NHS
Cambridgeshire and Peterborough
Clinical Commissioning Group

Shared Care Guideline

Stiripentol use for SCN1A related and Severe Myoclonic Epilepsies in Infancy

Executive Summary

1. **Indication** – Stiripentol is indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate.
   Stiripentol is also used for management of refractory tonic-clonic seizures in patients with ring chromosome 14, in combination with clobazam and valproate.

2. **Dosage adjustments to be carried out, where agreed –** The Paediatric Neurology Consultant will advise on the dose of Stiripentol and any dose changes that are required

3. **Responsibilities: -**

   Hospital – The hospital will ensure: -
   - The benefits and side effects of treatment have been discussed with the patient/carer.
   - Initiate treatment by providing four weeks supply of stiripentol or until dose is titrated to maintenance dose.
   - A letter is sent to the GP, requesting shared care for the patient, along with a copy of the shared care guidelines.
   - Advise the GP on continuing or stopping stiripentol therapy, following any medical review of the patient and associated drug therapy.
   - Be available for backup advice and support for both the parents/carer and GP.
   - Report any adverse effect to the Medicines and Healthcare products Regulatory Agency (MHRA) via the Yellow Card scheme.

   GP - The GP will:-
   - Continue to prescribe stiripentol after treatment has been initiated by the paediatric Neurology Team.
   - Communicate any adverse events or other problems with the drug to the Paediatric Neurology Team at Addenbrooke's Hospital.

4. **Treatment discontinuation** – The patient's Consultant should normally take the decision to stop treatment where appropriate and communicate this to the GP.

- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document here

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share 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. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

Shared Care Guideline

Stiripentol for paediatric patients

1. Scope

Trust-wide and general practice for paediatric patients up to 16 years of age.

2. Aim

Sharing of care assumes communication between the specialist, GP and the parent/carer. The intention to share care should be explained to, and accepted by, the patient. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

3. Introduction

Severe myoclonic epilepsy in infancy (SMEI) is a disease of early childhood. The onset is in the first years of life where affected infants develop myoclonic and clonic seizures and other fits. Myoclonic seizures are a form of movement marked by involuntary contractions and relaxations of a muscle, occurring in rapid succession. They are due to an imbalance in the electrical activity of the brain. Later, usually more than one year after onset, myoclonic jerks appear. These attacks are sudden and brief muscle contractions that may involve one part of the body or the entire body. The mental state of the child deteriorates after subsequent episodes of attacks, leading to delayed or hindered psychomotor development, with delayed skill acquisitions or regression. Severe myoclonic epilepsy in infancy is considered as chronically debilitating and life threatening condition.

Stiripentol is a chemical substance that might have an anticonvulsant effect. The mechanism of action is not yet completely understood.

Stiripentol is an inhibitor of cytochrome P450. Most of the actions of during adjunctive therapy in vivo are probably indirect and mediated by inhibition of cytochrome P450 enzymes, namely CYP3A4, CYP1A2, and CYP2C19.[2] As a result, STP increases the plasma concentrations of a wide variety of anti epileptic drugs, including phenytoin, carbamazepine, phenobarbital, valproate, and clobazam and decreases plasma concentrations of their metabolites (including the toxic ones).

Striripentol was granted an orphan drug status by EMEA in 2007 and is currently unlicensed in children less than 3 years of age. The clinical decision for use of Diacomit in children with SMEI less than 3 years of age needs to be made on an individual patient basis taking into consideration the potential clinical benefits and risks and needs to be initiated under close supervision of the Paediatric Neurology Consultant.

4. Abbreviations

GABA	-	Gamma-aminobutyric acid
LFTs	-	Liver Function Tests
SMEI	-	Severe Myoclonic epilepsy in infancy
U&E's	-	Urea and Electrolytes

5. Dose and Administration

5.1 Indications

Stiripentol is indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate.
Stiripentol is also used for management of refractory tonic-clonic seizures in patients with ring chromosome 14, in combination with clobazam and valproate.

5.2 Initiation Criteria:

Stiripentol should be prescribed in children with SMEI, where the child does not respond to clobazam and valproate.

5.3 Intended Duration of Treatment:

For as long as the patient's consultant considers the patient is gaining clinical benefit for the inclusion of stiripentol in their treatment regimen.

5.4 Discontinuation Criteria:

There is no benefit seen from the therapy, assessed by seizure activity.
This will be assessed on a 3 monthly basis.

5.5 Pharmacology

Stiripentol is an antiepileptic drug which is thought to work by increasing brain levels of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain.

5.6 Dose and Administration

Stiripentol is initiated over 3 days with a increasing dosing schedule to reach a dose of 50mg/kg/day administered in 2-3 divided doses.

Doses must always be taken with food to avoid stiripentol degrading in an acidic environment. Stiripentol should not be taken with milk or dairy products, carbonated drinks, fruit juice or food and drinks that contain caffeine or theophylline.

Bioavailability differs between the sachet and capsule preparations and therefore clinical supervision is recommended if switching between formulations.

5.7 Availability

Stiripentol is available as a 250mg and 500mg tablet or sachet with a brand name Diacomit®.
Bioavailability differs between the sachet and capsule preparations and therefore clinical supervision is recommended if switching between formulations.

Diacomit is an orphan medication and is available from Mawdsleys Clinical Services (Tel 01302 553000)

5.8 Patient Information

A patient Information leaflet can be downloaded from the Medicines for Children website www.medicinesforchildren.org.uk

6. Adverse Effects

The following adverse events have been reported with stiripentol: -

Very common (≥ 1 in 10)

- Drowsiness, ataxia, hypotonia and dystonia
- Loss of appetite, weight loss

Common (≥ 1 in 100 and < 1 in 10)

- Nausea and vomiting
- Neutropenia
- Aggressiveness, irritability, behaviour disorders, sleep disorders

Uncommon (≥ 1 in 1000 and < 1 in 100)

- Diplopia (when used in combination with carbamazepine)
- Photosensitivity, rash, cutaneous allergy and urticaria

Rare (≥ 1 in 10000 and < 1 in 1000)

- Abnormal liver function tests

7. Cautions

- Carbamazepine, phenytoin and phenobarbital should not be used in conjunction with stiripentol in the management of Dravet's syndrome.
- The daily dose of clobazam and/or valproate should be reduced according to the onset of side effects whilst on stiripentol. In these cases, the Consultant paediatric neurologist would be expected to review the child and provide advice on relevant dose reductions.

8. Contraindications

- Patients with liver and/or renal impairment.
- Stiripentol should not be used if there is any known hypersensitivity to the active ingredient or any of the excipients.
- Stiripentol should be avoided in patients with a past history of psychoses in the form of episodes of delirium.
- Stiripentol sachets contain aspartame and therefore should be avoided in patients with phenylketonuria.
- Stiripentol sachets contain glucose and should be avoided in patients with glucose-galactose malabsorption. Stiripentol sachets contain sorbitol and should be avoided in patients with hereditary fructose intolerance.

9. Interactions

Stiripentol is an inhibitor of cytochrome P450. As a result, stiripentol increases the plasma concentrations of several drugs, including antiepileptics.

Undesirable drug combinations (to be avoided unless strictly necessary)

- Immunosuppressants (tacrolimus, ciclosporin, sirolimus) – results in raised blood levels of immunosuppressants
- Statins – Increased risk of dose-dependant adverse reactions e.g. rhabdomyolysis.

Drug combinations requiring precautions

- Midazolam – increased plasma benzodiazepine levels which can lead to excessive sedation.
- Theophylline, caffeine – increased levels of theophylline and caffeine

- Phenobarbital, primidone, phenytoin, carbamazepine, clobazam, valproate, diazepam, ethosuxamide and tiagabine – increased plasma levels of these drugs with potential risk of overdose. Doses of these drugs must be reduced. The Consultant paediatric neurologist will be responsible for reviewing the child and adjusting doses of medication appropriately. Monitor plasma levels of anticonvulsants where this is possible, when combined with stiripentol.
- Drugs metabolised by CYP2D6 e.g. betablockers, antidepressants (fluoxetine, paroxetine, sertraline, imipramine, clomipramine), antipsychotics (haloperidol), analgesics (codeine, dextromethorphan, tramadol) may require a dose adjustment

Effect of food

- Stiripentol should not be taken with milk or dairy products, carbonated drinks, fruit juice or food and drinks that contain caffeine or theophylline.

10. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

All monitoring required will be carried out by the Paediatric Neurology team at Addenbrooke's hospital. GPs should not be asked to carry out any specific monitoring for this therapy. The Consultant paediatric neurologist will organise for full blood count, U&E's and LFT's to be monitored every 6 months.

If any unusual or serious adverse effect is reported or if an abnormality is detected in any laboratory result which may be relevant to stiripentol then the Paediatric Neurology Team should be contacted immediately.

11. Shared Care Responsibilities

a. Hospital specialist:

- Determine when initiation of treatment with stiripentol is appropriate.
- Discuss with the parents/carers:
    - potential benefits and side-effects
    - possible drug interactions
    - the need to be aware of what actions to take if adverse events are suspected.
- To provide any advice to the patient/carer when requested.
- Initiate treatment by providing four weeks supply of stiripentol or until dose is titrated to maintenance dose.
- Complete baseline monitoring.
- Send a letter to the GP requesting shared care for the patient.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments.
- Respond to any request from GP to review the patient due to adverse effects of therapy.
- Advise the GP on continuing or stopping stiripentol therapy, following any medical review of the patient and associated drug therapy.
- Be available for backup advice and support for both the parents/carer and GP.
- Report any adverse effect to the Medicines and Healthcare products Regulatory Agency (MHRA) via the Yellow Card scheme.

b. General Practitioner:

- Agreement to shared care guideline by the GP.
- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.
- Continue to prescribe stiripentol after treatment has been initiated by the paediatric Neurology Team.
- Communicate any adverse events or other problems with the drug to the Paediatric Neurology Team at Addenbrooke's Hospital.

c. Patient or parent/carer:

- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments (where relevant).
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist or GP.

12. Contact numbers for advice and support

Cambridge University Hospitals NHS Foundation Trust – Addenbrookes Hospital		
Specialist	**Post**	**Telephone**
Full name	Full job title	Full external number
Consultant Paediatric Neurologists		01223 216662
Zoya Dowd	Paediatric Epilepsy Nurse Specialist	01223 216662
Nigel Gooding	Consultant Pharmacist - Paediatrics	01223 254417
Medicines Information		01223 217502
Addenbrooke's Hospital Main Switchboard		01223 245151

Consultant and medical staff are always available to give advice and can be contacted through the main hospital switchboard
Out of hours, the on-call pharmacist is available for pharmacy advice via the switchboard.

Equality and diversity statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

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Document management

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