City and Hackney Clinical Commissioning Group
Homerton University Hospital Foundation Trust

SHARED CARE GUIDELINE

ZONISAMIDE

Treatment of epilepsy in adults, adolescents and children ≥6 years

DOCUMENT TO BE SCANNED INTO ELECTRONIC RECORDS AND FILED IN NOTES

INTRODUCTION – Indication and Licensing

Zonisamide appears to act on voltage-sensitive sodium and calcium channels, thereby disrupting synchronised neuronal firing, reducing the spread of seizure discharges and disrupting subsequent epileptic activity. Zonisamide also has a modulatory effect on GABA-mediated neuronal inhibition.

Licensed indications

- **Monotherapy** in the treatment of partial (focal) seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy.
- **Adjunctive therapy** in the treatment of partial (focal) seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above.

PATIENT PATHWAY

Clinical Speciality / Indication	**Prescribing Initiated by**	**Prescribing Continued by** ***(detail when suitable for transfer to occur)***	**Monitored by** ***(detail when suitable for transfer to occur IF APPROPRIATE)***	**Duration of treatment**
Neurology/ Epilepsy	Epilepsy Specialist	GP to take over after 2 months or after the patient has been titrated to a stable therapeutic dose.	Effect on seizure control monitored by hospital and GP.	Indefinite if treatment tolerated and effective.

Reviews & dosing adjustments

- The patient will be followed up by the Epilepsy Specialist Team at the hospital for review of treatment efficacy and tolerability. The patient will be given contact details for the team.
- Dosing adjustments are to be undertaken by the hospital and this information communicated to the GP in writing within 14 days.
- Correspondences from GP should be addressed to the 'Consultant Epileptologist' and NOT to neurology.

ORAL DOSE AND ADMINISTRATION

	Initial	**Titration**	**Maximum dose**
Monotherapy in adults	100mg once daily for 2 weeks	After initial dosing, increase in steps by 100mg at 2-week intervals according to response and tolerability. *Usual maintenance dose:* 300mg once daily.	500mg once daily
Adjunctive dosing in adults with CYP3A4 inducers	25mg twice daily for 7 days	After initial dosing, increase to 50mg twice daily for 7 days, then by 100mg at 7-day intervals in 1-2 divided doses according to response and tolerability. *Usual maintenance dose:* 300–500mg daily in 1-2 divided doses.	500mg daily
Adjunctive dosing in those 6–18 years with CYP3A4 inducers	1mg/kg once daily for 7 days	After initial dosing, increase by 1mg/kg at 7-day intervals. *Usual maintenance dose* Body-weight 20–55kg: 6–8mg/kg once daily. Body-weight over 55 kg: 300–500 mg once daily.	500mg once daily
Increase dose at 2-week intervals in the following patient groups: mild to moderate hepatic impairment, renal impairment (discontinue if renal function deteriorates), or in adjunctive therapy in patients who are not receiving concomitant carbamazepine, phenytoin, phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4.			

Other considerations:

- **Potential childbearing age** – discuss with the epilepsy specialist team regarding the benefits of treatment, risks in pregnancy and contraceptive advice. All women with epilepsy should be advised to take 5 mg daily of folic acid prior to conception and to continue taking this until at least the end of the first trimester to reduce the incidence of major congenital malformation.
- **Driving** – advise the patient to inform the Driver and Vehicle Licensing Agency (DVLA) about their epilepsy. See the Epilepsy Action website for more information.

CAUTIONS

- **Kidney stones, especially in those with a predisposition to nephrolithiasis** - increasing fluid intake and urine output may help reduce the risk of stone formation.
- **Concomitant carbonic anhydrase inhibitors (e.g. topiramate or acetazolamide)** – risk of metabolic acidosis.
- **Heat stroke** - avoid overheating and ensure adequate hydration especially in children, during strenuous activity or if in warm environment (fatal cases of heat stroke reported in children). Also caution in adult patients being treated with carbonic anhydrase inhibitors and drugs with anticholinergic properties.
- **Suicidal ideation and behaviour** have been reported in patients treated with anti-epileptic medicinal products in several indications. The available data do not exclude the possibility of an increased risk for zonisamide.
- **History of psychosis, depression or behavioural problems.**

CONTRAINDICATIONS

- Hypersensitivity to sulphonamides.
- Peanuts or soya allergies.
- Concomitant use of drugs that increase risk of hyperthermia or metabolic acidosis in children.
- Paediatric patients who are underweight (definition in accordance with the WHO age adjusted BMI categories) or have a decreased appetite.

INTERACTIONS

- **Carbonic anhydrase inhibitors** – AVOID concomitant use in children.
- Plasma concentration of zonisamide reduced by: carbamazepine, fosphenytoin, phenytoin, phenobarbital and primidone.
- **Anticonvulsant effect of antiepileptics reduced by**: selective serotonin reuptake inhibitors, tricyclic (and related) antidepressants, monoamine oxidase inhibitors, antipsychotics, mefloquine and orlistat.

MONITORING STANDARDS FOR MEDICATION AT THE ACUTE NHS TRUST

Seizure diary

- The patient will be given a seizure recording diary, which they will be encouraged to use for the first 6 months of therapy. The patient will be able to record in the diary the nature of the seizure and frequency, and any side effects or problems that they experienced with the treatment.
- A pdf copy of the seizure diary and the Epilepsy Toolkit smartphone app can be downloaded from the Epilepsy Society website (see page 4).

KEY ADVERSE EFFECTS & ACTIONS

Adverse effects	**Symptoms/signs** *(specify what would prompt action)*	**Actions (***what action should the GP take if identified in primary care)*
Raised liver enzymes	Raised ALT, AST, GGT and bilirubin (reported in paediatric in adolescent patients)	**Discuss** with the specialist team.
Pancreatitis	Severe abdominal pain, sometimes with nausea and vomiting.	Monitor pancreatic lipase and amylase levels. **Stop medication** after discussion with the specialist team.
Rhabdomyolysis	Severe muscle pain and/or weakness develop either in the presence or absence	Monitor markers of muscle damage. **Stop medication** after discussion with the

	of a fever.	specialist team.
Kidney stones	Symptoms vary and can include lower back pain, frequent urination, dysuria and haematuria.	Request renal ultrasound as necessary. **Stop medication** after discussion with the specialist team.
Gastrointestinal problems	Nausea, vomiting and abdominal pain	**Reduce dose if severe** after discussion with the specialist team.

Children and their carers should be made aware of how to prevent and recognise overheating and dehydration. Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients and their carer should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

The SCG lists only the key information. Please refer to the current British National Formulary and Summary of Product Characteristics for comprehensive information on cautions, contraindications, interactions and adverse effects.

PREGNANCY AND BREAST FEEDING

- **Pregnancy** – studies in animals have shown reproductive toxicity, the potential risk for humans is unknown. The specialist team will discuss options with the patient. If contraception is required then this should be used during treatment with zonisamide and for one month after discontinuation. All pregnant women with epilepsy, whether taking medication or not, should be encouraged to **notify the UK Epilepsy and Pregnancy Register** (Tel: 0800 389 1248).
- **Breastfeeding** – the concentration of zonisamide in breast milk is similar to maternal plasma. The specialist team will discuss this with the patient.
- **Fertility** – there are no human data on fertility. Studies in animals have shown changes in fertility parameters.

For comprehensive information please refer to the current British National Formulary and Summary of Product Characteristics.

SHARED CARE

Shared care guideline*:* is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The intention to shared care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use**.**

Consultant

1. Ensure that the patient/carer is an informed recipient in therapy.
2. Ensure that the patient/carer understands their treatment regimen and any monitoring or follow up that is required (using advocacy if appropriate). Issue any local patient information leaflets where appropriate.
3. Ensure baseline investigations are normal before commencing treatment.
4. Initiate treatment and prescribe until the GP formally agrees to share care (as a minimum, supply the first 2 months of treatment or until the patient is stabilised).
5. Send a letter to the GP requesting shared care for this patient.
6. Clinical supervision of the patient by routine clinic follow-up on a regular basis.
7. Send a letter/results notification to the GP after each clinic attendance ensuring current dose, and if applicable, most recent blood results and frequency of monitoring are stated.
8. Evaluation of any reported adverse effects by GP or patient.
9. Advise GP on review, duration or discontinuation of treatment where necessary. Where urgent action is required following tests the hospital team will telephone the patient and inform GP.
10. Inform GP of patients who do not attend clinic appointments.

11. Discuss benefits of treatment, risks in pregnancy and breastfeeding with the patient. Counsel the patient on contraception (if appropriate) and what to do if pregnancy occurs. Document in the notes.
12. Ensure that backup advice is available at all times.

General Practitioner

1. Ensure that the patient/carer understands the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate.
2. Monitor patient's overall health and well-being.
3. Report any adverse events to the consultant, where appropriate.
4. Report any adverse events to the MHRA / CHM, where appropriate.
5. Help in monitoring the progression of disease.
6. Prescribe the drug treatment as described.
7. Provide contraception advice and prescription as appropriate. Prescribe folic acid if appropriate.

City and Hackney Medicines Management Team

1. To provide feedback to acute trusts via Joint Prescribing and Medicines Management Group.
2. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
3. To support acute trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist
2. Ensure they have a clear understanding of their treatment.
3. Report any changes in disease symptoms to GP and/or specialist
4. Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy.
5. Take/ administer the medication as prescribed.
6. Undertake any monitoring as requested by the GP and/or specialist.

Costs

Drug Product	Cost in primary care
Zonegran® (Zonisamide) capsules	**25mg** (white), net price 14-cap pack = £8.82; **50mg** (white/grey), 56-cap pack = £47.04; **100mg** (white/red), 56-cap pack = £62.72.

Based on BNF edition 73 (March 2017).

RESOURCES AVAILABLE

- Epilepsy Society accessible via https://www.epilepsysociety.org.uk
- Epilepsy Action accessible via https://www.epilepsy.org.uk

Relevant contact details	
Consultant or Registrar on-call via switchboard	020 8510 5555
Clinical Nurse Specialist	020 8510 5912
Homerton University Hospital NHS Foundation Medicines Information	020 8510 7000
City and Hackney Medicines Management Team	0203 816 3224

References

- SCG template adapted from NELMMN and Barts Health NHS Trust
- Joint Formulary Committee British National Formulary edition 73. Available at https://ebnf.homerton.nhs.uk [accessed 21/06/2017].
- Summary of product characteristics – Zonegran® 25, 50, 100 mg hard capsules. Available at www.medicines.org.uk [accessed 21/06/2017].

- Royal College of Obstetricians & Gynaecologists. Epilepsy in pregnancy, green-top guideline 68. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg68_epilepsy.pdf [accessed 21/06/2017]

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