New Medicine Assessment

Zonisamide (Zonegran®)

For Migraine Prophylaxis

Recommendation: AMBER0 in patients when at least three prior prophylactic treatments have failed and erenumab, galcanezumab or fremanezumab are being considered. Periodical review by specialist services is necessary to ensure that a patient continues to benefit from treatment with zonisamide.

- Suitable for prescribing in primary care following recommendation or initiation by a specialist.
- Little or no specific monitoring required.
- Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.
- Brief prescribing document or information sheet may be required.

Summary of supporting evidence:

- Zonisamide has demonstrated comparable efficacy to two licensed treatments for migraine prophylaxis (topiramate and sodium valproate).
- Zonisamide is an established medicine with long term safety data in patients with epilepsy.
- Alternative licensed agents for the prophylaxis of migraine in refractory patients (e.g. erenumab, galcanezumab, fremanezumab, Botox) are significantly more expensive than zonisamide.
- Several alternative licensed treatment options are available for patients who have been unsuccessfully treated with topiramate or propranolol.

Date: July 2021

Details of Review

Name of medicine (generic & brand name)**:**

Zonisamide (Zonegran®)

Strength(s) and form(s):

25 mg, 50mg and 100 mg capsules

20 mg/ml oral suspension

Dose and administration:

50 – 200 mg once daily (Unlicensed use – dose range based on clinical studies)

BNF therapeutic class / mode of action:

Antiepileptics/ inhibitor of voltage-sensitive sodium and calcium channels and modulator of GABA-mediated neuronal inhibition.

Licensed indication(s):

Zonegran is indicated as:

• monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy;

• adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above. [1]

Proposed use (if different from, or in addition to, licensed indication above):

Migraine prophylaxis.

Course and cost:

Zonisamide 100mg capsules (56) £7.63

Zonisamide 25mg capsules (14) £8.95

Zonisamide 50mg capsules (56) £49.40

Depending on dose daily cost range = £0.14 to £1.02

Annual cost = £51.10 to £372.30

Costs based on Drug Tariff list prices April 2021.

Current standard of care/comparator therapies:

NICE recommends offering either topiramate or propranolol for migraine prophylaxis and considering amitriptyline as an alternative option.

Following failure/intolerance the other oral medicines which may be used are candesartan and sodium valproate.

Candesartan 16 mg tablets (28) £1.65

Annual cost = £21.51

Sodium Valproate 500 mg gastro-resistant tablets (100) £27.29

Sodium Valproate 200 mg gastro-resistant tablets (100) £11.14

Annual cost depending on dose = £239.87 to £298.83

Costs based on Drug Tariff list prices April 2021.

Relevant NICE guidance:

NICE CG150 Headaches in over 12s: diagnosis and management [2]

Prophylactic treatment

1.3.16 Discuss the benefits and risks of prophylactic treatment for migraine with the person, taking into account the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life. [2012]

1.3.17 Offer topiramate or propranolol for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Advise women and girls of childbearing potential that topiramate is associated with a risk of foetal malformations and can impair the effectiveness of hormonal contraceptives. Ensure they are offered suitable contraception if needed. [2015]

1.3.18 Consider amitriptyline for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. [new 2015]

1.3.19 Do not offer gabapentin for the prophylactic treatment of migraine. [new 2015]

1.3.20 If both topiramate and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5–8 weeks according to the person's preference, comorbidities and risk of adverse events. [2012, amended 2015]

1.3.21 For people who are already having treatment with another form of prophylaxis and whose migraine is well controlled, continue the current treatment as required. [2012, amended 2015]

1.3.22 Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment. [2012]

1.3.23 Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people. [2012]

Background and context

Migraine is a complex condition with a wide variety of symptoms. For many people the main feature is a painful headache. Other symptoms include disturbed vision, sensitivity to light, sound, and smells, feeling sick and vomiting.

The symptoms will vary from person to person and individuals may have different symptoms during different attacks. Length and frequency of attacks vary. Migraine attacks usually last from 4 to 72 hours and most people are free from symptoms between attacks. Migraine can have an enormous impact on work, family, and social lives.

The most common types of migraine fall into two categories:

- migraine without aura (affecting 70-90% of people with migraine)
- migraine with aura (migraine accompanied by a neurological symptom, most commonly visual disturbances). [3]

For the acute treatment of migraine, NICE recommends offering combination therapy with a triptan and an NSAID or paracetamol. For prophylaxis of migraine, NICE recommends offering topiramate or propranolol and considering amitriptyline. [2] Topiramate is an antiepileptic drug that has demonstrated efficacy as a prophylactic drug in migraine. [4] [5] Zonisamide is believed to have a similar mechanism of action to topiramate, therefore it has been proposed that it may be effective in the prevention of migraine. [6] Zonisamide has been added to the New Medicines Workplan following a request from Fylde Coast CCGs.

Summary of evidence

Summary of efficacy data in proposed use:

Cochrane review of antiepileptics in prophylaxis of migraine [7]

A Cochrane review conducted in 2013 identified a single study of Zonisamide for the prophylaxis of migraine. [6]

The prospective, randomised, double-blind, parallel-group trial compared the effect of Zonisamide 200 mg daily against topiramate 100 mg daily for headache frequency (number of migraine attacks per month). The study of migraine patients with or without aura; frequency of 4-15 attacks per month or <4 prolonged/debilitating attacks per month was undertaken over a 12-week period. Patients had a history of unsuccessful prophylactic treatment with one or more regimens. Patients with other primary headaches (cluster headache or tension-type headaches), overuse of acute medicines were excluded from the study. Of the 80 patients recruited to the study, 75 patients were randomly assigned either 200 mg of Zonisamide or 100 mg of topiramate daily. There was no significant difference between them in reduction of headache frequency from baseline during the third month of treatment (Mean difference 0.10; CI95% -0.68 to 0.88).

Assarzadegan et al RCT [8]

This was a double-blind, parallel, randomized, controlled trial of 96 patients with a migraine diagnosis based on the international headache society (HIS) criteria. Included patients had a history of more than four moderate to severe migraine attacks and no prior history of using the interventional medicines. The 96 patients were randomly assigned to two parallel groups, initially in a 1: 1 ratio, to receive zonisamide (50 - 150mg) in the treatment group and sodium valproate (200 - 600 mg) in the control group. In a three-month follow-up period, the frequency (number of headaches per month), duration, and severity of headache attacks were measured and calculated. Improvement of these variables translated into success of treatment. Duration of headaches was categorized as headaches that last for 4 - 24 hours, 24 - 48 hours, and 48 - 72 hours. Severity of headache attacks were based upon a the visual analog scale (VAS). In this scoring system, mild, moderate, and severe headaches are scored 0 - 3, 4 - 6, and 7 - 10, respectively. Both drugs reduced migraine attacks in three months of follow-up, although there was no statistically significant correlation between frequency or severity of migraine attacks and the medication used for treatment ($P > 0.05$). Similarly, there was no significant difference in terms of days of disability due to headaches between these two groups ($P > 0.05$).

Variables	Sodium Valproate	Zonisamide	PValue
Mean of attack frequency in a month			
Start of treatment	5.48 ± 1.61	5.42 ± 1.56	0.86
After 3 months	3.55 ± 1.23	3.24 ± 1.41	0.27
Difference	1.93 ± 1.1	2.18 ± 1.17	0.30
Mean of attack severity in a month			
Start of treatment	6.84 ± 1.83	6.76 ± 1.9	0.84
After 3 months	3.82 ± 1.43	4.24 ± 1.76	0.22
Difference	3.02 ± 1.01	2.52 ± 1.13	0.03
Mean of attack days in a month			
Start of treatment	8.3 ± 1.78	7.91 ± 1.92	0.21
After 3 months	5.07 ± 1.65	4.69 ± 1.56	0.27
Difference	3.23 ± 1.34	2.62 ± 1.09	0.13

[a] Values are expressed as mean ± SD.

Other efficacy data:

N/A

Summary of safety data:

In the original public assessment report published by the European Medicines Agency in patients with refractory partial epilepsy, 1207 patients received zonisamide. [9] Doses received were either the same or of a higher magnitude than used in the clinical studies of zonisamide in migraine prophylaxis. The most common adverse reactions in a randomised, controlled monotherapy trial comparing zonisamide with carbamazepine prolonged release were decreased bicarbonate, decreased appetite, and decreased weight. The full list of adverse events is detailed in the table below. [1]

System Organ Class	Very Common	Common	Uncommon
Infections and infestation			Urinary tract infection Pneumonia
Blood and lymphatic disorders			Leukopenia Thrombocytopenia
Metabolism and nutrition disorders		Decreased appetite	Hypokalaemia
Psychiatric Disorders		Agitation Depression Insomnia Mood swings Anxiety	Confusional state Acute psychosis Aggression Suicidal ideation Hallucination
Nervous system disorders		Ataxia Dizziness Memory impairment Somnolence Bradyphrenia Disturbance in attention Paraesthesia	Nystagmus Speech disorder Tremor Convulsion
Eye disorders		Diplopia	
Respiratory, thoracic, and mediastinal disorders			Respiratory disorder

Gastrointestinal disorders		Constipation Diarrhoea Dyspepsia Nausea Vomiting	Abdominal pain
Hepatobiliary disorders			Cholecystitis acute
Skin and subcutaneous tissue disorders		Rash	Pruritus Ecchymosis
General disorders and administration site conditions		Fatigue Pyrexia Irritability	
Investigations	Decreased bicarbonate	Weight decreased Blood creatinine phosphokinase increased Alanine aminotransferase increased Aspartate aminotransferase increased	Urine analysis abnormal

Zonisamide is contraindicated in patients with hypersensitivity to the active substance, its excipients or to sulphonamides.

There is also an extensive list of precautions for zonisamide including the need to be vigilant for unexplained serious rashes (including Stevens-Johnson syndrome); acute myopia and secondary angle closure glaucoma; suicidal ideation and behaviour; kidney stones; hepatic dysfunction; metabolic acidosis; heat stroke; weight loss; rhabdomyolysis; and pancreatitis.

Women of childbearing potential must use effective contraception during treatment and for one month after cessation of treatment.

Strengths and limitations of the evidence:

Strengths

- Zonisamide has demonstrated comparable efficacy to two licensed treatments for migraine prophylaxis (topiramate and sodium valproate).
- Zonisamide is an established medicine with long term safety data in patients with epilepsy.
- Alternative licensed agents for the prophylaxis of migraine in refractory patients (e.g. erenumab, galcanezumab, fremanezumab, Botox) are significantly more expensive than zonisamide.

Limitations

- There is an absence of placebo-controlled trials for zonisamide in the prophylaxis of migraine.
- The outcome data was incomplete in the trial comparing zonisamide with topiramate.
- The available trials are in small numbers of patients with a treatment duration of no more than 12 weeks.
- Several alternative licensed treatment options are available for patients who have been unsuccessfully treated with topiramate or propranolol.
- A Cochrane review concluded that the absence of a significant difference in effect between zonisamide and active comparator is not proof of an actual effect of zonisamide.

Summary of evidence on cost effectiveness:

None.

Prescribing and risk management issues:

Gradual withdrawal is only necessary if patients also have a history of epilepsy. Women of childbearing potential must use effective contraception during treatment and for one month after cessation of treatment.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per year (ex VAT)
Zonisamide capsules	**50 to 200 mg daily**	**100mg capsules (56) £7.63** **25mg capsules (14) £8.95** **50mg capsules (56) £49.40**	**£51 to £372**
Candesartan tablets	16 mg daily	16 mg tablets (28) £1.65	£22
Sodium Valproate gastro-resistant tablets	1.2 g to 1.5 g daily	500 mg g/r tablets (100) £27.29 200 mg g/r tablets (100) £11.14	£240 to £299
Costs based on Drug Tariff list prices April 2021. This table does not imply therapeutic equivalence of drugs or doses.			

Innovation, need and equity implications of the intervention:

Zonisamide provides an additional treatment option when other migraine prophylaxis treatments have been unsuccessful.

Financial implications of the intervention:

Estimates of the number of patients likely to require treatment following failure of at least three prophylactic migraine treatments can be extrapolated from the NICE technology appraisal costing template for erenumab. [10]

It is estimated that approximately 6,200 patients have tried at least 3 preventative medicines for

migraine in the Lancashire and South Cumbria health economy. If 5% (uptake aligned with uptake rate for erenumab in the costing template) of these patients (310) used zonisamide for migraine prophylaxis the total annual cost is estimated to be: 310 x £51 to £372 = **£15, 810 to £115,320**
Service Impact Issues Identified:
No additional service impact is expected, patients would not require any additional appointments for the safe provision of zonisamide.
Equality and Inclusion Issues Identified:
Non identified.
Cross Border Issues Identified:
Zonisamide is an “Amber Recommended” medicine in Pan Mersey for the prophylaxis of migraine. This means zonisamide requires specialist assessment to enable patient selection. Following specialist assessment, the medicine is suitable for prescribing in Primary Care. GMMMG do not have a commissioning position for zonisamide for the prophylaxis of migraine.
Legal Issues Identified:
N/A
Media/ Public Interest:
N/A

References

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[3] The Migraine Trust, "More than "just a headache"," [Online]. Available: https://www.migrainetrust.org/about-migraine/migraine-what-is-it/more-than-just-a-headache/. [Accessed April 2021].

[4] SD Siberstein et al, "Topiramate in migraine prevention results of a large controlled trial," *Arch Neurol,* vol. 61, pp. 490-495, 2004.

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[6] SE Mohammadianinejad et al, "Zonisamide Versus Topiramate in Migraine Prophylaxis: A Double-Blind Randomized Clinical Trial," *Clinical Neuropharmacology,* vol. 34, no. 4, pp. 174-178, 2011.

[7] M Linde et al, "Antiepileptics other than gabapentin, pregabalin, topiramate and valproate for the prophylaxis of episodic migraine in adults (Review)," *Cochrane Databases of Systematic Reviews,* no. 6, p. DOI: 10.1002/14651858.CD010608., 2013.

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[9] European Medicines Agency, "Zonegran: EPAR -Scientific Discussion," January 2008. [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-discussion/zonegran-epar-scientific-discussion_en.pdf. [Accessed April 2021].

[10] National Institute for Health and Care Excellence, "Erenumab for preventing migraine (TA682)," 10 March 2021. [Online]. Available: https://www.nice.org.uk/guidance/ta682/chapter/1-Recommendations. [Accessed April 2021].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Produced by:

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