Effective Shared Care Agreement (ESCA)

Zonisamide *(Zonegran®▼)*

ESCA: For the treatment of the adjunctive treatment of partial epileptic seizures

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of zonisamide for epileptic seizures can be shared between the specialist and general practitioner (GP). You are **invited** to participate however, if you do not feel confident to undertake this role, then you are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care will be explained to the patient by the specialist initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients with epilepsy are usually under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

RESPONSIBILITIES and ROLES

Specialist responsibilities
1. Confirm the diagnosis of epilepsy
2. Discuss the potential benefits, treatment side effects, and possible drug interactions with the patient
3. Ask the GP whether he or she is willing to participate in shared care before initiating therapy so that appropriate follow on prescribing arrangements can be made
4. Do baseline monitoring prior to initiation of zonisamide
5. Initiate treatment and stabilise dose of zonisamide
6. Review the patient's condition and monitor response to treatment regularly
7. A written summary to be sent promptly to the GP i.e. within 10 working days of a hospital outpatient review or inpatient stay
8. Report serious adverse events to the MHRA
9. Ensure clear backup arrangements exist for GPs, for advice and support (Please complete details below)

General Practitioner responsibilities						
1. Reply to the request for shared care as soon as practicable i.e. within 10 working days						
2. Prescribe zonisamide at the dose recommended						
3. In the patient's notes, using the appropriate Read Code listed below, denote that the patient is receiving treatment under a shared care agreement						
GP Prescribing System	**Read Code**	**Description**		**GP Prescribing System**	**Read Code**	**Description**
EMIS and Vision	8BM5.00	Shared care prescribing		SystmOne	XaB58	Shared care
4. Monitor patient's response to treatment; make dosage adjustments if agreed with specialist						
5. Report to and seek advice from the specialist or clinical nurse specialist on any aspect of patient care that is of concern to the GP, patient or carer and may affect treatment						
6. Refer back to specialist if condition deteriorates						
7. Report serious adverse events to specialist and MHRA						
8. Stop treatment on advice of specialist						

Patient's role
1. Report to the specialist, clinical nurse specialist or GP if he or she does not have a clear understanding of the treatment
2. Share any concerns in relation to treatment with zonisamide with the specialist, clinical nurse specialist or GP
3. Report any adverse effects to the specialist or GP whilst taking zonisamide
4. Attend regular outpatient appointments with the specialist

BACK-UP ADVICE AND SUPPORT

Trust	Contact details	Telephone No.	Email address:
	Consultant:-		
	Specialist Nurse		

Based on MTRAC template
Prepared by Satnaam Singh Nandra
Interface Lead Pharmacist
Birmingham CrossCity CCG

SUPPORTING INFORMATION

<table>
<tr><td>Indication</td><td>
• 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.
</td></tr>
<tr><td>Dosage and Administration</td><td>
<u>Adults – recommended dosage escalation and maintenance regimen</u>
<table>
<tr><th>Treatment Regimen</th><th colspan="3">Titration Phase</th><th>Usual Maintenance Dose</th></tr>
<tr><td rowspan="2">Monotherapy - Newly diagnosed adult patients</td><td>Week 1 + 2</td><td>Week 3 + 4</td><td>Week 5 + 6</td><td rowspan="2">300 mg per day (once a day).
If a higher dose is required: increase at two-weekly intervals in increments of 100 mg up to a maximum of 500 mg.</td></tr>
<tr><td>100 mg/day (once a day)</td><td>200 mg /day (once a day)</td><td>300 mg / day (once a day)</td></tr>
<tr><td rowspan="2">Adjunctive therapy
- with CYP3A4-inducing agents</td><td>Week 1</td><td>Week 2</td><td>Week 3 to 5</td><td rowspan="2">300 to 500 mg per day (once a day or two divided doses).</td></tr>
<tr><td>50 mg/day (in two divided doses)</td><td>100 mg /day (in two divided doses)</td><td>Increase at weekly intervals in increments of 100 mg</td></tr>
<tr><td rowspan="2">- without CYP3A4-inducing agents; or with renal or hepatic impairment</td><td>Week 1 + 2</td><td>Week 3 + 4</td><td>Week 5 to 10</td><td rowspan="2">300 to 500 mg per day (once a day or two divided doses).
Some patients may respond to lower doses.</td></tr>
<tr><td>50 mg/day (in two divided doses)</td><td>100 mg / day (in two divided doses)</td><td>Increase at two-weekly intervals in increments of up to 100 mg</td></tr>
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</td></tr>
<tr><td>Renal Impairment</td><td>Caution must be exercised in treating patients with renal impairment, as there is limited information on use in such patients and a slower titration of zonisamide might be required. Since zonisamide and its metabolites are excreted renally, it should be discontinued in patients who develop acute renal failure or where a clinically significant sustained increase in serum creatinine is observed.</td></tr>
<tr><td>Hepatic impairment</td><td>Use in patients with hepatic impairment has not been studied. Therefore use in patients with severe hepatic impairment is not recommended. Caution must be exercised in treating patients with mild to moderate hepatic impairment, and a slower titration of zonisamide may be required.</td></tr>
<tr><td>Contra-indications / Special precautions</td><td>
Contraindications
Hypersensitivity to the active substance, to any of the excipients listed
Cautions
<u>Unexplained rash</u>
Serious rashes occur in association with zonisamide therapy, including cases of Stevens-Johnson syndrome.
Consideration must be given to discontinuing zonisamide in patients who develop an otherwise unexplained rash. All patients who develop a rash while taking zonisamide must be closely supervised, with additional levels of caution applied to those patients receiving concomitant antiepileptic agents that may independently induce skin rashes.
<u>Withdrawal seizures</u>
In accordance with current clinical practice, discontinuation of zonisamide in patients with epilepsy must be accomplished by gradual dose reduction, to reduce the possibility of seizures on withdrawal. Withdrawal of concomitant anti-epileptic medicinal products must be undertaken with caution.
<u>Sulphonamide reactions</u>
Zonisamide is a benzisoxazole derivative, which contains a sulphonamide group. Serious immune based adverse reactions that are associated with medicinal products containing a sulphonamide group include rash, allergic reaction and major haematological disturbances, including aplastic anaemia, which very rarely can be fatal.
Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.
<u>Suicide ideation and behaviour</u>
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in
</td></tr>
</table>

	several indications. 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 a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Nephrolithiasis may lead to chronic kidney damage. Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors. Metabolic acidosis Hyperchloraemic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with zonisamide treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of zonisamide on carbonic anhydrase. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or medicinal products) may be additive to the bicarbonate lowering effects of zonisamide. 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. If the decision is made to continue patients on zonisamide in the face of persistent acidosis, alkali treatment should be considered. 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 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 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 zonisamide should be considered.	
Side Effects	Very common	Anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence, diplopia, decreased bicarbonate
	Common	Ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, pruritis, alopecia, nephrolithiasis, fatigue, influenza-like illness, pyrexia, oedema peripheral, weight decreased

<table>
<tr><td>Monitoring</td><td>Urea, electrolytes
Liver function
Renal function
Monitoring of pancreatic lipase and amylase levels
Suicidal ideation and behaviour
Monitoring of serum bicarbonate levels
Monitoring of serum creatine phosphokinase and aldolase levels</td></tr>
<tr><td>Drug Interactions</td><td>Zonisamide has the following interaction information:
<table>
<tr><td>Carbamazepine</td><td>plasma concentration of zonisamide reduced by carbamazepine</td></tr>
<tr><td>Carbonic Anhydrase Inhibitors</td><td>manufacturer of zonisamide advises avoid concomitant use with carbonic anhydrase inhibitors in children</td></tr>
<tr><td>Fosphenytoin</td><td>plasma concentration of zonisamide reduced by fosphenytoin</td></tr>
<tr><td>Phenobarbital</td><td>plasma concentration of zonisamide reduced by phenobarbital</td></tr>
<tr><td>Phenytoin</td><td>plasma concentration of zonisamide reduced by phenytoin</td></tr>
<tr><td>Primidone</td><td>plasma concentration of zonisamide reduced by primidone</td></tr>
</table>
Zonisamide belongs to Antiepileptics and will have the following interactions:
<table>
<tr><td>Antidepressants, SSRI</td><td>anticonvulsant effect of antiepileptics antagonised by SSRIs(convulsive threshold lowered)</td></tr>
<tr><td>Antidepressants, Tricyclic</td><td>anticonvulsant effect of antiepileptics antagonised by tricyclics (convulsive threshold lowered)</td></tr>
<tr><td>Antidepressants, Tricyclic (related)</td><td>anticonvulsant effect of antiepileptics possibly antagonised by tricyclic-related antidepressants (convulsive threshold lowered)</td></tr>
<tr><td>Antipsychotics</td><td>anticonvulsant effect of antiepileptics antagonised by antipsychotics (convulsive threshold lowered)

Note: Increased risk of toxicity with myelosuppressive drugs</td></tr>
<tr><td>MAOIs</td><td>anticonvulsant effect of antiepileptics possibly antagonised by MAOIs (convulsive threshold lowered)

Note: For interactions of reversible MAO-A inhibitors (RIMAs) see Moclobemide, and for interactions of MAO-B inhibitors see Rasagiline and Selegiline; the antibacterial Linezolid is a reversible, non-selective MAO inhibitor</td></tr>
<tr><td>Mefloquine</td><td>anticonvulsant effect of antiepileptics antagonised by mefloquine</td></tr>
<tr><td>Orlistat</td><td>possible increased risk of convulsions when antiepileptics given with orlistat</td></tr>
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</table>

References

Zonisamide SmPC
Zonisamide BNF
NICE CG 137 - The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care

I agree to participate in this shared care agreement for the treatment of the below named patient with zonisamide for epileptic seizures

General Practitioner
Name (please print)_____Signature _____Date_____

Hospital Specialist/Consultant
Name (please print)_____Signature_____Date_____

Patient's name	Date of birth	Sex	Home Address	Hospital Number
				NHS Number

Please keep a copy of this agreement for your own records and forward the original to the above named Consultant at: