SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DIACOMIT 250 Capsules

DIACOMIT 500 Capsules

DIACOMIT 250 Powder for oral suspension

DIACOMIT 500 Powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DIACOMIT 250 Capsules: each hard capsule contains 250 mg stiripentol.

DIACOMIT 500 Capsules: each hard capsule contains 500 mg stiripentol.

DIACOMIT 250 Powder for oral suspension: each sachet contains 250 mg stiripentol as the active ingredient.

DIACOMIT 500 Powder for oral suspension: each sachet contains 500 mg stiripentol as the active ingredient.

DIACOMIT is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Powder for oral suspension.

DIACOMIT 250 Capsules: opaque pink capsules of size 2 with “Diacomit” printed in black on cap and “250 mg” printed in black on body with self-locking closure containing a white to pale yellow powder.

DIACOMIT 500 Capsules: opaque white capsules of size 0 elongated (0+) with “Diacomit” printed in black on cap and “500 mg” printed in black on body with self-locking closure containing a white to pale yellow powder.

DIACOMIT 250 and 500 Powder for oral suspension is a pale pink powder filled in a single dose sachet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DIACOMIT is indicated for adjunctive treatment of generalised tonic-clonic and clonic seizures associated with severe myoclonic epilepsy in infancy (SMEI, also known as Dravet syndrome) in patients whose seizures are not adequately controlled with a benzodiazepine (usually clobazam) and valproate.

4.2 Posology and method of administration

Posology

Prescriptions and treatment should be initiated by neurologists experienced in the diagnosis and management of epilepsy, with continuation of patient management by general paediatricians and practitioners when the initiating neurologist is unavailable.

General

The dose of DIACOMIT is calculated on a mg/kg body weight basis.

It is recommended to split the daily dose in two or three daily intakes (totalling the daily recommended dose per kg and per day). The initiation of adjunctive therapy with DIACOMIT should be undertaken gradually using upwards dose escalation to reach the recommended dose of 50 mg/kg/day.

DIACOMIT dosage escalation should be gradual, starting with 20 mg/kg/day for 1 week, then 30 mg/kg/day for 1 week. Further dosage escalation is age dependent:

- children less than 6 years should receive an additional 20 mg/kg/day in the third week, thus achieving the recommended dose of 50 mg/kg/day in three weeks;
- children from 6 to less than 12 years should receive an additional 10 mg/kg/day each week, thus achieving the recommended dose of 50 mg/kg/day in four weeks;
- children and adolescents 12 years and older should receive an additional 5 mg/kg/day each week until the optimum dose is reached based on clinical judgement.

The recommended dose of 50 mg/kg/day is based on the available clinical study findings and was the only dose of DIACOMIT evaluated in the pivotal studies (see Clinical Trials subheading under section 5.1).

There are no clinical study data to support the clinical safety of DIACOMIT administered at daily doses greater than 50 mg/kg/day.

There are no clinical study data to support the use of DIACOMIT as monotherapy in Dravet syndrome.

Dose adjustments of other antiepileptics used in combination with DIACOMIT

Despite the absence of comprehensive pharmacology data on potential drug interactions, the following advice regarding modification of the dose and dosage schedules of other antiepileptic medicines administered in conjunction with DIACOMIT is provided based on clinical experience.

Clobazam

In the pivotal studies, when the use of stiripentol was initiated, the daily dose of clobazam was 0,5 mg/kg/day usually administered in divided doses, twice daily. In the event of clinical signs of adverse reactions or overdose 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 fivefold increases in norclobazam plasma levels respectively have been reported with co-administration of DIACOMIT in children with Dravet syndrome.

Valproate

The potential for metabolic interaction between DIACOMIT and valproate is considered modest and thus, no modification of valproate dosage should be needed when DIACOMIT 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.

Effect of formulation

The sachet formulation (C_{max} = 7,32 µg/ml) has a slightly higher C_{max} than the capsules (C_{max} = 5,99 µg/ml) 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 (see section 5).

Renal and hepatic impairment

DIACOMIT is not recommended for use in patients with impaired hepatic and/or renal function (see section 4.4).

Method of administration

The capsule should be swallowed whole with a glass of water during a meal.

The powder should be mixed in a glass of water and should be taken immediately after mixing during a meal.

DIACOMIT must always be taken with food as it degrades rapidly in an acidic environment (e.g. exposure to gastric acid in an empty stomach).

DIACOMIT should not be taken with milk or dairy products (yoghurt, soft cream cheese, etc.), carbonated drinks, fruit juice or food and drinks that contain caffeine or theophylline.

Discontinuation of DIACOMIT

Antiepileptic medicines, including DIACOMIT, should be withdrawn gradually to minimise the potential for seizures or increased seizure frequency. In clinical trials in children with Dravet syndrome, dosages were gradually reduced over a period lasting at least one month.

In a situation where rapid withdrawal of DIACOMIT is medically required, appropriate monitoring is recommended.

4.3 Contraindications

Hypersensitivity to stiripentol or to any of the excipients of DIACOMIT as listed in section 6.1

A past history of psychoses in the form of episodes of delirium.

4.4 Special warnings and precautions for use

Identified precautions

The pivotal clinical evaluation of DIACOMIT was in children of 3 years of age and over with SMEI. Children under 3 years of age and adults were not studied in the pivotal trials therefore efficacy and safety for those populations were not established in the pivotal trials.

Medicine interactions

Carbamazepine, phenytoin and phenobarbitone

Carbamazepine, phenytoin, and phenobarbitone should generally not be used in conjunction with DIACOMIT in the management of Dravet syndrome.

Phenytoin and phenobarbitone can significantly decrease the serum concentration of stiripentol. DIACOMIT can significantly increase the serum concentration of carbamazepine, phenytoin, and phenobarbitone. Furthermore, there is evidence that these medicines have the potential to worsen seizure activity in patients with Dravet syndrome, even though these medicines may have a role in a subset of patients with Dravet syndrome.

It is recommended that carbamazepine, phenytoin, and phenobarbitone be used in conjunction with DIACOMIT only under expert supervision with appropriate monitoring.

Clobazam and valproate

The daily dosage of clobazam and/or valproate should be reduced according to the onset of side effects whilst on DIACOMIT therapy (see section 4.2).

Substances interfering with CYP enzymes

Stiripentol as contained in DIACOMIT is an inhibitor of the enzymes CYP1A2, CYP2C8, CYP2C19, CYP3A4, CYP2C9 and CYP2D6 and may markedly increase the plasma concentrations of substances metabolised by these enzymes and increase the risk of adverse reactions (see section 4.5). *In vitro* data also suggest that STP induces the activity of CYP1A2 and CYP2B/3A, but the clinical relevance of this is uncertain. *In vitro* studies suggested that stiripentol phase 1 metabolism is catalysed by CYP1A2, CYP2C9, CYP2C19 and CYP3A4/5 and possibly other enzymes. Caution is advised when combining stiripentol with other substances that inhibit or induce one or more of these enzymes.

Blood count

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

Neurologic/psychiatric

Patients should be monitored for somnolence and drowsiness, particularly when DIACOMIT is used concomitantly with other central nervous depressant. An adjustment of the dosage of or other anti-epileptic medicines could be considered. Patients (or their parents or carers) should be advised to not operate machinery or drive.

Movement disorders including ataxia, hypotonia, tremor hyperkinesia, dysarthria and equilibrium disorders have been reported in patients treated with DIACOMIT for Dravet syndrome.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic medicines in several indications.

All patients treated with antiepileptic medicines, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (or their parents or carers) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Use in hepatic impairment

Liver function

In patients newly prescribed DIACOMIT, raised γGT (notably when combined with valproate) are observed with a common frequency, whilst abnormal liver function tests (increases in AST and/or ALT) are also reported with a rare frequency. Liver function (γGT, AST and ALT levels) should therefore be assessed prior to starting treatment with DIACOMIT and, unless otherwise clinically indicated, should be checked every 6 months.

Stiripentol as contained in DIACOMIT is primarily metabolised by the liver and primarily excreted by the kidney.

In the absence of specific clinical data in patients with impaired hepatic or renal function, DIACOMIT is not recommended for use in patients with impaired hepatic and/or renal function.

Use in renal impairment

Stiripentol as contained in DIACOMIT is primarily metabolised by the liver and primarily excreted by the kidney.

In the absence of specific clinical data in patients with impaired hepatic or renal function, DIACOMIT is not recommended for use in patients with impaired hepatic and/or renal function.

Use in the elderly

No data are available.

Paediatric use

Growth rate of children

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

Effects on laboratory tests

In the event of an abnormal blood count or liver function test finding, the clinical decision for continuing use or adjusting the dose of DIACOMIT in conjunction with adjusting the doses of clobazam and valproate needs to be made on an individual patient basis taking into consideration the potential clinical benefits and risks.

4.5 Interaction with other medicines and other forms of interaction

Stiripentol as contained in DIACOMIT is subject to non-linear pharmacokinetics (see section 5.2).

Potential medicine interactions affecting DIACOMIT

The influence of other antiepileptic medicines on stiripentol pharmacokinetics is not well established.

The impact of macrolides and azole antifungal medicines, that are known to be inhibitors of CYP3A4 and substrates of the same enzyme, on stiripentol metabolism is not known. Likewise, the effect of DIACOMIT on their metabolism is not known.

In vitro studies suggested that stiripentol phase 1 metabolism is catalysed by CYP1A2, CYP2C19 and CYP3A4 and possibly other enzymes. Caution is advised when combining DIACOMIT with other substances that inhibit or induce one or more of these enzymes.

Effect of DIACOMIT on cytochrome P450 enzymes

Many of these interactions have been partially confirmed by *in vitro* studies and in clinical trials. The increase in steady state levels with the combined use of stiripentol, valproate, and clobazam is similar in adults and children, though inter-individual variability is marked.

At therapeutic concentrations, stiripentol significantly inhibits several CYP450 isoenzymes: for example, CYP2C19, CYP1A2, CYP2C8, CYP2D6, CYP2C9 and CYP3A4. As a result, pharmacokinetic interactions of metabolic origin with other medicines may be expected. These interactions may result in increased systemic levels of these active substances that may lead to enhanced pharmacological effects and to an increase in adverse reactions. *In vitro* data also suggest that stiripentol induces the activity of CYP1A2 and CYP2B/3A, but the clinical relevance of this is uncertain.

Caution must be exercised if clinical circumstances require combining stiripentol with CYP2C19 (e.g. citalopram, omeprazole) or CYP3A4 (e.g. HIV protease inhibitors, antihistamines such as astemizole and chlorpheniramine, calcium channel blockers, statins, oral contraceptives, codeine) due to the increased risk of adverse reactions (see further in this section for antiepileptic medicines). Monitoring of plasma concentrations or adverse reactions is recommended. A dose adjustment may be necessary.

Co-administration with CYP3A4 substrates with a narrow therapeutic index should be avoided due to the markedly increased risk of severe adverse reactions.

Data on the potential for inhibition of CYP1A2 are limited, and therefore, interactions with theophylline and caffeine cannot be excluded because of the increased plasma levels of theophylline and caffeine which may occur via inhibition of their hepatic metabolism, potentially leading to toxicity. Use in combination with DIACOMIT is not recommended. This warning is not only restricted to medicines but also to a considerable 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, substances that are metabolised 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 DIACOMIT. A dose-adjustment may be necessary for substances metabolised by CYP2D6 and that are individually dose titrated.

Effect of DIACOMIT on GABA receptor site

Stiripentol is a positive allosteric modulator of the $GABA_A$ receptor. There is a potential for it to act synergistically with other allosteric modulators at the same site (e.g. benzodiazepines, non-benzodiazepines, barbiturates, bromides or neuroactive steroids) to enhance GABAergic neurotransmission.

Potential for DIACOMIT to interact with other medicines

In the absence of available clinical data, caution should be taken with the following clinically relevant interactions with DIACOMIT:

Drug or drug class	**Clinical comment**
Undesirable combinations (to be avoided unless strictly necessary	
Rye ergot alkaloids (ergotamine, dihydroergotamine)	Ergotism with possibility of necrosis of the extremities (inhibition of hepatic elimination of rye ergot).
Cisapride, halofantrine, pimozide, quinidine, bepridil	Increased risk of cardiac dysrhythmias and torsades de pointes/wave burst dysrhythmia in particular.
Immunosuppressants (tacrolimus, ciclosporin, sirolimus)	Raised blood levels of immunosuppressants (decreased hepatic metabolism).
Statins (atorvastatin, simvastatin,etc.)	Increased risk of dose-dependent adverse reactions such as rhabdomyolysis (decreased hepatic metabolism of cholesterol-lowering medicine).
Combinations requiring precautions	

Midazolam, triazolam, alprazolam	Increased plasma benzodiazepine levels may occur via decreased hepatic metabolism leading to excessive sedation.
Chlorpromazine	Enhanced central depressant effect of chlorpromazine.

Effects on other Anti-epileptic medicines (AEDs)

Concomitant antiepileptic medicine	**Clinical comment**
Phenobarbitone, carbamazepine, phenytoin, primidone, clobazam, valproate, diazepam, ethosuximide, and tiagabine.	Inhibition of CYP450 isoenzyme CYP2C19 and CYP3A4 may provoke pharmacokinetic interactions (inhibition of their hepatic metabolism) with phenobarbitone, primidone, phenytoin, carbamazepine, clobazam, valproate (refer to section 4.4), diazepam (enhanced myorelaxation), ethosuximide, and tiagabine. The consequences are increased plasma levels of these anticonvulsants with potential risk of overdose. Phenytoin, phenobarbitone, carbamazepine should not be used in conjunction with DIACOMIT in Dravet patients. Clinical monitoring of plasma levels of other anticonvulsants when combined with DIACOMIT with possible dose adjustments is recommended.
Topiramate	In a compassionate use program for stiripentol, topiramate was added to stiripentol, clobazam and 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 CYP2C19 should not occur because

	it probably requires plasma concentrations 5-15 times higher than plasma concentrations obtained with the standard recommended topiramate dose and dosage schedules.
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.

CYP3A4 inhibitors, such a DIACOMIT, may increase the exposure of oestrogen or progestin containing contraceptives when used concomitantly. Oestrogen or progestin containing contraceptives may increase the exposure of CYP1A2 or CYP3A substrates, such a stiripentol. The clinical significance of these potential interactions is not known.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

The use of efficient methods of contraception is advisable.

Pregnancy

Risk related to epilepsy and antiepileptic medicines in general.

It has been shown that in the offspring of women with epilepsy, the prevalence of malformations is two to three times greater than reported in the general population. Although other factors, e.g. the epilepsy, can contribute, available evidence suggests that this increase, to a large extent, is caused by the treatment. In the treated population, an increase in malformations has been noted with polytherapy.

However, effective anti-epileptic therapy should not be interrupted during pregnancy, since the aggravation of the illness may be detrimental to both the mother and the foetus.

Risk related to stiripentol

No data on exposed pregnancies are available. DIACOMIT and/or its metabolites cross the placenta in rats. There was no evidence of teratogenicity in mice or rabbits treated with STP during the period of organogenesis at oral doses up to 800 mg/kg/day, which is about 2-fold (mice) and 6-fold (rabbits) the MRHD, based on body surface

area. Increased numbers of resorptions were reported in mouse embryofoetal development studies at doses of ≥200 mg/kg/day (0,4 times the MRHD based on BSA), and also in the rabbit embryofoetal development study at a dose of 800 mg/kg/day (6 times the MRHD based on BSA). Rats treated with oral STP from early or late gestation to weaning showed maternotoxicity and reduced pup survival and reflex development at 800 mg/kg/day (equivalent to about 3-fold the mg/m^2 MRHD); the no-effect dose was 200 mg/kg/day.

In view of the indication, administration of DIACOMIT during pregnancy and in women of childbearing potential would not be expected. The clinical decision for use of DIACOMIT in pregnancy needs to be made on an individual patient basis.

Breastfeeding

There are no human studies on the excretion of DIACOMIT in breast milk. DIACOMIT passes freely from plasma into milk in the goat. Women taking DIACOMIT should not breastfeed their infants as adverse events are expected.

Fertility

There were no effects on fertility in male and female rats following oral administration of STP at doses up to 800 mg/kg/day (equivalent to about 3-fold the MRHD, based on body surface area). As no human clinical data are available, the potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

Patients with Dravet syndrome would not be expected to drive or operate machinery due to the nature of the underlying disease and the effects of long-term administration of anticonvulsant medicines.

DIACOMIT may cause dizziness and ataxia that may affect ability to drive and use machines and patients should not drive or use machinery whilst on DIACOMIT therapy.

4.8 Undesirable effects

a. Summary of the safety profile

Two prospective, randomised, 8-week treatment, double-blind, placebo-controlled trials were conducted in Dravet syndrome patients (STICLO France and STICLO Italy). In both trials, stiripentol was added on to treatment with valproate and clobazam. The dose of stiripentol was 50 mg/kg/day.

The following table lists the adverse events that were reported during the studies. No patient died during these double-blind, placebo-controlled studies.

Table 1 Number and percentage of patients with Dravet syndrome who experienced adverse events in double-blind placebo-controlled clinical studies in which stiripentol (STP) was used as an adjunct treatment with valproate and clobazam

Body System / Adverse event	**STICLO Pooled Total**	
	STP N = 33	**Placebo N = 31**
Number of Patients with at Least One Adverse event	31 (94 %)	12 (39 %)
Body as a Whole – General Disorders		
Asthenia/fatigue	2 (6 %)	-
Central and Peripheral Nervous System Disorders		
Drowsiness/sleepiness	22 (67 %)	3 (10 %)
Ataxia	4 (12 %)	3 (10 %)
Hypotonia	5 (15 %)	1 (3 %)
Tremor	3 (9 %)	1 (3 %)
Hyperkinesia	(3 %)	2 (6 %)
Dysarthria	2 (6 %)	-
Equilibrium disorders	1 (3 %)	-
Status epilepticus	1 (3 %)	1 (3 %)
Motor deficiency	-	1 (3 %)
Gastrointestinal System Disorders		
Loss of appetite	13 (39 %)	2 (6 %)
Weight loss	8 (24 %)	-
Nausea/vomiting	5 (15 %)	1 (3 %)
Sialorrhea	2 (6 %)	-
Body System / Adverse event	**STICLO Pooled Total**	
	STP N = 33	**Placebo N = 31**
Weight gain	5 (15 %)	4 (13 %)
Abdominal pain	3 (9 %)	1 (3 %)
Diarrhoea	-	1 (3 %)
Laboratory Parameters		
Neutropenia	3 (9 %)	-
Thrombocytopenia	2 (6 %)	-
Increase in aspartate aminotransferase	1 (3 %)	-
Eosinophilia	1 (3%)	-
Psychiatric Disorders		
Hyperexcitability/agitation	7 (21 %)	1 (3 %)
Aggressiveness/irritability	5 (15 %)	1 (3 %)
Insomnia/nightmares	2 (6 %)	-

Intellectual slowing	1 (3 %)	-
Respiratory System Disorders		
Bronchitis	1 (3 %)	1 (3 %)
Rhinitis	1 (3 %)	1 (3 %)
Skin and Appendages Disorders		
Face erythema	1 (3 %)	-
Dry skin	1 (3 %)	-
Urticaria	1 (3 %)	-
Urinary System Disorders		
Dysuria	1 (3 %)	-

Gastrointestinal adverse events

Weight loss and anorexia

Anorexia and weight loss are very common adverse effects.

In two double-blind, placebo-controlled trials in Dravet syndrome patients, gastrointestinal adverse events most often reported in patients receiving stiripentol were loss of appetite in 39 % of the treated patients and loss of weight in 24 % of the treated patients.

Nausea and vomiting

Nausea and vomiting are common adverse effects.

In 2 double-blind, placebo-controlled trials in Dravet syndrome patients, nausea and vomiting were observed in 15 % of the treated patients.

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

Abnormal liver function tests

Raised γGT (notably when combined with carbamazepine and valproate) is a common adverse effect.

Liver function should be assessed prior to starting treatment with DIACOMIT. Unless otherwise clinically indicated, liver function should be checked every 6 months. As the medicine is metabolised mainly by the liver, DIACOMIT is not recommended for use in patients with impaired hepatic function.

Central nervous system adverse events

Drowsiness, ataxia, hypotonia, dystonia and insomnia are very common adverse effects.

In 2 double-blind, placebo-controlled trials in Dravet syndrome patients, drowsiness/sleepiness were observed in 67 % of the treated patients, hyperexcitability/ agitation in 21 % of treated patients, aggressiveness/irritability in 15 % of treated patients, hypotonia in 15% of the treated patients, and ataxia in 12 % of the treated patients.

Patients should be monitored for somnolence and drowsiness, particularly when DIACOMIT is used concomitantly with other central nervous depressant. An adjustment of the dosage of concomitant clobazam or other anti-epileptic medicines could be considered. Patients should be advised to not operate machinery or drive.

Thrombocytopenia and neutropenia

Neutropenia is a common adverse effect. Thrombocytopenia is a rare adverse effect.

In 2 double-blind, placebo-controlled trials in Dravet syndrome patients, neutropenia was observed in 9 % of the treated patients and thrombocytopenia in 6 % of the treated patients.

Blood counts should be assessed prior to starting treatment with DIACOMIT. Unless otherwise clinically indicated, blood counts should be checked every 6 months.

Post marketing experience

The most frequent side effects with DIACOMIT are anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia and dystonia.

Table 2 Tabulated list of DIACOMIT Adverse Effects

System Organ Class (MedDRA)	**Frequent**	**Frequency unknown**

Blood and lymphatic system disorder	Neutropenia, persistent severe neutropenia usually resolves spontaneously when DIACOMIT is stopped*.	Thrombocytopenia*
Metabolism and nutrition disorders	Anorexia*, loss of appetite*, weight loss (especially when combined with sodium valproate)*	
Psychiatric disorder	Insomnia*, aggressiveness*, irritability*, behaviour disorders*, opposing behaviour*, hyperexcitability*, sleep disorders*	
Nervous system disorders	Drowsiness*, ataxia*, hypotonia*, dystonia*, hyperkinesias	
Eye disorders		Diplopia (when used in combination with carbamazepine)
Gastrointestinal disorders	Nausea*, vomiting*	
Skin and subcutaneous tissue disorders		Photosensitivity, rash, cutaneous allergy, urticaria
General disorders and administration site conditions		Fatigue
Investigations	Raised γGT (notably when combined with carbamazepine and valproate)	Liver function test abnormal

Many of the above adverse reactions are often due to an increase in plasma levels of other anticonvulsant medicines (see section 4.4 and section 4.5) and may regress when the dose of these medicines is reduced.

* Data are derived from both clinical trials and post-marketing experience.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Data on clinical overdose are not available. Treatment is supportive (symptomatic measures in intensive care units).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, other antiepileptics, ATC code: N03AX17

Mechanism of action

The mechanism of antiepileptic activity of stiripentol is based on the potentiation of the GABAergic transmissions in the CNS. *In vitro*, stiripentol has been shown to directly enhance GABAA receptor-mediated transmission by acting both post-synaptically at a neuronal site coupled to the GABAA receptor and pre-synaptically to increase GABA release from nerve terminals. In rodent models, stiripentol appears to increase brain levels of GABA. This could occur by inhibition of synaptosomal uptake of GABA and/or inhibition of GABA transaminase. Stiripentol has been shown to enhance GABAA receptor-mediated transmission in the immature rat hippocampus and increase the mean open-duration (but not the open-frequency) of GABAA receptor chloride channels.

Stiripentol also potentiates the efficacy of clobazam and other anticonvulsants, as a result of the pharmacokinetic interactions (see section 4.5). This effect of stiripentol is mainly based on metabolic inhibition of several isoenzymes, in particular CYP450 3A4 and 2C19, involved in the hepatic metabolism of other anti-epileptic medicines.

Clinical Trials

The efficacy of stiripentol, as an add-on therapy to optimised treatment with valproate and clobazam in patients presenting with Dravet syndrome has been demonstrated in two randomised, double-blind, placebo-controlled clinical trials. These trials, designated STICLO France and STICLO Italy, involved 41 (age range: 3,0-20,7) and 23 patients (age range: 3,5- 18,9) respectively. Both studies were conducted according to similar design to evaluate the responder rate to treatment, where the responder was defined as a patient who achieved ≥ 50 % decrease in the frequency of generalised clonic or tonic-clonic seizures during the double-blind treatment period compared to baseline (i.e., placebo run-in).

Eligible patients were randomly allocated to receive either stiripentol (50 mg/kg/day) or placebo added on to their antiepileptic treatment.

In study STICLO France, total of 41 patients were enrolled; 21 were randomised to receive stiripentol and 20 were randomised to receive placebo. One patient in the stiripentol group was excluded. For study STICLO Italy, 23 patients were enrolled; 12 were randomised to STP, and 11 to placebo. All were judged to be evaluable. A summary of the baseline demographic data is provided in Table 3.

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Table 3 Baseline Demographic and Illness Characteristics across the Pivotal Trials STICLO France and STICLO Italy

Baseline characteristics	**STICLO France N=41**		**STICLO Italy N=23**		**STICLO Pooled Total N=64**	
	STP N=21	**Placebo N=20**	**STP N=12**	**Placebo N=11**	**STP N=33**	**Placebo N=31**
Gender						
Male	6 (29 %)	11 (55 %)	8 (67 %)	5 (46 %)	14 (42 %)	16 (52 %)
Female	15 (71 %)	9 (45 %)	4 (33 %)	6 (54 %)	19 (58 %)	15 (48 %
Age (years)						
Mean ± SD	9,4 ± 4,0	9,3 ± 4,9	9,2 ± 3,6	8,7 ± 4,4	9,3 ± 3,8	9,1 ± 4,6
Median	9,8	9,2	8,6	8,2	8,6	8,8
Min-Max	3,0 – 16,7	3,2 – 20,7	3,7 – 15,5	3,5 – 18,9	3,0 – 16,7	3,2 – 20,7
Age Group (n, %)						
< 1	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
1 to < 6	4 (19 %)	6 (30 %)	3 (25 %)	3 (27 %)	7 (21 %)	9 (29 %)
6 to < 12	10 (48 %)	9 (45 %)	6 (50 %)	6 (54 %)	16 (48 %)	15 (48 %)
12 to < 17	7 (33 %)	2 (10 %)	3 (25 %)	1 (9 %)	10 (30 %)	3 (10 %)
≥ 17	0 (0 %)	3 (15 %)	0 (0 %)	1 (9 %)	0 (0 %)	4 (13 %)
Weight (kg)						
n	20	20	12	11	32	31
Mean ± SD	31,8 ± 12,7	30,5 ± 14,4	31,9 ± 11,7	29,2 ± 9,0	31,8 ± 12,1	30,0 ± 12,6
Median	30,0	25,5	29,2	27,0	30,0	27,0
Min - Max	14 - 60	15 – 70	16 -55	18 - 49	14 - 60	15 - 70
SCN1A mutation (n, %)*						
n	20	Not tested	9	Not tested	29	Not tested
Mutation	14 (70 %)		9 (100 %)		23 (79,3 %)	
No mutation	6 (30 %)		0 (0 %)		6 (20,7 %)	
Disease Duration (years)						
Mean ± SD	9,1 ± 3,8	9,0 ± 5,0	9,1 ± 3,6	8,7 ± 4,5	9,1 ± 3,7	8,9 ± 4,7
Min - Max	3,0 – 16,7	3,2 – 20,7	3,7 – 15,2	3,2 – 18,9	3,0 – 16,7	3,2 – 20,7
Seizure type (n, %)						

Generalised Seizures Tonic-clonic Myoclonic Unspecified generalised seizure	 21 (100 %) 10 (47,6 %) 12 (57,1 %)	 20 (100 %) 14 (70,0 %) 12 (60,0 %)	 12 (100 %) 10 (83,3 %) 5 (41,7 %)	 11 (100 %) 8 (72,7 %) 5 (45,5 %)	 33 (100 %) 20 (60,6 %) 17 (51,5 %)	 31 (100 %) 22 (71,0 %) 17 (54,8 %)
Number of tonic-clonic or clonic seizures during baseline Mean ± SD Median Min - Max	 17,9 ± 17,3 11,4 4 - 73	 18,5 ± 17,0 14,4 4 - 76	 33,6 ± 28,2 30,2 2 - 86	 27,5 ± 28,7 20,7 4 - 101	 23,6 ± 22,8 14,5 2 - 86	 27,1 ± 21,8 15,5 4 - 101
Daily dose Clobazam (mg/kg/day) n Mean ± SD Median Min - Max	 21 0,5 ± 0,2 0,5 0 - 1	 20 0,5 ± 0,2 0,5 0 - 1	 12 0,7 ± 0,2 0,6 0 - 1	 11 0,5 ± 0,1 0,5 0 – 1	 33 0,6 ± 0,2 0,5 0 - 1	 31 0,5 ± 0,2 0,5 0 – 1
Daily dose Valproate (mg/kg/day) n Mean ± SD Median Min - Max	 21 21,7 ± 9,6 17,0 11 - 43	 20 20,7 ± 8,3 16,7 14 - 44	 12 29,8 ± 7,8 29,1 21 - 44	 11 25,6 ± 7,3 26,9 11 - 38	 33 24,7 ± 9,7 21,9 11 - 44	 31 22,4 ± 8,2 22,5 11 - 44

STP = Stiripentol SD = Standard deviation

*: the presence or absence of the SCN1A mutation was measured after the blind was broken and the presence or absence of the mutation was only studied in the STP groups.

Table 4 summarises the antiepileptic efficacy of stiripentol in each STICLO trial, as well as the results of the pooled analysis ("STICLO Total").

Table 4 STICLO Efficacy Results Obtained at the End of Treatment in the Intent-to-Treat Population across the Pivotal Trials STICLO France and STICLO Italy

	STICLO France N=41		**STICLO Italy N=23**		**STICLO Pooled Total N=64**	
	STP	**Placebo**	**STP**	**Placebo**	**STP**	**Placebo**
Percentage change from baseline in seizure frequency*						
n	21	20	11	9	32	29
Mean ± SD	-62,0 ±	12,1 ± 44,4	-74 ± 26,7	-13 ± 62,0	-66 ± 44,2	4,3 ± 50,7
Median	-87,5	12,1	-81,2	-27,4	-84,4	-5,8
Min-Max	-100 – 72,6	-75 – 119	-100 – -33	-87 – 140	-100 – 72,6	-87 – 140
p-value[1]	0,0003		0,0056		<0,0001	
Responder analysis†						
No of responders/total	15/21	1/20	8/12	1/11	23/33	2/31
(Responder rate)	(71,4 %)	(5,0 %)	(66,7 %)	(9,1 %)	(69,7 %)	(6,5 %)
[95 %CI]	[52,1 –	[0,0 – 14,6]	[40,0 –	[0,0 – 26,1]	[54,0 –	[0,0 – 15,1]
p-value[2]	< 0,0001		0,0098		<0,0001	

*: Frequency of generalised tonic-clonic or clonic seizures.

†: Responder is defined as a patient with a ≥ 50% decrease in frequency of generalised tonic-clonic or clonic seizures.

[1] Wilcoxon Test; [2] Fisher's Exact Test.

CI=confidence interval; SD=standard deviation.

When efficacy results of both STICLO trials were pooled, 23 of 33 (69,7 %) patients on stiripentol versus 2 of 31 (6,5 %) patients on placebo met the criterion for response ($p < 0,0001$). Mean percent reduction in seizure frequency was 66 % in the pooled STP group versus an increase of 4 % in the pooled placebo groups ($p < 0,0001$).

5.2 Pharmacokinetic properties

Absorption

The T_{max} times were 2,42 hours for single doses of stiripentol 500 mg and 1 000 mg and 2,96 hours for 2 000 mg. According to Michaelis-Menten kinetics there is some evidence for non-linearity regarding stiripentol absorption. Following the oral administration of 500 mg, 1 000 mg and

2 000 mg of stiripentol in healthy volunteers the following data were determined.

	500 mg	**1 000 mg**	**2 000 mg**
C_{max} (mg/L) Mean ± SD	2,63 ± 1,18	6,63 ± 1,83	13,8 ± 4,83
Median	2,14	6,50	14,1
Min-max	1,21 – 4,1	3,90 – 10,4	8,31 – 24,0
$AUC_{0-30\ h}$ (mg/L.h) Mean ± SD	8,85 ± 3,77	32,1 ± 10,7	79,0 ± 24,2
Median	8,13	30,2	82,0
Min-max	3,74 – 15,7	18,3 – 51,1	48,2 - 128

The absolute bioavailability of stiripentol is not known since an intravenous formulation is not available for testing. It is well absorbed by the oral route since the majority of an oral dose is excreted in urine. Relative bioavailability between the capsules and powder for oral suspension in sachet formulations has been studied in healthy male volunteers after a 1 000 mg single oral administration. C_{max} of the sachet was slightly higher (23 %) compared with the capsule and did not meet the criteria for bioequivalence. T_{max} was similar with both formulations. Clinical supervision is recommended if switching between the stiripentol capsule and powder for oral suspension in sachet formulations.

Distribution

Stiripentol binds extensively to circulating plasma proteins (about 99 % at clinical plasma concentrations).

In a population pharmacokinetic study conducted in Dravet syndrome patients at steady state receiving the combination valproate + clobazam + stiripentol, the apparent volume of stiripentol distribution according to weight was as follows.

Body weight (kg)	V/F (L)
10	32,0 ± 3,8
30	95,9 ± 11,5
60	191,8 ± 23,0

Biotransformation

Stiripentol is primarily metabolised by the liver.

Stiripentol undergoes extensive first-pass metabolism in the liver with CYP1A2, CYP2C19 and CYP3A4 being the main isozymes involved in stiripentol metabolism. Stiripentol is mainly metabolised by glucuronidation and oxidative cleavage.

Stiripentol is supplied as a racemic mixture, and after administration R-enantiomer is the predominant enantiomer, but glucuronidation appears to favour the S-enantiomer. Elimination of a single dose was mainly (73 %) via the kidney after extensive metabolization (13 different metabolites) by the liver (Cytochrome P 450).

Elimination

Stiripentol is primarily excreted by the kidney.

Systemic exposure to stiripentol increases markedly compared to dose proportionality. In healthy adults, plasma clearance decreases markedly at high doses; it falls from approximately 40 l/kg/day at the dose of 600 mg/day to about 8 l/kg/day at the dose of 2,40 mg. Clearance is decreased after repeated administration of stiripentol, probably due to inhibition of the cytochrome P450 isoenzymes responsible for its metabolism. The half-life of elimination was in the range of 4,5 hours to 13 hours, increasing with dose.

Similarly, in a population pharmacokinetic study conducted in Dravet syndrome patients at steady state receiving the combination valproate + clobazam + stiripentol, the apparent volume of stiripentol distribution according to weight was as follows.

Body weight (kg)	CL/F (L/h)	$T_{½}$ (h)
10	2,60 ± 0,18	8,5 ± 1,3
30	4,19 ± 0,29	15,9 ± 2,4
60	5,65 ± 0,40	23,5 ± 3,5

5.3 Preclinical safety data

Genotoxicity

There was no evidence for genotoxic potential in *in vitro* assays for gene mutation or unscheduled DNA synthesis. A positive *in vitro* chromosomal aberration assay in Chinese Hamster Ovary cells (observed at the highest concentration) was not confirmed in a similar assay with human lymphocytes or in a mouse micronucleus test *in vivo*. The genotoxic potential of STP is considered to be low.

Carcinogenicity

There was no evidence of carcinogenicity in rats following oral administration of STP for 2 years at doses up to 800 mg/kg/day. This dose is approximately 3-4 times the MRHD based on body surface area, and systemic exposure (plasma AUC) was about 4-fold the estimated exposure in adults at the MRHD. In mice treated orally for 78 weeks, there was an increase in the incidence of hepatic adenomas and carcinomas at doses of 200 or 600 mg/kg/day. These doses are about 0,5 to 2-fold the MRHD based on body surface area, and plasma exposure was about 2-fold the paediatric C_{max}; the no-effect dose was 60 mg/kg/day. In view of the lack of genotoxicity of STP and the known susceptibility of the mouse liver to tumour formation in response to hepatic enzyme induction, this finding is not considered to indicate a risk of tumorigenicity in patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule:

Magnesium stearate

Povidone

Sodium starch glycolate, type A

Capsule shell (Body & cap):

Erythrosine (E127)

Gelatin

Indigotin carmine (E132)

Titanium dioxide (E171)

Powder for oral suspension:

Aspartame

Spray-dried liquid glucose

Povidone

Sodium starch glycolate type A

Erythrosine

Titanium dioxide

Carmellose

Hyetellose

Arome Polv Tutti Frutti 25 H 245

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original container to protect from light.

6.5 Nature and contents of container

Diacomit Capsules

DIACOMIT 250 and 500 mg capsules are packaged in opaque polyethylene bottles closed with a child-resistant tamper-evident polypropylene screw cap.

The DIACOMIT 250 mg capsules are packaged in 60 mL bottles and the DIACOMIT 500 mg capsules in 100 mL bottles in cardboard cartons.

Each bottle of 250 or 500 mg capsules contains 60 capsules.

Diacomit Powder for oral suspension

Diacomit 250 & 500 Powder for oral suspensions are packaged in sachets consisting of a paper, aluminium foil and polyethylene film composite. The sachets supplied in cardboard boxes with 30, 60 or 90 sachets.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene, 0157

Pretoria

8. REGISTRATION NUMBER(S)

Diacomit 250 Capsule: 550281

Diacomit 500 Capsule: 550282

Diacomit 250 Powder for oral suspension: 550283

Diacomit 500 Powder for oral suspension: 550284

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 June 2022

10. DATE OF REVISION OF THE TEXT