Specialist Initiated Drugs

Prescribing Information Sheet September 2014

Zonisamide (Zonegran®) –adjunctive treatment of refractory focal seizures

Formulary Status

Zonisamide, as adjunctive therapy in the treatment of refractory focal seizures, with or without secondary generalisation in adult patients, should be initiated by a specialist who will prescribe the initial supply.

The specialist will titrate the dose until the patient is stable. This may take about 6 to 12 weeks and will vary per patient.

On-going prescribing can be continued by the GP

The responsibility for increasing/decreasing the dose or stopping treatment due to lack of effect or side effects remains with the specialist. They should be consulted if a change in treatment is required.

Full prescribing guidance – Summary of Product Characteristics
www.emc.medicines.org.uk

Indication and Dosage

Indication- Zonisamide is indicated as adjunctive therapy in the treatment of refractory focal seizures, with or without secondary generalisation in adult patients.

Presentation- Hard capsules 25mg, 50mg and 100mg.

Dosage and Administration – Zonisamide during titration is taken in two divided doses, with or without food, swallowed whole with a drink of water. The maintenance can be taken once daily or in two divided doses.

Week 1 and 2: 50mg/day given in two divided doses

Week 3 and 4: 100mg/day given in two divided doses

Week 5 to 10 :The dose can then be increased according to efficacy and tolerability at **two-weekly** intervals in increments of up to 100 mg

The usual maintenance dose is 300 to 500 mg per day (given as once a day or two divided doses). Some patients may respond to lower doses

Patients on concomitant CYP3A4 inducing agents
CYP3A4-inducing agents reduce the half-life of zonisamide. The dose titration should be every 7 days.

Approved by: East Kent Prescribing Group *(Representing Ashford CCG, Canterbury and Coastal CCG, South Kent Coast CCG and Thanet CCG)*
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Week 1: 50mg/day given in two divided doses
Week 2: 100mg/day given in two divided doses
Week 3 to 5: The dose can then be increased according to efficacy and tolerability at **weekly** intervals in increments of up to 100 mg

The usual maintenance dose is 300 to 500 mg per day (given once a day or two divided doses).

Renal impairment – Slower titration is advised in patients with renal impairment. Zonisamide should be discontinued in patients with acute renal failure or where a clinically significant sustained increase in serum creatinine is observed

Hepatic impairment – Slower titration is advised in patients with mild to moderate hepatic impairment Use in patients with severe hepatic impairment is not recommended.

Monitoring
The SPC for zonisamide states that there is no requirement for on-going blood or other tests. Baseline measurement of urea, electrolytes, and liver function is recommended because a slower dose titration may be necessary if renal or hepatic function is impaired

End of treatment
It is recommended that discontinuation is undertaken gradually to minimise the potential for rebound seizures. In adult patients, dose reductions of 100mg at weekly intervals have been used with concurrent adjustment of other antiepileptic medication (where necessary).

Adverse effects, special warnings and precautions for use (consult SPC for full list)

Unexplained rash
Serious dermatological reactions including Stevens-Johnson syndrome have been reported with zonisamide. Consideration must be given to discontinuing therapy in patients who develop an otherwise unexplained rash. All patients who develop rashes while taking zonisamide must be supervised closely, particularly patients receiving concomitant antiepileptic agents that may independently induce rashes.

Sulphonamide reactions
Zonisamide contains a sulphonamide group. Serious immune based adverse reactions have been associated with medicinal products containing a sulphonamide group including rashes, allergic reactions and major haematological disturbances.

Suicidal ideation
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicinal products in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for zonisamide.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Kidney stones
Some patients, especially those with predisposition to nephrolithiasis or taking other medications associated with nephrolithiasis may be at increased risk of renal stone formation and associated signs and symptoms such as renal colic.

Metabolic acidosis
Hyperchloraemic non-anion gap, metabolic acidosis is associated with zonisamide treatment. This is caused by renal bicarbonate loss due to inhibitory effect of zonisamide on carbonic anhydrase. The risk of zonisamide induced metabolic acidosis appears to be more frequent and severe in younger patients. Appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in patients taking zonisamide who have underlying conditions which might increase the risk of acidosis, in patients who are at an increased risk of adverse consequences of metabolic acidosis and in patients with symptoms suggestive of metabolic acidosis. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing zonisamide (by gradual discontinuation or reduction of a therapeutic dose) as osteopenia may develop. Zonisamide should be used with caution in adult patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate or acetazolamide, as there are insufficient data to rule out a pharmacodynamic interaction

Heat stroke
Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric patients. Caution should be used in adults when zonisamide is prescribed with other medicinal products that predispose patients to heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity.

Pancreatitis
In patients taking zonisamide who develop the clinical signs and symptoms of pancreatitis, it is recommended that pancreatic lipase and amylase levels are monitored. If pancreatitis is evident, in the absence of another obvious cause, it is recommended that discontinuation of zonisamide n be considered and appropriate treatment initiated.

Rhabdomyolysis
In patients taking zonisamide in whom severe muscle pain and/or weakness develop either in the presence or absence of a fever, it is recommended that markers of muscle damage be assessed, including serum creatine phosphokinase and aldolase levels. If elevated, in the absence of another obvious cause such as trauma or grand mal seizures, it is recommended that zonisamide discontinuation be considered and appropriate treatment initiated.

Women of child-bearing potential
Women of child-bearing potential must use adequate contraception during treatment with zonisamide and for one month after discontinuation. Physicians treating patients with zonisamide should try to ensure that appropriate contraception is used, and should use clinical judgement when assessing whether oral contraceptives (OCs), or the doses of the OC components, are adequate based on the individual patient's clinical situation.

Body weight
Zonisamide may cause weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight or is underweight whilst on this medication. If substantial undesirable weight loss occurs, discontinuation of Zonegran should be considered. Weight loss is potentially more serious in children.

Drug Interactions (consult SPC for full list)

Interactions listed in BNF 67 (March 2014) are with medications that antagonise the effects of anti-epileptics such as antidepressants, antimalarials, antipsychotics and orlistat.

Oral contraceptives
In clinical studies in healthy subjects, steady-state dosing with zonisamide did not affect serum concentrations of ethinylestradiol or norethisterone in a combined oral contraceptive.

Carbonic anhydrase inhibitors
Zonisamide should be used with caution in adult patients treated concomitantly with carbonic anhydrase inhibitors such as topiramate and acetazolamide, as there is insufficient data to rule out a possible pharmacodynamic interaction
Zonisamide should not be used as co-medication in paediatric patients with other carbonic anhydrase inhibitors such as topiramate and acetazolamide

P-gp substrate
An *in vitro* study shows that zonisamide is a weak inhibitor of P-gp (MDR1) with an IC_{50} of 267 µmol/l and there is the theoretical potential for zonisamide to affect the pharmacokinetics of substances which are P-gp substrates. Caution is advised when starting or stopping zonisamide treatment or changing the zonisamide dose in patients who are also receiving medicinal products which are P-gp substrates (e.g. digoxin, quinidine).

Enzyme inducers
Zonisamide is metabolised partly by CYP3A4 enzymes therefore exposure to zonisamide is lower in epileptic patients receiving CYP3A4-inducing agents such as phenytoin, carbamazepine, and phenobarbitone. These effects are unlikely to be of clinical significance when zonisamide is added to existing therapy; however, changes in zonisamide concentrations may occur if concomitant CYP3A4-inducing anti-epileptic or other medicinal products are withdrawn, dose adjusted or introduced. An adjustment of the zonisamide dose may be required.

Rifampicin is a potent CYP3A4 inducer. If co-administration is necessary, the patient should be closely monitored and the dose of zonisamide and other CYP3A4 substrates adjusted as needed.

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