The Pennine Acute Hospitals NHS
NHS Trust

NHS

Greater Manchester Interface Prescribing Group Shared Care Template

Shared Care Guideline for ***Stiripentol***	**Reference Number**
Author(s)/Originator(s): *Dr Rob Levy Paediatrician FGH* *Adele Gothard Paediatric Pharmacist NMGH*	**To be read in conjunction with the following documents:** Current Summary of Product characteristics (http://www.medicines.org.uk) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000664/WC500036518.pdf BNFC
Date approved by Commissioners: 08/07/11	**Review Date: July 2014**

Please complete all sections

1. Licensed 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 sodium valproate.	
2. Therapeutic use & background	Stiripentol should only be initiated under the supervision of a paediatrician / paediatric neurologist experienced in the diagnosis and management of epilepsy in infants and children	
3. Contraindications (please note this does not replace the SPC or BNF and should be read in conjunction with it).	*Avoid in hepatic and renal impairment* Hypersensitivity to the active substance or to any of the excipients. A past history of psychoses in the form of episodes of delirium.	
4. Prescribing in pregnancy and lactation	This drug cannot be prescribed in the *pregnant/breastfeeding* patient. Under these circumstances prescribing should be the responsibility of *the specialist*	
5. Dosage regimen for continuing care	Route of administration	*Oral*
	Preparations available Capsules 250mg/500mg Powder 250mg/500mg	
	Child 3-18 years *10mg/kg in 2-3 divided doses; titrate dose over minimum of 3 days to max 50mg/kg/day in 2-3 divided doses* There is no clinical study data to support the use of stiripentol as monotherapy in Dravet's syndrome	

	The sachet formulation has a slightly higher C_{max} than the capsules and thus the formulations are not bioequivalent. It is recommended that if a switch of formulations is required this is done under clinical supervision, in case of problems with tolerability		
	Is titration required	**Yes**	
	Titrate dosage up by *minimum of 3 days to max 50mg/kg/day in 2-3 divided doses* There are no clinical study data to support the clinical safety of Stiripentol administered at daily doses greater than 50 mg/kg/day. There are no clinical study data to support the use of stiripentol as monotherapy in Dravet's syndrome.		
	Adjunctive treatment regime - Clobazam In the pivotal studies, when the use of stiripentol was initiated, the daily dose of clobazam was 500 micrograms/kg/day usually administered in divided doses, twice daily. In the event of clinical signs of side effects or overdosage of clobazam (i.e., drowsiness, hypotonia, and irritability in young children), this daily dose was reduced by 25% every week. Approximately two to three fold increases in clobazam and five fold increases in norclobazam plasma levels respectively have been reported with co-administration of stiripentol in children with Dravet's syndrome. - Sodium Valproate The potential for metabolic interaction between stiripentol and sodium valproate is considered modest and thus, no modification of valproate dosage should be needed when stiripentol is added, except for clinical safety reasons. In the pivotal studies in the event of gastrointestinal adverse reactions such as loss of appetite, loss of weight, the daily dose of valproate was reduced by around 30% every week		
	Conditions requiring dose reduction In the event of an abnormal blood count or liver function test finding, the clinical decision for continuing use or adjusting the dose of stiripentol in conjunction with adjusting the doses of clobazam and sodium valproate needs to be made on an individual patient basis taking into consideration the potential clinical benefits and risks		
	Usual response time *2-3 weeks*		
	Duration of treatment *to be directed by the paediatric neurologist*		
	Treatment to be terminated by *paediatric neurologist*		
	NB. All dose adjustments will be the responsibility of the initiating specialist care unless directions have been specified in the medical letter to the GP.		

6.Drug Interactions ***For a comprehensive list consult the BNF or Summary of Product Characteristics***	**The following drugs must <u>not</u> be prescribed without consultation with the specialist:** Stiripentol is an inhibitor of the enzymes CYP2C19, CYP3A4 and CYP2D6 and may markedly increase the plasma concentrations of drugs metabolised by these enzymes and increase the risk of adverse effects. *In vitro* studies suggested that stiripentol phase 1 metabolism is catalyzed by CYP1A2, CYP2C19 and CYP3A4 and possibly other enzymes. Caution is advised when combining stiripentol with other drugs that inhibit or induce one or more of these enzymes. Carbamazepine, phenytoin and phenobarbital should not be used in conjunction with stiripentol in the management of Dravet's syndrome. The daily dosage of clobazam and/or sodium valproate should be reduced according to the onset of side effects whilst on stiripentol therapy. The influence of other antiepileptic medicinal products on stiripentol pharmacokinetics is not well established. The impact of macrolides and azole antifungal agents on stiripentol metabolism, that are known to be inhibitors of CYP3A4 and substrates of the same enzyme, is not known. Likewise, the effect of stiripentol on their metabolism is not known. Caution must be exercised if clinical circumstances require combining stiripentol with drugs metabolised by CYP2C19 (e.g. citalopram, omeprazole) or CYP3A4 (e.g. HIV protease inhibitors, antihistamines such as astemizole, chlorpheniramine, calcium channel blockers, statins, oral contraceptives, codeine) due to the increased risk of adverse events . Data on the potential for inhibition of CYP1A2 are limited, and therefore, interactions with theophylline and caffeine cannot be excluded. Use in combination with stiripentol is not recommended. This warning is not only restricted to medicinal products but also to a considerable. A number of foods and nutritional products aimed at children, such as cola drinks, which contain significant quantities of caffeine or chocolate, which contains trace amounts of theophylline. As stiripentol inhibited CYP2D6 *in vitro* at concentrations that are achieved clinically in plasma, drugs that are metabolized by this isoenzyme like: beta-blockers (propranolol, carvedilol, timolol), antidepressants (fluoxetine, paroxetine, sertraline, imipramine, clomipramine), antipsychotics (haloperidol), analgesics (codeine, dextromethorphan, tramadol) may be subject to metabolic interactions with stiripentol. A dose-adjustment may be necessary for drugs metabolised by CYP2D6 and that are individually dose titrated. *Potential for stiripentol to interact with other medicinal products* In the absence of available clinical data, caution should be taken with the following clinically relevant interactions with stiripentol: Undesirable combinations (to be avoided unless strictly necessary) - Rye ergot alkaloids (ergotamine, dihydroergotamine) - Cisapride, halofantrine, pimozide, quinidine, bepridil - Immunosuppressants (tacrolimus, cyclosporine, sirolimus) - Statins (atorvastatin, simvastatin, etc.) *Monoamine oxidase inhibitors* *St John's Wort* *Chloroquine, Hydroxychloroquine, Mefloquine* *Orlistat*

The following drugs may be prescribed with caution:
Combinations requiring precautions
- Midazolam, triazolam, alprazolam
Increased plasma benzodiazepine levels may occur via decreased hepatic metabolism leading to excessive sedation.
- Theophylline, caffeine
Increased plasma levels of theophylline and caffeine may occur via inhibition of their hepatic metabolism, potentially leading to toxicity. These combinations should be avoided.
- Chlorpromazine
Stiripentol enhances the central depressant effect of chlorpromazine.
- Effects on other AEDs
Inhibition of CYP450 isoenzyme CYP2C19 and CYP3A4 may provoke pharmacokinetic interactions (inhibition of their hepatic metabolism) with phenobarbital, primidone, phenytoin, carbamazepine, clobazam, sodium valproate, diazepam (enhanced myorelaxation), ethosuximide, and tiagabine. The consequences are increased plasma levels of these anticonvulsants with potential risk of overdose. Clinical monitoring of plasma levels of other anticonvulsants when combined with stiripentol with possible dose adjustments is recommended.
- Topiramate
In a French compassionate use program for stiripentol, topiramate was added to stiripentol, clobazam and sodium valproate in 41% of 230 cases. Based on the clinical observations in this group of patients, there is no evidence to suggest that a change in topiramate dose and dosage schedules is needed if co-administered with stiripentol. With regard to topiramate, it is considered that potential competition of inhibition on
- Levetiracetam
Levetiracetam does not undergo hepatic metabolism to a major extent. As a result, no pharmacokinetic metabolic drug interaction between stiripentol and levetiracetam is anticipated.

7. Adverse drug reactions

For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult Summary of Product Characteristics or BNF

Specialist to detail below the action to be taken upon occurrence of a particular adverse event as appropriate. Most serious toxicity is seen with long-term use and may therefore present first to GPs.

Adverse event System – symptom/sign	**Action to be taken** **Include whether drug should be stopped prior to contacting secondary care specialist**	**By whom**
Rash/Allergies	*Contact Paediatrician for advice*	*GP*
Increasing drowsiness	*Contact Paediatrician for advice*	*GP*
Worsening seizure control	*Contact Paediatrician for advice*	*GP*
Weight Loss	*Contact Paediatrician for advice*	*GP*

The patient should be advised to report any of the above signs or symptoms to their GP without delay.

Other important co morbidities (e.g. Chickenpox exposure). Include advice on management and prevention and who will be responsible for this in each case:
n/a

Any adverse reaction to a black triangle drug or serious reaction to an established drug should be reported to the MHRA via the "Yellow Card" scheme.

8.Baseline investigations

Given the frequency of gastrointestinal adverse reactions to treatment with stiripentol and sodium valproate (anorexia, loss of appetite, nausea, vomiting), the growth rate of children under this combination of treatment should be carefully monitored.

Neutropenia may be associated with the administration of stiripentol, clobazam and valproate. Blood counts should be assessed prior to starting treatment with stiripentol. Unless otherwise clinically indicated, blood counts should be checked every 6 months.

Liver function should be assessed prior to starting treatment with stiripentol. Unless otherwise clinically indicated, liver function should be checked every 6 months.

The pivotal clinical studies did not include children below 3 years old. As a consequence, it is recommended that children between 6 months and 3 years of age are carefully monitored whilst on stiripentol therapy.

9. Ongoing monitoring requirements to be undertaken by GP	**Is monitoring required?**		**Yes or No (if yes complete following section) YES**		
	Monitoring	**Frequency**	**Results**	**Action**	**By whom**
	FBC	*6 monthly*	*Outside Normal limits*	*Contact paediatrician*	*GP*
	LFT	*6 monthly*	*Outside Normal Limits*	*Contact paediatrician*	*GP*
	Growth Rate	*6 monthly*	*As per growth chart*	*Contact paediatrician*	*GP*
	Seizure Control	*Every visit*	*Increasing frequency*	*Contact Paediatrician*	*GP*
10. Pharmaceutical aspects	*no special considerations*				
11. Secondary care contact information	**If stopping medication or needing advice please contact:**				
	Dr Levy				
	Contact Number: 0161 7783708				
	Hospital: Fairfield General Hospital **Rochdale Old Road, Bury, BL9 7TD**				
12. Criteria for shared care	Prescribing responsibility will only be transferred when ▪ Treatment is for a specified indication and duration. ▪ Treatment has been initiated and established by the secondary care specialist. ▪ The patient's initial reaction to and progress on the drug is satisfactory. ▪ The GP has agreed in writing/verbally(delete where appropriate) in each individual case that shared care is appropriate. ▪ The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements				

13. Responsibilities of initiating specialist	Initiate treatment and prescribe until dose is stable Undertake baseline monitoring. Dose adjustments. Monitor patient's initial reaction to and progress on the drug. Ensure that the patient has an adequate supply of medication until GP supply can be arranged. Continue to monitor and supervise the patient according to this protocol, while the patient remains on this drug, and agree to review the patient promptly if contacted by the GP Provide GP with diagnosis, relevant clinical information and baseline results, treatment to date and treatment plan, duration of treatment before consultant review. Provide GP with details of outpatient consultations, ideally within 14 days of seeing the patient *or* inform GP if the patient does not attend appointment Provide GP with advice on when to stop this drug. Provide patient with relevant drug information to enable Informed consent to therapy Provide patient with relevant drug information to enable understanding of potential side effects and appropriate action Provide patient with relevant drug information to enable understanding of the role of monitoring. ----------
14. Responsibilities of the GP	Continue treatment as directed by the specialist Ensure no drug interactions with concomitant medicines To monitor and prescribe in collaboration with the specialist according to this protocol Symptoms or results are appropriately actioned, recorded and communicated to secondary care when necessary. ----------
15. Responsibilities of the patient	To take medication as directed by the prescriber, or to contact the GP if not taking medication To attend hospital and GP clinic appointments Failure to attend will result in medication being stopped (on specialist advice). To report adverse effects to their Specialist or GP.

Shared Care Agreement Form

Specialist request

*IMPORTANT: ACTION NEEDED

Dear Dr *[insert Doctors name here]*

Patient name: *[insert Patients name here]*
Date of birth: *[insert date of birth]*
Diagnosis: *[insert diagnosis here]*

This patient is suitable for treatment with *[insert drug name]* for the treatment of *[insert indication]*

This drug has been accepted for Shared Care according to the enclosed protocol (as agreed by Trust / LHB / AWMSG). I am therefore requesting your agreement to share the care of this patient.

Treatment was started on *[insert date started]* *[insert dose].*

If you are in agreement, please continue monitoring and treatment from *[insert date]*
NB: date must be at least 1 month from initiation of treatment.

Baseline tests: *[insert information]*

Next review with this department: *[insert date]*
You will be sent a written summary within 14 days. The medical staff of the department are available at all times to give you advice. The patient will not be discharged from out-patient follow-up while taking *[insert text here]*.

Please use the reply slip overleaf and return it as soon as possible.

Thank you.

Yours

[insert Specialist name]

Shared Care Agreement Form

GP Response

Dear Dr *[insert Doctors name]*

Patient *[insert Patients name]*

Identifier *[insert patient date of birth/address]*

I have received your request for shared care of this patient who has been advised to start *[insert text here]*

A I am willing to undertake shared care for this patient as set out in the protocol

B I wish to discuss this request with you

C I am unable to undertake shared care of this patient.

GP signature Date

GP address/practice stamp