

Partial seizures in children and young people with epilepsy: zonisamide as adjunctive therapy

Evidence summary

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[nice.org.uk/guidance/esnm37](https://www.nice.org.uk/guidance/esnm37)

Key points from the evidence

The content of this evidence summary was up-to-date in March 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#), [BNF for children \(BNFc\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

In a double-blind, randomised controlled trial (RCT) in 207 children and young people aged 6–17 years with partial seizures, zonisamide (as adjunctive treatment) statistically significantly increased the number of participants achieving at least a 50% reduction in seizure frequency from baseline compared with placebo. Although the general safety profile for zonisamide in children and young people is similar to that in adults, certain adverse events raise concerns because they may have greater implications in children than in adults.

Effectiveness	Safety
<ul style="list-style-type: none">• In a double-blind RCT (n=207) in patients receiving a stable regimen of 1 or 2 antiepileptic drugs for at least 1 month, zonisamide compared with placebo statistically significantly:<ul style="list-style-type: none">- increased the number of participants achieving at least a 50% reduction in seizure frequency from baseline (responder rate: 50% with zonisamide compared with 31% with placebo; p=0.0044)- reduced 28-day seizure frequency from baseline (50% reduction in zonisamide group compared with 24.5% reduction in the placebo group; median difference between the groups: 25.2%; 95% CI 12.2% to 38.7%, p<0.0001).	<ul style="list-style-type: none">• General safety profile for zonisamide in children and young people is similar to that in adults. However, some adverse events may have greater implications in children than in adults; for example, weight loss, changes in bicarbonate levels, and decreased sweating and elevated body temperature that can lead to heat stroke.

Patient factors	Resource implications
<ul style="list-style-type: none">• Zonisamide is only available in capsule formulation, and capsules have to be swallowed whole. This may mean it is unsuitable for children and young people with swallowing difficulties.• Administration in children and young people is once daily, which may be preferable to some.• Treatment-emergent adverse events that occurred more frequently in the zonisamide group than in the placebo group included decreased appetite (6.5% compared with 4.0%), weight loss (4.7% compared with 3.0%), somnolence (4.7% compared with 2.0%), vomiting (3.7% compared with 2.0%), and diarrhoea (3.7% compared with 1.0%).	<ul style="list-style-type: none">• Zonisamide (Zonegran, Eisai Limited) capsules cost:<ul style="list-style-type: none">- £8.82 for 14×25 mg capsules- £47.04 for 56×50 mg capsules- £62.72 for 56×100 mg capsules.• Cost per year for a maintenance dose for a child or young person aged 6 years and over weighing between 20 and 55 kg is estimated to be between £638.75 and £1941.80 depending on the dose and child's weight• Cost per year for a maintenance dose for a child or young person aged 6 years or over, weighing more than 55 kg, is £1226.40 to £2044.00.

Key points

In October 2013, the approved licence for zonisamide (Zonegran, Eisai Limited; adjunctive treatment of partial seizures, with or without secondary generalisation, in adults) was extended to include 'adolescents' and children aged 6 years and over (see the [European public assessment report \(EPAR\) for Zonegran](#)).

NICE published an evidence summary on [zonisamide monotherapy for treating partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy in April 2013 \(ESNM17\)](#).

This evidence summary is based on a phase III double-blind RCT that assessed the efficacy and safety of adjunctive zonisamide therapy in 207 children and young people with partial epilepsy ([Guerrini et al. 2013](#)). This trial was the main efficacy study assessed by the European Medicines Agency when a licence extension application was submitted for zonisamide (see the [EPAR for Zonegran](#)). An open-label extension study ([Guerrini et al. 2014](#)) assessing the longer term

(45–57 weeks) efficacy and safety of adjunctive zonisamide therapy in children and young people with partial epilepsy has been published and is discussed in the [safety](#) section.

In Guerrini et al. (2013), zonisamide statistically significantly increased the number of participants who experienced a 50% or greater reduction in seizure frequency from baseline compared with placebo (responder rate: 50% with zonisamide compared with 31% with placebo; $p=0.0044$). Zonisamide also resulted in a greater reduction in 28-day seizure frequency from baseline during the maintenance period compared with placebo (50% reduction in the zonisamide group compared with 24.5% in the placebo group, median between group difference: 25.2%, 95% [confidence interval](#) [CI] 12.2% to 38.7%, $p<0.0001$).

The incidence of treatment-emergent adverse events was similar in the zonisamide and placebo groups (55.1% compared with 50.0% respectively). However, the incidence of treatment-related, treatment-emergent adverse events was higher in the zonisamide group than the placebo group (33.6% compared with 24.0% respectively). Treatment-emergent adverse events that were reported more frequently in the zonisamide group than in the placebo group included decreased appetite (6.5% compared with 4.0%), weight loss (4.7% compared with 3.0%), somnolence (4.7% compared with 2.0%), vomiting (3.7% compared with 2.0%), and diarrhoea (3.7% compared with 1.0%). Four participants in the zonisamide group and 2 in the placebo group experienced serious treatment-emergent adverse events, including 1 participant in the zonisamide group who died. The death was considered to be possibly treatment-related: the young person experienced weight loss and diarrhoea which weakened his general condition to such an extent he was unable to take his anti-epileptic medications, triggering a fatal episode of status epilepticus.

The primary outcome in [Guerrini et al. \(2013\)](#) was assessed using the last observation carried forward (LOCF) approach to take account of missing data. This approach can affect the robustness of trial results; however, in [Guerrini et al. \(2013\)](#) sensitivity analyses showed similar results for responder rates (the primary outcome), which provides reassurance about the reliability of the results. The trial was undertaken in 41 centres in Europe and India meaning some centres would have enrolled fewer than 10 children and young people. It is possible that this may have affected how rigorously and consistently trial outcomes were assessed.

In the [EPAR](#), the Committee for Medicinal Products for Human Use concluded that although the general safety profile for zonisamide in children is similar to that in adults, there are several important issues that raise concerns such as weight loss, dehydration and decrease in bicarbonate levels, because they may have greater implications in children than in adults. The product information has been updated to include warnings about adverse events that may more relevant to children.

The NICE clinical guideline [The Epilepsies: the diagnosis and clinical management of the epilepsies in adults and children in primary and secondary care](#) (NICE clinical guideline 137) advises that monotherapy with carbamazepine or lamotrigine should be offered as first-line treatment to children, young people and adults with newly diagnosed partial (focal) seizures. If carbamazepine and lamotrigine are unsuitable or not tolerated, the person should be offered monotherapy with levetiracetam, oxcarbazepine or sodium valproate (bearing in mind the teratogenic risks of sodium valproate). If the first anti-epileptic drug tried is ineffective, an alternative from these 5 anti-epileptic drugs should be offered. If standard first-line treatments are ineffective or not tolerated, the person should be offered adjunctive treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate.

If adjunctive treatment is ineffective or not tolerated, the [guideline](#) recommends that decisions about treatment options should be made after advice from a tertiary epilepsy specialist. Anti-epileptic drugs that may be considered include eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.

Prescribers should be aware that not all the drugs mentioned above currently have a UK marketing authorisation for use for the particular indication or population mentioned (for example, depending on the age of the person). In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using drugs outside their authorised indications.

Local decision makers will need to consider the place of zonisamide alongside other available adjunctive treatments for partial seizures. It is unclear how zonisamide compares with other drugs used at this stage in the care pathway; however the European Medicines Agency states that the efficacy of zonisamide appears similar to other anti-epileptic drugs already indicated for adjunctive use in children. The nature of potential adverse effects, cost, and individual patient/parent/carer preference will all influence the decision to use a particular adjunctive anti-epileptic drug in each person.

Key evidence

Guerrini R, Rosati A, Segieth J et al. (2013) [A randomized phase III trial of adjunctive zonisamide in pediatric patients with partial epilepsy](#). *Epilepsia* 54: 1473–80

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 adjunctive therapy for treating partial seizures, with or without secondary generalisation, in children and young people aged 6 years and over was not considered appropriate for a NICE technology appraisal.

NICE published an evidence summary on [zonisamide monotherapy for treating partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy in April 2013 \(ESNM17\)](#).

Zonisamide as adjunctive therapy for partial (focal) 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 \(NICE clinical guideline 137\)](#). Based on evidence that was available at the time (up to June 2010), 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.

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 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 NICE technology appraisal final scope on [retigabine for the adjunctive treatment of partial onset seizures in epilepsy](#)).

It is estimated that 34,000 children and young people in England with a diagnosis of epilepsy are currently receiving anti-epileptic drugs (see the NICE quality standard on [the epilepsies in children and young people](#)).

The NICE clinical guideline on [epilepsy](#) advises that children, young people and adults with newly diagnosed partial (focal) seizures should be offered monotherapy with carbamazepine or lamotrigine as first-line treatment. If carbamazepine and lamotrigine are unsuitable or not tolerated, the person should be offered monotherapy with levetiracetam, oxcarbazepine or sodium valproate (bearing in mind the teratogenic risks of sodium valproate). 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 to children, young people and adults with partial (focal) seizures.

If adjunctive treatment is ineffective or not tolerated, the [guideline](#) recommends that advice should be sought from a tertiary epilepsy specialist. Anti-epileptic drugs that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. The NICE technology appraisal guidance on [retigabine for the adjunctive treatment of partial onset seizures in epilepsy](#) (NICE technology appraisal guidance 232) recommends retigabine as a treatment option for adults aged 18 years and over at this point.

Prescribers should be aware that not all the drugs mentioned above currently have a UK marketing authorisation for use for the particular indication or population mentioned (for example, depending on the age of the person). In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using drugs outside their authorised indications.

Product overview

Drug action

Zonisamide is a benzisoxazole derivative that is chemically unrelated to other anti-epileptic drugs (see the [summary of product characteristics for Zonéggran](#)). 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 disturbing subsequent epileptic activity. Zonisamide also has a modulatory effect on gamma-aminobutyric acid (GABA)-mediated neuronal inhibition (see the [European public assessment report \(EPAR\) for Zonéggran](#)).

New therapeutic indication

In October 2013, the approved licence for zonisamide (Zonegran, Eisai Limited; adjunctive treatment of partial seizures, with or without secondary generalisation, in adults) was extended to include 'adolescents' and children aged 6 years and over (see the [EPAR for Zonegran](#)).

Zonisamide (Zonegran, Eisai Limited) is also licensed for monotherapy treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy (see the [summary of product characteristics for Zonegran](#)).

Course and cost

When used as adjunctive therapy in children aged 6 years and over, the [summary of product characteristics for Zonegran](#) advises that zonisamide should be initiated at a dose of 1 mg/kg/day, titrated upwards according to clinical response in increments of 1 mg/kg at weekly intervals in those taking CYP3A4-inducing agents, and at 2-weekly intervals in those who are not taking CYP3A4-inducing agents. The usual maintenance dose for children weighing from 20 kg to 55 kg is 6–8 mg/kg taken once daily up to a maximum of 500 mg daily. To ensure a therapeutic dose is maintained, the child's weight should be monitored and the dose reviewed as weight changes occur, up to a weight of 55 kg. For children weighing more than 55 kg, the usual maintenance dose is 300–500 mg taken once daily. Some children, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

The current NHS cost of zonisamide (excluding VAT; costs taken from [Drug Tariff](#), February 2014) is:

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

The cost per year for a child weighing between 20 and 55 kg taking 6–8 mg/kg once daily as a maintenance dose is estimated to be between £638.75 and £1941.80 depending on the dose and child's weight. The cost per year for a child weighing more than 55 kg taking 300–500 mg once daily as a maintenance dose is estimated to be £1226.40 to £2044. Comparison costs with other treatment alternatives are given in the [Costs of treatment alternatives](#) section.

Evidence review

This evidence summary is based on a phase III trial that assessed the efficacy and safety of adjunctive zonisamide therapy in children and young people with partial epilepsy ([Guerrini et al. 2013](#)). This trial was the main efficacy study assessed by the European Medicines Agency (EMA) when a licence extension application was submitted for zonisamide (see the [European public assessment report \(EPAR\) for Zonegran](#)). An open-label extension study ([Guerrini et al. 2014](#)) assessing the longer term (45–57 weeks) efficacy and safety of adjunctive zonisamide therapy in children and young people with partial epilepsy has been published and is discussed in the [safety](#) section.

- Design: [randomised](#), [double-blind](#), placebo-controlled trial in 41 centres in Europe and India.
- Population: 207 children and young people (aged 6–17 years, mean age 11 years) with a clinical diagnosis of epilepsy with partial-onset seizures, with or without secondary generalisation. Participants needed to have experienced at least 4 partial seizures (simple or complex, with or without secondary generalisation) per month during the 8-week baseline period, with at least 1 seizure in each 4-week period and no 21-day period without any seizures. In addition, participants needed to be receiving a stable regimen of 1 or 2 anti-epileptic drugs for at least 1 month before the first visit (1 anti-epileptic drug: 44% in the zonisamide group compared with 39.0% in the placebo group; 2 anti-epileptic drugs: 58.9% in the zonisamide group compared with 60.0% in the placebo group). Exclusion criteria included body weight less than 20 kg at screening, progressive neurological disease, history of idiopathic generalised epilepsy, psychogenic seizures, cluster seizures, history of status epilepticus within the previous year, previous treatment with zonisamide, and concomitant treatment with felbamate, acetazolamide, any carbonic anhydrase inhibitor, or any drug with anticholinergic activity. Baseline and demographic characteristics were similar between the groups apart from mean seizure frequency which was lower in the zonisamide group than the placebo group (mean number of seizures per 28 days: 32.9 in the zonisamide group compared with 43.8 in the placebo group). Median baseline seizure frequency however was similar in the zonisamide and placebo groups (median number of seizures per 28 days: 10.5 in the zonisamide group compared with 10.0 in the placebo group).
- Intervention and comparison: the study consisted of an 8-week baseline period including a 4-week screening period and historical seizure data from the 4 weeks before screening. Eligible people were then randomised 1:1 to zonisamide (n=107) or placebo (n=100), added to 1 or 2 anti-epileptic drugs. Allocation was appropriately [concealed](#). Zonisamide was started at a dosage of 1 mg/kg/day and increased by 1 mg/kg at weekly intervals, up to a target dose of 8 mg/kg/day over 8 weeks (maximum 500 mg daily). Five participants in the placebo group and

2 in the zonisamide group had a single dose reduction during titration. Participants then remained on the same dose for a 12-week maintenance period, apart from 1 participant in the placebo group who had a dose reduction. Most participants received a dosage of 5 mg/kg/day up to less than 9 mg/kg/day (92.9% in the zonisamide group compared with 83.9% in the placebo group) and almost all other participants received a dosage 9–12 mg/kg/day (7.1% in the zonisamide group compared with 15.1% in the placebo group). At the end of the 12-week maintenance period, participants either entered an extension study, or were down-titrated over 3–4 weeks and withdrawn. Outcomes: the primary efficacy outcome was the proportion of responders (that is the number of participants with a 50% or greater reduction in seizure frequency from baseline) during the 12-week maintenance period in the intention-to-treat (ITT) population using last observation carried forward (LOCF) data. Seizure data were obtained from seizure diaries completed by the child or young person's parent or guardian. Secondary efficacy outcomes included the median percentage change from baseline in 28-day seizure frequency; the proportion of participants with a reduction in seizure frequency of 75% or more; and the proportion of participants with an increase in seizure frequency of 25% or more, and 100% or more. Other efficacy outcomes included the proportion of participants experiencing seizure freedom; the percentage change from baseline in 28-day seizure frequency by seizure type; and the relationship between zonisamide plasma level and responder rate. Sensitivity analyses were performed, including for the ITT-observed case data set. Safety assessments included the incidence of treatment-emergent adverse events, and whether these were serious or resulted in withdrawal of study treatment; clinical laboratory parameters; physical and neurological evaluations; vital signs; height and weight; and electrocardiography.

Table 1 Summary of the trial:[Guerrini et al. \(2013\)](#)

	Population	Zonisamide at a target dose of 8 mg/kg/day	Placebo	Analysis
Randomised		n=107	n=100	
Efficacy ^a		n=107	n=100	
Primary outcome: proportion of responders during the 12-week maintenance period ^b	ITT-LOCF	50.0%	31.0%	p=0.0044
	ITT-OC	48.0%	31.0%	p=0.0143

Selected secondary outcomes:				
Median percentage reduction from baseline in 28-day seizure frequency during the 12-week maintenance period	ITT-LOCF	50.0%	24.5%	Median difference between the groups: 25.2%, 95% CI 12.2 to 38.7%, p<0.0001
Proportion of participants with seizure frequency reduction of 75% or more from baseline during the 12-week maintenance period	ITT-LOCF	27.0%	12.0%	p=0.0064
Proportion of participants with increase in seizure frequency of 25% or more from baseline during the 12-week maintenance period	ITT-LOCF	10.0%	21.0%	p=0.0330
Proportion of participants with increase in seizure frequency of 100% or more from baseline during the 12-week maintenance period	ITT-LOCF	5.0%	9.0%	p value not reported but stated to be non-significant
Safety		n=107	n=100	
Participants reporting treatment-emergent adverse events	Safety ^c	55.1% (59/107)	50.0% (50/100)	p value not stated
Participants reporting treatment-related treatment-emergent adverse events	Safety	33.6% (36/107)	24.0% (24/100)	p value not stated
Participants reporting serious treatment-emergent adverse events	Safety	3.7% (4/107)	2.0% (2/100)	p value not stated
Participants reporting serious treatment-related treatment-emergent adverse events	Safety	1.9% (2/107)	1.0% (1/100)	Includes 1 person in the zonisamide group who died due to de novo status epilepticus

Participants with treatment-emergent adverse events leading to withdrawal	Safety	0.9% (1/107)	3.0% (3/100)	
Participants with treatment-emergent adverse events leading to dose reduction	Safety	2.8% (3/107)	5.0% (5/100)	
<p>Abbreviations: CI, <u>confidence interval</u>; ITT-LOCF, intention-to-treat last observation carried forward population; ITT-OC, intention-to-treat observed case population; p, <u>p value</u>.</p> <p>^a The intention-to-treat population consisted of all randomised participants who received at least 1 dose of double-blind study medication. Analysis of the primary efficacy outcome was performed for the intention-to-treat population using last observation carried forward data and sensitivity analyses were performed using the intention-to-treat observed case, and per-protocol last observation carried forward data.</p> <p>^b Responders were defined as participants with a 50% or more reduction in seizure frequency from baseline.</p> <p>^c The safety population consisted of all randomised participants who received at least 1 dose of double-blind study medication.</p>				

Clinical effectiveness

During the maintenance period, in the ITT-LOCF population, zonisamide statistically significantly increased the responder rate (that is, the number of participants who experienced a 50% or greater reduction in seizure frequency from baseline) compared with placebo (responder rate: 50% with zonisamide compared with 31% with placebo; $p=0.0044$). This finding was supported by sensitivity analyses in the ITT observed cases (responder rate: 48% with zonisamide compared with 31% for placebo; $p=0.0143$) and per-protocol LOCF populations (responder rate: 51% with zonisamide [$n=100$] compared with 31% for placebo [$n=91$]; $p=0.0046$).

In the ITT-LOCF population, the median reduction in 28-day seizure frequency from baseline during the maintenance period was 50% in zonisamide group compared with 24.5% in the placebo group. The median difference between the groups was 25.2% and was statistically significant (95% confidence interval [CI] 12.2% to 38.7%, $p<0.0001$). The authors report that these findings were consistent in the ITT observed cases, and per-protocol LOCF populations, however no data were reported.

In the ITT-LOCF population, the proportion of participants who had a reduction in seizure frequency of 75% or more was statistically significantly greater in the zonisamide group compared with the placebo group (27% compared with 12% respectively; $p=0.0064$). The proportion of participants whose seizures increased in frequency by 25% or more was statistically significantly lower in the zonisamide group than in the placebo group (10% compared with 21% respectively; $p=0.0330$). However, the proportion of participants whose seizures increased in frequency by 100% or more was not statistically significantly different between the zonisamide and placebo groups (5% compared with 9% respectively; p value not reported but the result was stated to be non-significant).

In the ITT-LOCF population, the number of participants achieving seizure freedom during the maintenance period was statistically significantly greater in the zonisamide group compared with the placebo group (14% compared with 3% respectively; $p=0.0049$). When comparing the median reduction in 28-day seizure frequency from baseline during the maintenance period by seizure type, reductions were statistically significantly greater in the zonisamide group compared with the placebo group for complex partial seizures, but not for simple partial seizures or secondarily generalised seizures. However, interpretation of these analyses is difficult as the study was not powered to detect differences in efficacy outcomes by seizure type.

Safety

In the [Guerrini et al. \(2013\)](#) trial, the incidence of treatment-emergent adverse events was similar in the zonisamide and placebo groups (55.1% compared with 50.0% respectively). However, the incidence of treatment-emergent adverse events judged to be treatment-related was higher in the zonisamide group than the placebo group (33.6% compared with 24.0% respectively).

Treatment-emergent adverse events that were reported more frequently in the zonisamide group than in the placebo group included decreased appetite (6.5% compared with 4.0%), weight loss (4.7% compared with 3.0%), somnolence (4.7% compared with 2.0%), vomiting (3.7% compared with 2.0%), and diarrhoea (3.7% compared with 1.0%). One participant (0.9%) in the zonisamide group withdrew from the study because of a treatment-emergent adverse event (allergic dermatitis) compared with 3 (3.0%) in the placebo group (1 participant withdrew because of upper abdominal pain, 1 because of aggressive behaviour and sleep disorder, and 1 because of complex partial seizures). Four participants in the zonisamide group and 2 in the placebo group experienced serious treatment-emergent adverse events, including 1 child in the zonisamide group who died. The death was considered to be possibly treatment related: the young person (a 14-year-old male) experienced weight loss and diarrhoea which weakened their general condition to such an extent they were unable to take their anti-epileptic medications. This triggered a fatal episode of status

epilepticus. Another participant in the zonisamide group experienced severe weight loss, moderately decreased blood glucose, and moderate dehydration, which were all considered to be possibly treatment related. One participant in the placebo group experienced severe vomiting and moderate somnolence.

Bicarbonate levels decreased in the zonisamide group. The proportion of participants who experienced a reduction in bicarbonate level of at least 3.5 mmol/L from baseline to final visit was greater in the zonisamide group than the placebo group (50.5% compared with 16.0%). The authors report there were no other clinically significant changes in laboratory values or electrocardiography from baseline to final visit.

Guerrini et al. (2014) report an open-label extension study assessing the longer term (45–57 weeks) efficacy and safety of zonisamide in 144 children and young people recruited from the Guerrini et al. (2013) study (72 children who had received zonisamide, and 72 who had previously received placebo). During the first 11 weeks of this study, children who received zonisamide in Guerrini et al. (2013) remained on this treatment and children who received placebo changed their treatment to zonisamide and up-titrated, after which the study became open-label. Treatment-emergent adverse events were reported in 48.6% of the study population (51.4% in children who had previously received zonisamide and 45.8% in children who had previously received placebo). The most commonly reported adverse events were nasopharyngitis, weight loss and headache. Serious treatment-emergent adverse events were reported in 10 (6.9%) children and were considered to be treatment related in 3 cases (renal colic, foot fracture, and abdominal pain). Decreases in bicarbonate level of more than 3.5 mmol/L were observed in 64 (44.4%) children, but there were no reports of metabolic acidosis. These changes in bicarbonate levels were considered to be similar to those described in previous trials of zonisamide.

The EPAR for Zonegran also presents pooled safety data in children and young people from all available completed studies at the time of the licence submission (17 studies; children aged under 12 years: n=191, children and young people aged 12–16 years: n=207). These pooled data included data from the Guerrini et al. (2013) study, but not from the extension study.

Treatment-emergent adverse events were reported in 82.9% of those who received zonisamide, and 55% who received placebo. The most common treatment-emergent adverse events in children aged 6–11 years were pyrexia (21.9%), headache (21.2%), upper respiratory tract infection (21.1%), decreased appetite (20.5%), rash (12.3%), somnolence (18.5%), vomiting (14.4%), fatigue (13.7%), nasopharyngitis (13.7%), sinusitis (11.0%), viral infection (11.0%), upper abdominal pain (10.3%), cough (10.3%), insomnia (10.3%) and nasal congestion (10.3%). In children and young people aged

12–16 years, the most common adverse events included headache (18.4%), decreased appetite (17.4%), fatigue (12.6%), dizziness (12.1%) and somnolence (11.1%).

In the pooled data, serious treatment-emergent adverse events were reported in 57 children (14.3%) who received zonisamide. This included 7 children who died (including the 1 young person in Guerrini et al. 2013), 4 of whom had pre-existing functional neurological conditions or remote symptomatic epilepsy. Of the 7 deaths, 2 were considered to be related to zonisamide. The most frequently reported serious adverse events overall were convulsion (4.3%), status epilepticus (2.5%), and dehydration (1.8%). Apart from those which resulted in death, most serious adverse events resolved.

In the [EPAR for Zonegran](#), the Committee for Medicinal Products for Human Use concluded that although the general safety profile for zonisamide in children is similar to that in adults, there are several important issues that raise concerns because they may have greater implications in children than in adults. The product information has been updated to include warnings about adverse events that may be more relevant to children. Within the EPAR, the Committee for Medicinal Products for Human Use state that overall the number of children and young people that died during the studies was concerning, although the number was similar to mortality rates in people taking other anti-epileptic drugs.

The [summary of product characteristics for Zonegran](#) warns that because of the potential seriousness of decreased body weight in children, weight should be monitored in this population. In addition, the risk of zonisamide-induced metabolic acidosis appears to be more frequent and severe in children; appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in this population. Cases of decreased sweating and elevated body temperature, leading to heat stroke resulting in hospitalisation and in some cases death, have been reported in children. The summary of product characteristics for Zonegran gives advice on preventing overheating and dehydration in children who are being treated with zonisamide.

Evidence strengths and limitations

The [EPAR for Zonegran](#) states that the study design of [Guerrini et al. \(2013\)](#) was broadly in line with the [Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders](#). It also stated that inclusion and exclusion criteria, participants included in the study and the choice of primary and secondary end points were considered appropriate for the indication being applied for.

The proportion of responders (that is, the number of participants with a 50% or greater reduction in seizure frequency from baseline) in Guerrini et al. (2013) was 50% with zonisamide compared with 31% with placebo. The [EPAR for Zonegran](#) states that this is of the same order of magnitude as that seen in trials of other anti-epileptic drugs used as adjunctive treatment in partial epilepsy in children. There are currently no studies comparing zonisamide with an active comparator in adjunctive treatment of partial epilepsy in children.

As the European Medicines Agency (EMA) notes in its [guideline on missing data in confirmatory clinical trials](#), it is unrealistic to expect that all patients in any clinical trial will receive treatment with full compliance to the treatment schedule and with a complete follow-up as per protocol. The study by Guerrini et al. (2013) used the LOCF approach to take account of missing data. The EMA's [guideline](#) notes that, because people who do not complete a clinical trial may be more likely to have extreme values than those who do, the loss of these 'non-completers' could artificially narrow the confidence interval for the treatment effect. The EMA guideline advises that it will almost always be necessary to investigate the robustness of trial results through appropriate sensitivity analyses that make different assumptions. In Guerrini et al. (2013), the analyses of ITT-observed cases and per-protocol LOCF populations showed similar results for responder rates (the primary outcome), which provides reassurance about the reliability of the results

Safety data from Guerrini et al. (2013) were limited in that children and young people received zonisamide for a mean of only 131 days (range: 7–156 days). The [European Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders](#) requires a study to include at least 100 children and last for at least 1 year to appropriately assess the long-term safety of anti-epileptic drugs. Therefore, during the licence extension application, the manufacturer submitted data from the longer-term (45–57 weeks) extension study ([Guerrini et al. 2014](#)). In addition, the EMA looked at pooled safety data in children from all available completed studies at the time of the licence application.

The Guerrini et al. (2013) study was undertaken in 41 centres in Europe and India meaning some centres would have enrolled fewer than 10 children and young people. It is possible that this may have affected how rigorously and consistently trial outcomes were assessed.

Context

Treatment alternatives

Zonisamide is indicated for the adjunctive treatment of partial seizures with or without secondary generalisation. The NICE clinical guideline on [epilepsy](#) advises that adjunctive treatment of partial

(focal) seizures in children, young people and adults should normally be with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate. If this is ineffective or not tolerated, advice should be sought from a tertiary epilepsy specialist. Anti-epileptic drugs that may be considered by the tertiary epilepsy specialist at this stage in the care pathway are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.

Prescribers should be aware that not all the drugs mentioned above currently have a UK marketing authorisation for use for the particular indication or population mentioned (for example, depending on the age of the person). In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using drugs outside their authorised indications. The table below details the costs of treatment alternatives that are licensed for use in children or young people and includes those recommended as first- or second-line adjunctive treatments in the NICE clinical guideline on [epilepsy](#).

Costs of treatment alternatives

Drug ^a	Usual maintenance dose for children and young people ^b	28-day cost excluding VAT
Carbamazepine ^c	5–18 years: 400–1200 mg daily in several divided doses depending on age	Tegretol tablets: £2.55 to £7.53 ^d
Clobazam ^e	6 years and over: 0.3–1.0 mg/kg daily	Depends on child's weight; for a 32 kg child: £2.34 to £7.03 (Frisium tablets) ^d , £2.51 to £7.53 (generic tablets) ^f
Gabapentin ^g	6–11 years: 25–35 mg/kg daily in 3 divided doses	Depends on child's weight; for a 32 kg child: £4.01 to £4.13 (generic capsules) ^f
	12 years and over: 900–3600 mg daily in 3 divided doses	£3.77 to £12.02 (generic capsules) ^f
Lacosamide ^g	Not recommended for use in people less than 16 years For young people aged 16–18 years: 100–200 mg twice daily	£86.50 to £144.16 (tablets) ^d

Lamotrigine ^e	2–12 years: 1–15 mg/kg daily depending on concomitant medications, in 1 or 2 divided doses	Depends on child's weight; for a 32 kg child: £9.81 to £97.79 (Lamictal tablets) ^d , £0.75 to £3.77 (generic tablets) ^f
	13 years and over: 100–400 mg daily depending on concomitant medications, in 1 or 2 divided doses	£28.77 to £97.79 (Lamictal tablets) ^d £1.24 to £3.77 (generic tablets) ^f
Levetiracetam ^g	6–17 years weighing less than 50 kg: 10–30 mg/kg twice daily	Depends on child's weight; for a 32 kg child: £1.80 to £4.72 (generic tablets) ^f
	12–17 years weighing 50 kg or more: 500–1500 mg twice daily	£2.37 to £7.52 (generic tablets) ^f
Oxcarbazepine ^e	6 years and over: approximately 30 mg/kg daily in 2 divided doses	Depends on child's weight; for a 32 kg child: £34.27 (Trileptal tablets) ^d , £44.44 (generic tablets) ^f
Perampanel ^e	12 years and over: 4–8 mg once daily	£140 (Fycompa tablets, no generic available) ^d
Phenobarbital ^c	Children: 2.5–8 mg/kg daily	For a 32 kg child: £2.73 to £26.28 (no branded product available) ^f
	Adults: 60–180 mg once daily	£6.57 to £19.71 (no branded product available) ^f
Phenytoin sodium ^c	Infants and children: 4–8 mg/kg daily	Depends on child's weight; for a 32 kg child: £47.40 to £76.48 (Flynn hard capsules) ^f
	Adults: 200–500 mg daily in single or divided doses	£45.00 to £112.50 (Flynn hard capsules) ^f
Sodium valproate ^e	Child or young person weighing over 20 kg: initially 400 mg daily, usual range 20–30 mg/kg daily in 2 divided doses	Depends on child's weight; for a 32 kg child: £6.47 to £10.78 (Epilim gastro-resistant tablets) ^d , £3.47 to £4.52 (generic gastro-resistant tablets) ^f
	Adults: 1000–2000 mg daily in 2 divided doses	£10.78 to £21.56 (Epilim gastro-resistant tablets) ^d £4.52 to £9.04 (generic gastro-resistant tablets) ^f

Tiagabine ^g	12 years and over: 15–45 mg daily depending on concomitant medications, in 2 or 3 divided doses	£43.71 to £131.15 (Gabitril tablets, no generic available) ^d
Topiramate ^e	2 years and over: 5–9 mg/kg daily in 2 divided doses	Depends on child's weight; for a 32 kg child: £54.01 to £88.73 (Topamax tablets) ^d £7.76 to £8.71 (generic tablets) ^f
Vigabatrin ^g	Child or young person weighing 10 kg and over: 0.5–3 g daily in 1 to 2 divided doses depending on weight	Tablets: £10.36 to £62.18 (Sabril tablets, no generic available) ^f
Zonisamide ^e	Child or young person 6 years and over weighing 20–55 kg: 6–8 mg/kg once daily	Depends on child's weight; for a 32 kg child: £62.72 to £86.24 (Zonegran capsules, no generic available) ^f
	Child or young person 6 years and over weighing more than 55 kg: 300–500 mg once daily	£94.08 to £156.80 (Zonegran capsules, no generic available) ^f

^a For a number of antiepileptic drugs, several different formulations are available: only one has been selected here for reasons of clarity. If the [MHRA has advised prescribers](#) to ensure that their patient is maintained on a specific manufacturer's product, the cost for the originator product has been given as an example where possible; other manufacturer's products may also be available. If the MHRA has advised that the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with patient and/or carer, the cost for the originator product and the generic (Drug Tariff) price has been given. For other products the Drug Tariff price has been given.

^b Doses taken from the relevant [summary of product characteristics](#) or the [British National Formulary for Children](#). The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

^c The [MHRA has advised prescribers](#) to ensure that their patient is maintained on a specific manufacturer's product.

^d Costs taken from [MIMS](#) February 2014.

^e The [MHRA has advised](#) that the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency and treatment history.

^f Costs taken from [Drug Tariff](#) February 2014.

^g The [MHRA has advised](#) that it is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product unless there are specific reasons such as patient anxiety and risk of confusion or dosing errors.

Estimated impact for the NHS

Likely place in therapy

Zonisamide as adjunctive therapy for partial (focal) seizures in epilepsy was considered during the development of the NICE clinical guideline on [epilepsy](#). Based on evidence that was available at the time (up to June 2010), 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. However at the time of publication of the guideline (January 2012), zonisamide did not have UK marketing authorisation for use in children and young people aged less than 18 years.

The NICE clinical guideline on [epilepsy](#), advises that 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 to children, young people and adults with partial (focal) seizures.

The [guideline](#) advises that if standard adjunctive treatment is ineffective or not tolerated, decisions about treatment options should be made after advice from a tertiary epilepsy specialist. Efficacy, cost, safety and individual patient factors will all influence the decision to use a particular adjunctive anti-epileptic drug in each person. Although no studies are available comparing zonisamide with other anti-epileptic drugs, the European Medicines Agency (EMA) states that the efficacy of zonisamide appears similar to other anti-epileptic drugs already indicated for adjunctive use in children.

Estimated usage

It is not possible to estimate usage of zonisamide based on the available data; however, it is likely that zonisamide may provide an additional licensed treatment in a proportion of children and young people with partial seizures that are refractory to current treatment.

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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**.

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

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