup> The ITT and safety populations were defined as all randomly assigned patients who received at least 1 dose of study medication.

<sup>c</sup> The PP population included patients in the ITT population who had no major protocol violations or deviations that might affect efficacy including less than 80% overall compliance, loss to follow-up before end of flexible dosing, missing seizure diaries during flexible-dosing period, dosing outside protocol requirements, and not receiving an up-titrated dose after a seizure. Protocol variations and deviations were monitored and classified by the study team before database lock.

<sup>d</sup> Adjustment was made for country group. Any country group with fewer than 10 patients was pooled with its geographical neighbour until all groups had more than 10 patients.

## *Clinical effectiveness*

In the per-protocol population, 79.4% of patients taking zonisamide were seizure free for at least 26 weeks compared with 83.7% of patients taking carbamazepine. The absolute difference between the groups (adjusted for country group) was -4.5% (95% confidence interval [CI] -12.2% to 3.1%). Zonisamide was not shown to be non-inferior to carbamazepine in this analysis: the lower limit of the confidence interval is outside the -12% non-inferiority margin that was pre-specified in the study protocol. A similar result was obtained in the sensitivity analysis in the intention-to-treat population.

When the relative treatment difference (-5.4%, 95% CI -14.7% to 3.7%) was considered for the outcome of seizure freedom at 26 weeks, zonisamide was found to be non-inferior to carbamazepine: the lower limit of the confidence interval is inside the -20% margin required by the International League Against Epilepsy guidelines to show non-inferiority in monotherapy studies in epilepsy.

The study also considered the proportions of patients who were seizure free for at least 52 weeks. However, it is difficult to draw any firm conclusions for this analysis because non-inferiority margins were not pre-specified. In the per-protocol population, 67.6% of patients taking zonisamide were seizure free at 52 weeks compared with 74.7% taking carbamazepine (absolute difference -7.9%, 95% CI -17.2% to 1.5%). A similar result was seen in the intention-to-treat population.

No statistically significant difference was found between zonisamide and carbamazepine in median time to seizure freedom at 26 weeks (204 days in both groups, HR 0.92, 95% CI 0.75 to 1.14) or 52 weeks (381 days in both groups, HR 0.88, 95% CI 0.70 to 1.11). The results were similar in the intention-to-treat population.

## *Safety*

The incidence of treatment-emergent adverse events that were considered to be treatment related was similar for zonisamide and carbamazepine (36% compared with 38% respectively). These were considered to be serious in 3 patients taking zonisamide (1%) and 7 patients taking carbamazepine (2%). Treatment-emergent adverse events led to discontinuation in 31 patients taking zonisamide (11%) and 35 taking carbamazepine (12%). The statistical significance of any differences between the groups is not reported in the safety analyses.

The most frequently reported treatment-emergent adverse events (5% or more in either group) were headache, decreased appetite, somnolence, dizziness and weight loss. Decreased appetite and weight loss were more frequently reported in the zonisamide group (8% and 7% respectively, compared with 2% and 0% respectively in the carbamazepine group). Dizziness was more commonly reported in the carbamazepine group (8% compared with 4% in the zonisamide group). Bicarbonate concentration decreased by 3.5 mmol/l or more in 51% of patients taking zonisamide compared with 17% of patients taking carbamazepine. However, this was not reported as an adverse event in any patients and there were no reports of metabolic acidosis.

According to the [summary of product characteristics](#) the most common adverse events associated with zonisamide are anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence, diplopia and decreased bicarbonate, with an incidence of more than 1 in 10 reported during clinical studies looking at zonisamide for adjunctive therapy and post-marketing surveillance.

Zonisamide is a benzisoxazole derivative, which contains a sulphonamide group. Serious immune-based adverse reactions that are associated with medicinal products containing a sulphamide group include rash, allergic reaction and major haematological disturbances including aplastic anaemia, which very rarely can be fatal (see the [summary of product characteristics](#)).

## *Evidence strengths and limitations*

In their [assessment of zonisamide](#), the European Medicines Agency (EMA) states that this study (Baulac et al. 2012) was carried out in line with EMA guidance and scientific advice. The study had a clinically meaningful outcome and a duration of at least 1 year, and used flexible dosing to closely mimic clinical practice.

The EMA notes that there is no guidance on appropriate inferiority margins to be used in studies in epilepsy, and that the [Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders](#) states that non-inferiority margins will need to be justified by the applicant on the basis of a clinically important difference in efficacy. This study used the [International League Against Epilepsy guidelines](#), which specify that any relative difference between treatments in the primary outcome should not be more than 20% in order to show non-inferiority in monotherapy studies in epilepsy.

The EMA states that zonisamide showed consistently lower response rates compared with carbamazepine. In the per-protocol population, there was a difference of -4.5% in favour of carbamazepine and the lower confidence interval of 12.2% was outside the pre-defined absolute

non-inferiority margin of 12%. However, the EMA concluded that a lower level of efficacy was acceptable because, overall, the response rates were high in both study groups (around 80%); the difference in absolute and relative point estimates was less than 5%; and retention rates were similar in both groups.

A large number of patients dropped out of the study. More patients discontinued treatment with zonisamide compared with carbamazepine (43% compared with 36% respectively). However, the discontinuations due to adverse events and lack of efficacy were similar between the groups (around 11% and 8% in both groups respectively).

The study was undertaken in 120 centres worldwide with some enrolling fewer than 5 people. It is possible that this may have affected how rigorously and consistently trial outcomes were assessed.

Of the patients included in the study, 15% had generalised tonic-clonic seizures, a proportion of whom may not have had partial-onset seizures. Although including these patients reflects clinical practice where there is reliance on initial witness reports and diagnostic decisions are made based on few witnessed seizures, this is a potential limitation of the study.

The study was funded by the manufacturer of zonisamide, Eisai Ltd.

## Context

### *Treatment alternatives*

Zonisamide is licensed as monotherapy for the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy. The NICE clinical guideline on [epilepsy](#) advises that people with newly diagnosed partial-onset seizures should be offered monotherapy with carbamazepine or lamotrigine as first-line treatment. If carbamazepine and lamotrigine are unsuitable or not tolerated, levetiracetam, oxcarbazepine or sodium valproate is the next treatment option. If the first anti-epileptic drug tried is ineffective, an alternative from these 5 anti-epileptic drugs should be offered.

### *Costs of treatment alternatives*

	Usual adult maintenance dose <sup>a</sup>	Estimated 28-day cost excluding VAT
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Carbamazepine	800–1200 mg daily in 2 or 3 divided doses	£5.02 to £7.53 <sup>b</sup>
Carbamazepine controlled release	800–1200 mg daily in 2 divided doses	£10.24 to £15.44 <sup>b</sup>
Lamotrigine	100–200 mg once daily or in 2 divided doses	£1.54 to £3.08 <sup>b</sup>
Levetiracetam	1000–2000 mg daily in 2 divided doses	£5.52 to £11.53 <sup>b</sup>
Oxcarbazepine	600–2400 mg daily in 2 divided doses	£24.83 to £99.34 <sup>b</sup>
Sodium valproate	1000–2000 mg daily in 2 divided doses	£5.24 to £10.47 <sup>b</sup>
Sodium valproate controlled release	1000–2000 mg once daily or in 2 divided doses	£16.30 to £32.60 <sup>c</sup>
Zonisamide	300–500 mg daily	£94.08 to £156.80 <sup>b</sup>
<p><sup>a</sup> Doses taken from the relevant <a href="#">summary of product characteristics</a>. The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.</p> <p><sup>b</sup> Costs for solid dose forms; taken from <a href="#">Drug Tariff</a> March 2013.</p> <p><sup>c</sup> Costs taken from <a href="#">MIMS</a> March 2013.</p>		

## Estimated impact for the NHS

### *Likely place in therapy*

The NICE clinical guideline on [epilepsy](#) advises that people with newly diagnosed partial-onset seizures should be offered monotherapy with carbamazepine or lamotrigine as first-line treatment. If carbamazepine and lamotrigine are unsuitable or not tolerated, levetiracetam, oxcarbazepine or sodium valproate is the next treatment option. If the first anti-epileptic drug tried is ineffective, an alternative from these 5 anti-epileptic drugs should be offered.

Zonisamide provides a further option for monotherapy in adults with newly diagnosed partial-onset seizures in epilepsy. Local decision makers will need to consider the available evidence when making decisions about using it. The likely benefits of its use will need to be balanced against the possible risks, as well as the relatively high acquisition costs.

Although response rates in the study were consistently lower with zonisamide compared with carbamazepine, a high response rate was still observed in those patients taking zonisamide. The incidence of adverse events was similar between the groups and the adverse events reported for each drug were consistent with their established safety profiles.

The European Medicines Agency (EMA) concluded that zonisamide could offer an alternative to other anti-epileptic drugs in some people because of its different mechanism of action, once daily dosing, and adverse event and interaction profiles (unlike some other anti-epileptic drugs, zonisamide is not thought to affect the pharmacokinetics of other medicines, such as oral contraceptives, through cytochrome P450-mediated mechanisms). Choice of the most appropriate treatment will depend on an individual person's medical and drug history, and dosing preferences.

A randomised controlled trial funded by the NHS National Institute for Health Research [Health Technology Appraisal Programme](#) is underway comparing the effectiveness and cost effectiveness of zonisamide and levetiracetam with standard treatments for epilepsy ([A comparison of Standard And New Antiepileptic Drugs, SANAD-II](#)). This study may help to determine zonisamide's likely place in therapy; however, the results are not expected to be published until 2020.

### *Estimated usage*

The number of people in England and Wales estimated to have epilepsy ranges from 260,000 to 416,000; partial-onset seizures affect between 118,800 and 228,800 of these people. It has been estimated that recurrent seizures could be controlled with anti-epileptic drugs in approximately 70% of people with active epilepsy (see the final scope for the NICE technology appraisal on [retigabine](#)), which suggests that around 35,640 to 68,640 people in England and Wales have partial-onset seizures that are refractory to current treatment and may benefit from further treatment options. It is not possible to estimate usage of zonisamide based on the available data; however, it is likely that it could be used in a proportion of these people.

### References

Baulac M, Brodie MJ, Patten A et al. (2012) [Efficacy and tolerability of zonisamide versus controlled-release carbamazepine for newly diagnosed partial epilepsy: a phase 3, randomised, double-blind, non-inferiority trial](#). *The Lancet Neurology* 11: 579–88

Eisai Ltd (2013) [Zonegran summary of product characteristics](#) [online; accessed 25 March 2013]

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National Institute for Health and Clinical Excellence (2012) [The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care](#). NICE clinical guideline 137

National Institute for Health and Clinical Excellence (2011) [Retigabine for the adjunctive treatment of partial onset seizures in epilepsy](#). NICE technology appraisal guidance 232

National Institute for Health and Clinical Excellence (2010) [Retigabine for the adjunctive treatment of partial onset seizures in epilepsy](#). NICE technology appraisal final scope

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For information about the process used to develop this evidence summary, see [Evidence summaries: new medicines – interim process statement](#).

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