PRODUCT MONOGRAPH

^{Pr}DIACOMIT™*

stiripentol capsules
stiripentol powder for suspension

Capsules, 250 mg and 500 mg
Powder for suspension, 250 mg and 500 mg

Antiepileptic

Biocodex SA
7 Avenue Gallieni
94250 Gentilly
France

Date of Preparation:
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C.R.I.
Dundas, Ontario
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Non-medicinal Ingredients
Oral	Capsule/ 250 and 500 mg	erythrosine (250 mg capsule only), gelatine, indigotine (250 mg capsule only), magnesium stearate, povidone, sodium starch glycolate, titanium dioxide
Oral	Powder for suspension/ 250 and 500 mg	aspartame, carmellose sodium, erythrosine, glucose, hydroxyethylcellulose, povidone, sodium starch glycolate, sorbitol, titanium dioxide, tutti frutti flavour

INDICATIONS AND CLINICAL USE

DIACOMIT (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 syndrome) whose seizures are not adequately controlled with clobazam and valproate alone.

Geriatrics (>65 years of age):

There is no information in Dravet syndrome patients over 65 years of age (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics**). The possibility of age-associated hepatic and renal function abnormalities should be considered when using DIACOMIT in patients >65 years of age (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**).

Pediatrics (<18 years of age):

DIACOMIT when used in conjunction with clobazam and valproate was demonstrated to be effective and safe in patients 3 years of age or older with SMEI.

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. In this younger group of patients, adjunctive therapy with DIACOMIT should only be started when the diagnosis of SMEI has been clinically confirmed. Data are limited about the use

of DIACOMIT under 12 months of age and use in this age group should be under the close supervision of a doctor.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions:

Drug Interaction:

Carbamazepine, phenytoin and phenobarbital should not be used in conjunction with DIACOMIT (stiripentol) in the management of Dravet syndrome.

The daily dosage of clobazam and/or valproate should be reduced according to the onset of side effects while on DIACOMIT therapy.

DIACOMIT is a cytochrome P450 inhibitor and inhibits CYP2C19, CYP3A4, and CYP2D6. DIACOMIT may therefore markedly increase the plasma concentrations of concomitantly administered drugs metabolized by these enzymes, increasing the risk of adverse events (AEs) (see **DRUG INTERACTIONS**).

Delirium and Hallucinations:

Rare episodes of delirium and hallucinations have been reported in adult patients taking DIACOMIT. Patients with past history of psychoses in the form of episodes of delirium should be monitored closely when prescribed DIACOMIT.

General

DIACOMIT when used in conjunction with clobazam and valproate has been shown to be effective for the management of patients with Dravet syndrome. It has not been found effective for the management of other epilepsies or epileptic syndromes (see **CLINICAL TRIALS**).

Antiepileptic drugs, including DIACOMIT, should be withdrawn gradually to minimize 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 (see **DOSAGE AND ADMINISTRATION**).

In situations where rapid withdrawal of DIACOMIT is medically required, appropriate monitoring is recommended (see **DOSAGE AND ADMINISTRATION**).

Neurologic

In 2 double-blind, placebo-controlled studies, drowsiness/sleepiness was reported in up to 71% of patients receiving stiripentol. Patients and their caregivers should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating. Patients and their caregivers should be advised that patients treated with DIACOMIT should not operate machinery or drive until they have gained sufficient experience on DIACOMIT to assess whether it affects their mental and/or motor performance.

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

Gastrointestinal

In 2 double-blind, placebo-controlled trials in Dravet syndrome patients, gastrointestinal AEs most often reported in patients receiving stiripentol were loss of appetite in up to 50% of patients and loss of weight in up to 29% of patients. Given the frequency of digestive AEs, the growth rate of children should be carefully monitored.

A dietary supplement or increased food intake may be considered if the patient is losing weight while on DIACOMIT. In some cases, decreasing the dose of concomitant valproate by 30% per week can be helpful to minimize loss of appetite and weight loss.

Hematologic

Neutropenia may be associated with the administration of DIACOMIT in conjunction with clobazam and valproate. In 2 double-blind, placebo-controlled studies, neutropenia was observed in 3 of 33 patients treated with DIACOMIT (see **ADVERSE REACTIONS**, **Abnormal Hematologic and Clinical Chemistry Findings)**. In long-term studies, neutropenia was diagnosed in 5 patients (out of 317 patients treated with DIACOM IT), 2 of them were severe. Blood counts should be measured prior to starting treatment with DIACOMIT. Blood counts should be checked every 6 months or as clinically indicated.

Carcinogenesis and Mutagenesis

In rats, stiripentol was not carcinogenic. Liver carcinomas seen in mice with doses up to 600 mg/kg were considered to be due to enzyme induction, a finding confirmed by negative mutagenicity and genotoxicity tests. See **TOXICOLOGY, Carcinogenicity** and **Mutagenicity.**

Hepatic/Biliary/Pancreatic

Liver function should be assessed prior to starting treatment with DIACOMIT. Liver function should be checked every 6 months or as clinically indicated. There has been no formal study of the pharmacokinetics and metabolism of stiripentol in patients with impaired liver function.

Therefore, in hepatically impaired patients, DIACOMIT should be administered with caution as the drug is metabolized mainly by the liver.

In 2 double-blind, placebo-controlled studies, mild increases in liver transaminases were reported in 2 of 33 patients enrolled and treated with DIACOMIT (see **ADVERSE REACTIONS**, **Abnormal Hematologic and Clinical Chemistry Findings**). In long term studies, 7 of 8 patients who were diagnosed with elevated transaminase had mild elevations and 1 was moderate.

Peri-Operative Considerations

DIACOMIT is a potent inhibitor of certain CYP P450 enzymes and therefore it might affect the metabolism of certain drugs used during or after surgeries. See **DRUG INTERACTIONS**.

Psychiatric

Psychiatric-related events have been reported in DIACOMIT treated patients in the placebo controlled studies. These include: hyperexcitability/agitation, aggressiveness/irritability and insomnia/nightmares.

Suicidal Ideation and Behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour 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.

An FDA meta-analysis of randomized placebo-controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43,892 patients treated in the placebo-controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo-controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drugs). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the

minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Renal

In renally impaired patients, DIACOMIT should be administered with caution as the drug's metabolites are eliminated by the kidney. There has, however, been no formal study of the pharmacokinetics and metabolism of stiripentol with impaired renal function.

Patient and Caregiver Counselling Information

Caregivers/patients receiving DIACOMIT should be given the following instructions by the physician:

1. Caregivers/patients should be warned about the risk of drug interactions when taking DIACOMIT. Interactions with theophylline and caffeine cannot be excluded. Patients should not consume medicinal products and food containing caffeine or theophylline (for example cola, chocolate, coffee, tea, and energy drinks).

2. Caregivers/patients should be warned that DIACOMIT may be associated with neutropenia. Blood counts should be assessed prior to starting treatment with DIACOMIT and should be checked every 6 months or as clinically indicated.

3. Caregivers/patients should be warned about the potential for somnolence, dizziness, confusion, difficulty concentrating while taking DIACOMIT.

4. Caregivers/patients should be warned about the frequent gastrointestinal adverse reactions in children treated with DIACOMIT in combination with clobazam and valproate (anorexia, loss of appetite, nausea, vomiting) and that growth rate should be monitored.

5. Caregivers/patients should be instructed that patients should be advised not to drive a car or operate other complex machinery, and refrain from other activities requiring mental alertness or physical coordination until they are familiar with the effects of DIACOMIT on their ability to perform such activities.

6. Patients, their caregivers, and families should be informed that antiepileptic drugs, including DIACOMIT, may increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the patient's physician.

Special Populations

Pregnant Women:

Risk related to antiepileptic drugs: Antiepileptic drugs can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to antiepileptic drugs in utero have an increased risk for malformations. The prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population.

No data on exposed pregnancies with DIACOMIT are available and there are no studies of DIACOMIT in pregnant women. Unlike many other antiepileptic drugs, DIACOMIT is not teratogenic in rats and rabbits. Animal studies did not indicate direct or indirect harmful effects with respect to pregnancy, fetal development, parturition or postnatal development at non-maternotoxic doses (see **TOXICOLOGY**, **Reproductive and Development Toxicity**).

DIACOMIT should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Caution should be exercised when prescribing DIACOMIT to pregnant women.

Nursing Women: In the absence of human studies on excretion in breast milk, and given that stiripentol passes freely from plasma into milk in the goat, breast-feeding is not recommended for patients treated with DIACOMIT.

Pediatrics (<18 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. In this younger group of patients, adjunctive therapy with DIACOMIT should only be started when the diagnosis of SMEI has been clinically confirmed. Data are limited about the use of DIACOMIT under 12 months of age and use in this age group should be done under the close supervision of a doctor.

Geriatrics (>65 years of age)

There is no information in Dravet syndrome patients over 65 years of age. The possibility of age-associated hepatic and renal function abnormalities should be considered when using DIACOMIT in patients >65 years of age (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**).

Monitoring and Laboratory Tests

Given the frequency of gastrointestinal adverse reactions to treatment with DIACOMIT and valproate (anorexia, loss of appetite, nausea, vomiting), the growth rate of children treated with these antiepileptic drugs should be carefully monitored.

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

Liver toxicity has been observed with valproate, clobazam, and DIACOMIT. Liver function should be assessed prior to starting treatment with DIACOMIT and should be checked every 6 months or as clinically indicated.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety and tolerability of DIACOMIT (stiripentol) were evaluated in 42 healthy volunteers, 272 Dravet syndrome patients, and 551 patients with other forms of epilepsies.

Across all the studies in patients, the majority of AEs could be categorized as either neurological (sleepiness/drowsiness/somnolence) or gastrointestinal (loss of appetite, nausea, and loss of weight) in origin. There were no major differences in the type or incidence of AEs across studies in Dravet syndrome patients. In studies that enrolled both Dravet syndrome and non-Dravet syndrome patients, there was no difference in the AE profile between patients with Dravet syndrome and patients with other types of epilepsies.

In the placebo-controlled studies, AEs that led to treatment discontinuation included *status epilepticus*, drowsiness/balance impaired, and drowsiness/motor deficit (see **ADVERSE REACTIONS**, **Clinical Trial Adverse Drug Reactions**, **Adverse Events in Double Blind Placebo-Controlled Trials**).

Across all studies, 2 patients presented with a skin rash. In one case, treatment with stiripentol was maintained, and the skin rash recovered spontaneously. In the other case, treatment with stiripentol was suspended, the patient recovered, and stiripentol treatment was resumed uneventfully.

Clinical Trial Adverse Drug Reactions

Note that because clinical trials are conducted under very specific conditions the adverse reaction rates observed in clinical trials may not reflect the rates observed in practice and should not be compared to the rates in clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related AEs and for approximating rates.

Adverse Events in Double Blind Placebo-Controlled Trials

Two prospective, randomized, 8-week treatment, double-blind, placebo-controlled trials were conducted in Dravet syndrome patients. In both trials, DIACOMIT was added on to treatment with valproate and clobazam. The dose of DIACOMIT was 50 mg/kg/day. At the end of the trial, plasma concentrations of valproate were not significantly different from baseline. By contrast, plasma concentrations of clobazam were increased by a factor of 2 to 3 and plasma concentrations of clobazam's main metabolite (norclobazam) were increased by a factor of 5 (see **CLINICAL TRIALS**, **Efficacy of DIACOMIT in Dravet Syndrome Patients Treated in Double-Blind, Well-Controlled Trials**, **Study Results**). The following Table 1 lists the AEs 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 was Added on to Valproate (VPA) and Clobazam (CLB)

	Study 1		Study 2	
Body System / AE	**Stiripentol** added to VPA and CLB **N=21**	**Placebo** added to VPA and CLB **N=20**	**Stiripentol** added to VPA and CLB **N=12**	**Placebo** added to VPA and CLB **N=11**
Number of Patients with at Least One AE	21 (100%)	9 (45%)	10 (83%)	3 (27%)
Body as a Whole – General Disorders				
Asthenia/fatigue	2 (10%)	-	-	-
Central and Peripheral Nervous System Disorders				
Drowsiness/sleepiness	15 (71%)	2 (10%)	7 (58%)	1 (9%)
Ataxia	3 (14%)	1 (5%)	1 (8%)	2 (18%)
Hypotonia	2 (10%)	1 (5%)	3 (25%)	-
Tremor	3 (14%)	-	-	1 (9%)
Hyperkinesia	-	-	1 (8%)	2 (18%)
Dysarthria	2 (10%)	-	-	-
Equilibrium disorders	-	-	1 (8%)	-
Status epilepticus	1 (5%)	1 (5%)	-	-
Motor deficiency	-	1 (5%)	-	-
Gastrointestinal System Disorders				
Loss of appetite	7 (33%)	1 (5%)	6 (50%)	1 (9%)
Weight loss	6 (29%)	-	2 (17%)	-
Nausea/vomiting	2 (10%)	1 (5%)	3 (25%)	-
Sialorrhea	-	-	2 (17%)	-
Weight gain	5 (24%)	4 (20%)	-	-
Abdominal pain	2 (10%)	1 (5%)	1 (8%)	-
Diarrhea	-	1 (5%)	-	-
Laboratory Parameters				
Neutropenia	3 (14%)	-	-	-
Thrombocytopenia	2 (10%)	-	-	-
Increase in aspartate aminotransferase	-	-	1 (8%)	-
Eosinophilia	1 (5%)	-	-	-
Psychiatric Disorders				
Hyperexcitability/agitation	5 (24%)	-	2 (17%)	1 (9%)
Aggressiveness/irritability	3 (14%)	-	2 (17%)	1 (9%)
Insomnia/nightmares	2 (10%)	-	-	-

Body System / AE	Study 1		Study 2	
	Stiripentol added to VPA and CLB N=21	**Placebo** added to VPA and CLB N=20	**Stiripentol** added to VPA and CLB N=12	**Placebo** added to VPA and CLB N=11
Intellectual slowing	1 (5%)	-	-	-
Respiratory System Disorders				
Bronchitis	1 (5%)	1 (5%)	-	-
Rhinitis	1 (5%)	1 (5%)	-	-
Skin and Appendages Disorders				
Face erythema	-	-	1 (8%)	-
Dry skin	1 (5%)	-	-	-
Urticaria	1 (5%)	-	-	-
Urinary System Disorders				
Dysuria	1 (5%)	-	-	-

Across the 2 double-blind, randomized, placebo-controlled studies conducted with DIACOMIT in patients with Dravet syndrome, 2 of 33 (6%) patients randomized to DIACOMIT and 2 of 31 (6%) patients randomized to placebo were withdrawn from the studies for AEs. In patients treated with DIACOMIT, 1 patient was withdrawn due to *status epilepticus* and 1 patient was withdrawn for drowsiness/balance impaired. In patients treated with placebo, 1 patient was withdrawn due to *status epilepticus* and 1 patient was withdrawn for drowsiness/motor deficit.

Adverse Events in Long-Term Studies

Forty-five (45) Dravet syndrome patients who had participated in short-term clinical studies were treated long-term with DIACOMIT added to clobazam and valproate. Most patients were on concomitant valproate and clobazam. DIACOMIT dosage was 49.6 ± 13.8 mg/kg/day in patients <10 years of age; 42.5 ± 10.1 mg/kg/day in patients aged 10 to 16 years; and 37.6 ± 11.6 mg/kg/day in patients over 16 years of age. Overall, in patients with Dravet syndrome, the mean (± SD) total duration of exposure to DIACOMIT was 6.21 ± 1.44 years, ranging from 2 to 12 years, and over 85% of patients had a total exposure of greater than 5 years. AEs in these patients were not different from those observed during the placebo-controlled short-term studies. A similar observation was made in a series of 46 patients treated long-term (median 2.9 years) with DIACOMIT. One death (sudden death) was reported in this series. Additional serious adverse events (not necessarily drug-related) reported in the above studies included coma, convulsion, muscle contractions involuntary, testicular disorder and infection.

The following additional adverse events were reported in the Compassionate Program: General physical health deterioration, cytolytic hepatitis, gamma-glutamyltransferase increased.

Abnormal Hematologic and Clinical Chemistry Findings

Abnormal laboratories values measured in controlled studies consisted mainly of elevated transaminases (10 patients) and neutropenia (9 patients). In the long-term studies, neutropenia resolved spontaneously or with stiripentol dose reduction.

Table 2. Abnormal Laboratory Values Reported in Dravet Syndrome Patients

Abnormal Laboratory Value	Double-blind, placebo-controlled studies			Long-term studies and TUA-EAP			
	NCI Grade 1 (mild)	NCI Grade 2 (moderate)	NCI Grade 3 (severe)	NCI Grade 1 (mild)	NCI Grade 2 (moderate)	NCI Grade 3 (severe)	Unknown
Elevated Transaminases	2	0	0	7	1	0	0
Neutropenia	0	3	0	1	2	2	1

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been reported in patients receiving marketed DIACOMIT from worldwide use since approval. Because these adverse events are reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency. Furthermore, a causal relationship between DIACOMIT and the emergence of these events has not been clearly established.

A postmarketing survey of 73 patients with Dravet syndrome (48 patients) or other types of epilepsy (25 patients) showed a safety profile similar to that seen in clinical trials.

Malnutrition-related events directly or indirectly resulting from eating disorder have been reported. Nervous system disorders related to motor dysfunction and/or CNS depression have also been reported. Other drug-related serious adverse events reported include alanine aminotransferase increased, apathy, blood creatinine phosphokinase increased, oesophageal pain, pancreatitis, hyperthermia, Stevens-Johnson syndrome and thyroiditis.

DRUG INTERACTIONS

Overview

DIACOMIT (stiripentol) inhibits several cytochrome P450 enzymes notably CYP2C19, CYP3A4, CYP1A2, CYP2C8 and CYP2D6. Stiripentol may therefore markedly increase the plasma concentrations of concomitantly administered drugs metabolized by these enzymes, increasing the risk of AEs. Among antiepileptic drugs used in Dravet syndrome, stiripentol increases the plasma concentrations of clobazam by a factor of two or three, and those of its metabolite, norclobazam, by a factor of five usually requiring clobazam dose reduction. No dose reduction of valproate is required. Co-administration with CYP3A4 substrates with narrow therapeutic range (dihydroergotamine, ergotamine, cyclosporine, sirolimus, tacrolimus, quinidine, fentanyl) should be considered on an individual patient basis, taking into account the potential clinical benefits and risks.

Drug-Drug Interactions

Potential Medicinal Product Interactions Affecting Stiripentol

In vitro studies suggested that stiripentol phase 1 metabolism is catalyzed by CYP1A2, CYP2C19 and CYP3A4 and possibly other enzymes. The influence of other antiepileptic

medicinal products on the pharmacokinetics and metabolism of stiripentol is not well established.

Caution is advised when combining DIACOMIT with other drugs that inhibit or induce one or more of these enzymes.

Effect of Stiripentol on Cytochrome P450 Enzymes
Many of these interactions have been partially confirmed by *in vitro* studies and in clinical trials.

Co-administration with CYP3A4 substrates with a narrow therapeutic index should be avoided due to the markedly increased risk of severe adverse effects. It should be noted that the impact of macrolides and azole antifungal agents (known to be inhibitors and substrates of CYP3A4) on the metabolism of DIACOMIT is not known. Conversely, the effect of stiripentol on their metabolism is not known. Co-administration with CYP3A4 substrates may result in adverse events such as: elevations in clonazepam levels associated with somnolence, confusion, coma and diminished reflexes; elevations in ethosuximide levels associated with nausea, vomiting and CNS depression; inhibition of metabolism of macrolide antibiotics (azithromycin, clarithromycin, erythromycin) associated with gastrointestinal symptoms, dizziness, skin rash, altered state of consciousness, hypotonia and myoclonus.

At therapeutic concentrations, stiripentol significantly inhibits several CYP450 isoenzymes: for example, CYP2C19, CYP2D6, CYP1A2, CYP2C8, 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 side effects and adverse reactions.

Caution must be exercised if clinical circumstances require combining stiripentol with drugs metabolized 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 AEs (see further in this section for antiepileptic drugs). Monitoring of plasma concentrations or adverse effects is recommended. A dose adjustment may be necessary.

Co-administration with CYP2C19 substrates may result in adverse events such as: elevations in phenytoin levels associated with nystagmus, ataxia, lethargy and dysarthria; elevations in phenobarbital levels associated with nystagmus, ataxia, CNS depression, hypothermia and hypotension; elevations in methsuximide associated with nausea, vomiting and CNS depression

Data on the potential for inhibition of CYP1A2 are limited, and therefore, interactions with theophylline and caffeine cannot be excluded. Use in combination with DIACOMIT is not recommended. This warning is not only restricted to medicinal products 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.

Data on the potential for inhibition of CYP2C8 are limited, and therefore, interactions with other drugs cannot be excluded. Use in combination with DIACOMIT is not recommended. Co-administration with CYP2C8 substrates such as carbamazepine (metabolized also by CYP3A4) may result in elevation of substrate blood levels, and adverse events (for carbamazepine) such as: dizziness, drowsiness, disturbances of coordination, confusion, transient diplopia, and abnormal involuntary movements.

Stiripentol has been shown to inhibit CYP2D6 *in vitro* at concentrations that are achieved clinically in plasma, consequently drugs that are metabolized by this isoenzyme such as: 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 metabolized by CYP2D6 and that are individually dose titrated.

Co-administration of DIACOMIT with CYP2D6 substrates such as duloxetine may result in elevations of substrate levels, and adverse events as: somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension and vomiting.

Interactions with Antiepileptic Drugs

Inhibition of the CYP450 isoenzymes CYP2C19 and CYP3A4 may lead to pharmacokinetic interactions with phenobarbital, primidone, phenytoin, carbamazepine, clobazam, diazepam, ethosuximide, and tiagabine by inhibiting the hepatic metabolism of these drugs. As a consequence, the plasma concentrations of these antiepileptic drugs may increase with a risk of overdose. Clinical monitoring of plasma concentrations of concomitantly administered anticonvulsants with DIACOMIT and possible dose adjustments are recommended.

Table 3. Established or Potential Drug-Drug Interactions with Antiepileptic Drugs

Concomitant antiepileptic drug	Clinical comment
Valproate	The potential for metabolic interaction between stiripentol 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 2 double-blind, placebo controlled studies, the daily dose of valproate could be decreased by about 30% per week in the event of gastrointestinal adverse reactions such as loss of appetite or loss of weight.
Clobazam	In 2 double-blind placebo-controlled trials conducted in patients with Dravet syndrome, approximately 2- to 3-fold increases in clobazam and 5-fold increases in norclobazam plasma concentrations respectively were observed when DIACOMIT was added on to clobazam. When treatment with DIACOMIT 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 side effects or overdosage of clobazam (i.e., drowsiness, hypotonia, and irritability in young children), this daily dose was reduced by 25% every week.
Topiramate	In plasma concentrations 5 – 15 times higher than plasma concentrations obtained with the standard recommended topiramate dose and dosage schedule, topiramate

	interacts with CYP2C19. Thus, a potential pharmacokinetic and metabolic interaction between topiramate and stiripentol is viewed as unlikely. In a long-term study, a significant percentage of patients were receiving topiramate in combination with DIACOMIT. Based on the clinical observations in this group of patients, there is no evidence to suggest that a change in topiramate dose and dosage schedule is needed when topiramate is co-administered with DIACOMIT.
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.
Carbamazepine	In clinical trials in which DIACOMIT was added on to carbamazepine in patients suffering from epileptic syndromes other than Dravet syndrome, clear increases of plasma carbamazepine concentrations were observed. Carbamazepine should not be used in conjunction with DIACOMIT in Dravet patients (see **WARNINGS AND PRECATIONS, Serious Warning and Precautions, Drug Interactions**).
Phenytoin	In studies including small numbers of patients, addition of stiripentol was associated with increases in phenytoin concentrations. This was attributed to inhibition of CYP2C19 and CYP2C9 by stiripentol. Phenytoin should not be used in conjunction with DIACOMIT in Dravet patients (see **WARNINGS AND PRECATIONS, Serious Warning and Precautions, Drug Interactions**).
Phenobarbital	Phenobarbital is considered a substrate and an inducer of CYP2C19. In clinical studies involving small numbers of patients, phenobarbital concentrations increased when DIACOMIT was introduced. Phenobarbital should not be used in conjunction with DIACOMIT in Dravet patients (see **WARNINGS AND PRECATIONS, Serious Warning and Precautions, Drug Interactions**).

Interactions with Other Drugs

In the absence of available clinical data, caution should be used with the following drugs concerning potential interactions with stiripentol.

Table 4. Established or Potential Drug-Drug Interactions with Other Drugs

Drug or drug class	Clinical comment
Rye ergot alkaloids (ergotamine, dihydroergotamine)	Increased risk of ergotism with possibility of necrosis of the extremities (inhibition of hepatic elimination of rye ergot).
Cisapride, halofantrine, pimozide, quinidine, bepridil	Increased risk of cardiac arrhythmias and torsades de pointes/wave burst arrhythmia in particular.
Immunosuppressants (tacrolimus, cyclosporine, sirolimus)	Risk of increased 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 agent).
Midazolam, triazolam, alprazolam	Increased plasma concentrations of benzodiazepines may occur via decreased hepatic metabolism leading to excessive sedation.
Theophylline, caffeine	Increased plasma concentrations of theophylline and caffeine may occur via inhibition of their hepatic metabolism, potentially leading to toxicity.
Chlorpromazine	In animals, stiripentol enhances the central depressant effect of chlorpromazine.

Potentiation of Alcohol

There has been no clinical trial to examine the effects of alcohol in subjects treated with DIACOMIT. However, in animals, alcohol was shown to potentiate the sedating effects of stiripentol (see **DETAILED ANIMAL PHARMACOLOGY**, **Secondary Pharmacodynamics**). Patients and their caregivers should therefore be advised that consumption of alcohol should be avoided while on DIACOMIT treatment.

Drug-Food Interaction
DIACOMIT should 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 (such as yogurt; soft cream cheese), carbonated drinks, fruit juice or food and drinks that contain caffeine or theophylline (see **DOSAGE AND ADMINISTRATION**).

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
There are no known interactions of DIACOMIT with commonly used laboratory tests.

Drug-Lifestyle Interactions
Patients taking DIACOMIT should avoid using alcohol (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**, **Potentiation of Alcohol**).

DOSAGE AND ADMINISTRATION

Dosing Considerations

- There are possible pharmacokinetic interactions with other antiepileptic drugs, the dosage of clobazam and valproate may need to be adjusted.
- Patients' blood count should be assessed prior starting treatment and every 6 months.
- Switch in formulation (powder or capsule) should be under clinical supervision since the powder for suspension formulation has a slightly higher C_{max} than the capsules.
- In patients with hepatic disease and /or renal impairment, the dose titration should be guided by clinical outcomes (seizure control and side effects).

Recommended Dose and Dosage Adjustment

The daily dosage of DIACOMIT (stiripentol) may be administered in 2 or 3 divided doses.

The initiation of adjunctive therapy with DIACOMIT should be undertaken over 3 days using upwards dose escalation to reach the recommended dose of 50 mg/kg/day administered in conjunction with clobazam and valproate. The dose of valproate and clobazam might need to be adjusted when DIACOMIT is co-administered (see **DOSAGE AND ADMINISTRATION, Possible Pharmacokinetic Interactions with Other Antiepileptic Drugs)**.

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.

Drug Discontinuation

In case of discontinuation of DIACOMIT treatment, the drug should be withdrawn gradually to minimize the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were gradually reduced over a period lasting at least one month.

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

Possible Pharmacokinetic Interactions with Other Antiepileptic Drugs

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

CLOBAZAM: In the pivotal studies, the daily dose of clobazam was adjusted before stiripentol was initiated, so it was not greater than 0.5 mg/kg/day (administered in divided doses, twice daily). In the event of clinical signs of adverse reaction 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 five fold increases in norclobazam plasma levels respectively have been reported with co-administration of stiripentol in children with Dravet syndrome.

VALPROATE: The potential for metabolic interaction between stiripentol and 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.

Abnormal Laboratory Findings

In the event of an abnormal blood count or liver function test finding, the clinical decision to continue treatment or to adjust the dose of DIACOMIT and/or adjust the dose of concomitant antiepileptic medications needs to be made on an individual patient basis taking into consideration the potential clinical benefits and risks (see **ADVERSE REACTIONS**, **Abnormal Hematologic and Clinical Chemistry Findings**).

Effect of Formulation

The powder for suspension formulation has a slightly higher C_{max} than the capsules. It is recommended that if a switch in formulation is required, this should be done under clinical supervision.

Patients with Hepatic Disease

There is no formal study of the pharmacokinetics and metabolism of DIACOMIT in hepatically impaired patients. However, since DIACOMIT is metabolized primarily by the liver, caution should be used when treating patients with liver impairment. Treatment should be initiated with the same dose and dose regimen as for patients with normal hepatic function. The dose titration in these patients should be guided by clinical outcome, i.e., seizure control and avoidance of adverse effects.

Patients with Renal Impairment

There is no formal study of the pharmacokinetics and metabolism of DIACOMIT in patients with renal impairment. However, since DIACOMIT metabolites are eliminated mainly through the kidney, caution should be used when treating patients with renal impairment. Treatment should be initiated with the same dose and dose regimen as for patients with normal renal function. The dose titration in these patients should be guided by clinical outcome, i.e., seizure control and avoidance of adverse effects.

Missed Dose

The missed dose should be taken as soon as possible. If it is almost time for the next dose, the missed dose should not be taken. Instead, the next scheduled dose should be taken. Doses should not be doubled.

Administration

Capsules: The capsule should be swallowed whole with a glass of water during a meal. Capsules should not be broken or opened.

Powder for suspension: A powder for suspension formulation is provided for those patients who cannot swallow capsules. The powder should be mixed in a glass of water and should be taken immediately after mixing during a meal.

DIACOMIT should 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 (such as yogurt; soft cream cheese), carbonated drinks, fruit juice or food and drinks that contain caffeine or theophylline.

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is no data concerning overdose in humans. In mice treated with high doses of stiripentol (600 to 1,800 mg/kg i.p.), decreased motor activity and decreased respiration were observed (see **DETAILED ANIMAL PHARMACOLOGY**, **Secondary Pharmacodynamics**). Treatment should be supportive (symptomatic measures in intensive care units).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism by which stiripentol exerts its antiepileptic effect in humans is unknown. Stiripentol inhibits several isoenzymes, in particular CYP450 3A4 and 2C19, involved in the hepatic metabolism of other antiepileptic drugs. In addition the effect appears to be related to modulation of the GABAergic system (see **DETAILED ANIMAL PHARMACOLOGY**, **Primary Pharmacodynamics**).

Pharmacokinetics

The following pharmacokinetic properties of stiripentol have been reported from studies in adult healthy volunteers and adult patients.

Absorption / Bioavailability: Stiripentol is quickly absorbed, with a time to peak plasma concentration of about 1.5 hours. 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.

Distribution: Stiripentol binds extensively to circulating plasma proteins (about 99%).

Elimination: Systemic exposure to stiripentol increases markedly compared to dose proportionality. 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 2,400 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 ranges from 4.5 hours to 13 hours, increasing with dose.

Metabolism: Stiripentol is extensively metabolized, 13 different metabolites having been found in urine. The main metabolic processes are demethylenation and glucuronidation, although precise identification of the enzymes involved has not yet been achieved.

On the basis of *in vitro* studies, the main liver cytochrome P450 isoenzymes involved in phase 1 metabolism are considered to be CYP1A2, CYP2C19 and CYP3A4.

Excretion: Stiripentol metabolites are excreted mainly via the kidney. Urinary metabolites of stiripentol accounted collectively for the majority (73%) of an oral acute dose whereas a further 13-24% was recovered in feces as unchanged drug.

Bioequivalence: Relative bioavailability between the capsules and powder for suspension formulations has been studied in healthy male volunteers after a 1,000 mg single oral administration. The powder for suspension formulation has been a slightly higher C_{max} than the capsule. Clinical supervision is recommended if switching between the DIACOMIT capsule and powder for suspension formulations.

Special Populations and Conditions

Pediatrics: A population pharmacokinetic study was conducted in 35 children with Dravet syndrome (median age 7.3 years) treated with DIACOMIT, valproate and clobazam. The data were best fitted with a one compartment model with first order absorption and elimination processes. Clearance and volume of distribution were related to body weight. As a result, elimination half life increased from 8.5hr (for 10 kg) to 23.5 hr (for 60 kg). The population estimate for the absorption rate constant Ka was 2.08 hr -1 (standard deviation of random effect = 122%).

Geriatrics: The pharmacokinetics of DIACOMIT have not been evaluated in elderly subjects. However, since the drug is mainly metabolized by the liver, caution should be used when considering using the drug in elderly people.

Race, Gender and Age: The effects of race, age, and gender on the pharmacokinetics of DIACOMIT have not been studied.

Hepatic Insufficiency: There has been no formal study of the pharmacokinetics of DIACOMIT in patients with liver impairment. However, since the drug is mainly metabolized by the liver, caution should be used when considering using the drug in people with liver impairment.

Renal Insufficiency: There has been no formal study of the pharmacokinetics of stiripentol in patients with renal impairment. However, since the drug is mainly excreted through the kidney, caution should be used when considering using the drug in people with renal impairment.

Genetic Polymorphism: Genetic polymorphisms in metabolic enzymes have only an indirect relevance linked to the use of clobazam. Clobazam has an active circulating metabolite, norclobazam, whose elimination is highly dependent on CYP2C19 (an enzyme that is inhibited by DIACOMIT). As a consequence, DIACOMIT will not affect norclobazam concentrations in poor metabolizers (5 to 8% of Caucasians and 20 to 25 % of Asians), but will increase norclobazam levels in all other types of metabolizers (intermediate, extensive, ultrarapid).

STORAGE AND STABILITY

DIACOMIT (stiripentol) should be stored in the original package to protect from light. Store at room temperature (15 to 30°C) in a dry place.

Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

DIACOMIT (stiripentol) capsules are available in the following strengths and colours:

250 mg: size 2 pink capsules
500 mg: size 0 white capsules

Supplied as: 250 mg capsules: 60 count in bottles
500 mg capsules: 60 count in bottles

DIACOMIT powder for suspension is available in the following strengths:

250 mg
500 mg

Supplied as: 250 mg powder for suspension: 30, 60, or 90 count in carton
500 mg powder for suspension: 30, 60, or 90 count in carton

Composition

DIACOMIT capsules contain the following inactive ingredients: erythrosine (250 mg capsule only), gelatin, indigotine (250 mg capsule only), magnesium stearate, povidone, sodium starch glycolate, titanium dioxide.

DIACOMIT powder for suspension contains aspartame, carmellose sodium, erythrosine, glucose, hydroxyethylcellulose, povidone, sodium starch glycolate, sorbitol, titanium dioxide, tutti frutti flavour.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

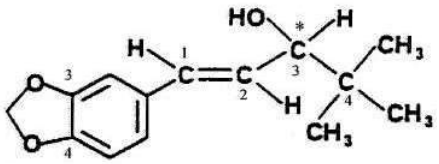
Proper name: Stiripentol

Chemical names:

- (±)-(E)- 4,4-dimethyl-1-[(3,4-methylenedioxy)phenyl]-1-penten-3-ol;
- 1-penten-3-ol, 1-(1,3-benzodioxol)-4,4-dimethyl.

Molecular formula and molecular mass: $C_{14}H_{18}O_3$, 234.3

Structural formula:



* : identifies an asymmetric carbon.

Physicochemical properties:

Physical Description:	White to pale yellow crystalline powder
Physical Form (polymorphic form, solvate, hydrate):	No polymorphism exhibited as determined by differential thermal analysis and X-ray powder diffraction
Solubility:	Practically insoluble in water (at 25°C) Sparingly soluble in chloroform Soluble in acetone, ethanol, ether, acetonitrile, dichloromethane
pKa:	14.2
Melting Point:	~75°C
Partition Coefficient (water-octanol):	LogP = 2.94

CLINICAL TRIALS

The following Table 5 lists the clinical trials that were conducted with DIACOMIT (stiripentol) in patients with Dravet syndrome.

Table 5. Clinical Trials Conducted with DIACOMIT in Dravet Syndrome Patients

Study	Treatment/ Number of Patients	Study Design
STEV	DIACOMIT: 25	Open-label, exploratory study
STICLO France	DIACOMIT: 21, Placebo: 20	Randomized, double-blind, placebo-controlled, add-on
STICLO Italy	DIACOMIT: 12, Placebo: 11	Randomized, double-blind, placebo-controlled, add-on
STILON	DIACOMIT: 45	Open-label, long-term (up to several years), add-on
Thanh et al. (2002)	DIACOMIT: 46	Open-label, long-term (up to several years), add-on

Efficacy of DIACOMIT in Dravet Syndrome Patients Treated in Double-Blind, Well-Controlled Trials

The efficacy of DIACOMIT, as an add-on therapy to clobazam and valproate, in children presenting with Dravet syndrome, was studied in two randomized, double-blind, placebo-controlled studies (STICLO France and STICLO Italy). The numbers of patients involved in the STICLO France and STICLO Italy studies were 41 and 23, respectively. Results of STICLO France have been published (Chiron et al, 2000).

Study Demographics and Trial Design

Both studies use similar designs. DIACOMIT or placebo was added-on to antiepileptic treatment with valproate and clobazam. The protocol specified that to be enrolled, patients had to present with Dravet syndrome according to the diagnostic criteria established by Dravet (1982) and included in the ILAE classification of epilepsy (ILAE, 1989), be aged 3 to 18 years (maximum weight: 60 kg), and have at least 4 generalized clonic or tonic-clonic seizures per month despite optimized therapy.

Eligible patients were included initially in a 1-month baseline period during which they continued to receive their antiepileptic treatment. During the baseline period, the daily dose of clobazam was adjusted so it was not greater than 0.5 mg/kg/day (administered in divided doses, twice daily). Following this 1-month baseline, patients were randomly allocated to receive either DIACOMIT (50 mg/kg/day) or placebo, added-on to their antiepileptic treatment. The frequency of generalized clonic or tonic-clonic seizures during the study was recorded by the parents or the caregivers, using a diary. Patients were treated double-blind for 2 months.

The primary efficacy endpoint for this study was response rate. A responder was defined as a patient who experienced a ≥50% decrease in the frequency of generalized clonic or tonic-clonic seizures during the double-blind treatment compared to baseline. Patients were also evaluated on several secondary endpoints, notably mean change from baseline in frequency of generalized clonic or tonic-clonic seizures. Note that although patients with Dravet syndrome have several different types of seizures, only generalized clonic or tonic-clonic seizures were recorded, as other seizure types can be difficult to recognize as seizures by the parents or the caregivers.

Study Results

In both STICLO France and STICLO Italy, the demographic and baseline clinical characteristics were similar for the stiripentol and placebo groups. Seizure frequency during the 1-month baseline run-in ranged from 4 to 76 in STICLO France and ranged from 2 to 101 in STICLO Italy.

In STICLO France, 5 patients withdrew from the study during the double-blind period, with 1 patient in the stiripentol group (*status epilepticus*) and 4 patients in the placebo group (*status epilepticus*: 1; no improvement: 2; drowsiness and motor deficit: 1). In STICLO Italy, 3 patients withdrew during the double-blind period, with 1 patient in the stiripentol group (drowsiness; balance impaired) and 2 patients in the placebo group (worsening seizures; lack of improvement).

Table 6 summarizes the antiepileptic efficacy of DIACOMIT in each study.

Table 6. STICLO Studies – Efficacy Results in the Intent-to-Treat Population

	STICLO France			STICLO Italy		
Efficacy Endpoint	**DIACOMIT**	**Placebo**	**p value**	**DIACOMIT**	**Placebo**	**p value**
Number of responders [95% CI]	15 (71%) [52 – 91] *N=21*	1 (5%) [0 – 15] *N=20*	<0.00002	8 (67%) [35 – 90] *N=12*	1 (9%) [0 – 41%] *N=11*	0.009
Mean change (%) from baseline in frequency of generalized clonic or tonic-clonic seizures during Month 2 (± SD)	-69 ± 42 *N=20*	8 ± 38 *N=16*	<0.0001	-74 ± 27 *N=11*	-11 ± 62 *N=9*	0.0018
Number of patients free of generalized clonic or tonic-clonic seizures	9 (45%) *N=20*	0 (0%) *N=16*	0.0019	3 (27%) *N=11*	0 (0%) *N=9*	0.218

CI = confidence interval; SD = standard deviation

In both studies, DIACOMIT was significantly more efficacious than placebo, as judged by the number of responders (primary efficacy endpoint; ≥50% decrease in the frequency of generalized clonic or tonic-clonic seizures). In STICLO France, 15 of 21 (71%) patients on DIACOMIT versus 1 out of 20 (5%) patients on placebo were responders ($p<0.00002$). In STICLO Italy, 8 of 12 (67%) patients on DIACOMIT versus 1 out of 11 (9%) patients on placebo were responders ($p=0.009$).

DIACOMIT was also superior to placebo as judged by reduction in mean frequency of generalized clonic or tonic-clonic seizures in STICLO France ($p<0.0001$) and in STICLO Italy ($p=0.0018$).

Nearly half the patients (45%) in STICLO France and approximately one third of patients (27%) in STICLO Italy became free of generalized clonic or tonic-clonic seizures on DIACOMIT.

The dose of DIACOMIT was similar in the 2 STICLO studies with the daily dose of DIACOMIT ranging from 43.1 mg/kg to 58.3 mg/kg. The corresponding mean (± SD) minimal plasma concentrations at steady state (C_{min}) as measured at the end of the 8-week treatment period were

10.0 ± 3.6 mg/L (range 6.0-18.8 mg/L) in STICLO France and 10.2 ± 2.98 mg/L (range 5.70-14.0 mg/L) in STICLO Italy.

Table 7 au-dessous presents plasma concentrations for concomitant antiepileptic drugs at baseline and after 7 weeks of treatment with DIACOMIT or placebo for STICLO France and STICLO Italy.

Table 7. Trough Plasma Levels (C_{min}) for Concomitant Antiepileptic Drugs at Baseline and After 7 Weeks Treatment with DIACOMIT or Placebo

Antiepileptic Drug	STICLO France			STICLO Italy		
	DIACOMIT	Placebo	p value	DIACOMIT	Placebo	p value
Baseline						
Valproate (mg/L)	70.5 ± 22.0 N=21	72.1 ± 33.5 N=18	NS	83.4 ± 29.6 N=11*	72.5 ± 13.6 N=11	NS
Clobazam (mg/L)	0.182 ± 0.039 N=21	0.178 ± 0.074 N=19	NS	0.192 ± 0.090 N=11*	0.213 ± 0.131 N=11	NS
Norclobazam (mg/L)	1.54 ± 1.72 N=21	0.95 ± 0.69 N=19	NS	0.763 ± 0.346 N=11*	0.633 ± 0.482 N=11	NS
After 7 Weeks Treatment with Stiripentol or Placebo						
Valproate (mg/L)	73.0 ± 27.2 N=20	69.6 ± 30.5 N=17	NS	93.6 ± 29.3 N=11	78.8 ± 21.6 N=9	NS
Clobazam (mg/L)	0.314 ± 0.154 N=20	0.199 ± 0.067 N=17	p <0.01	0.299 ± 0.146 N=11	0.218 ± 0.086 N=9	NS
Norclobazam (mg/L)	4.32 ± 1.18 N=20	0.951 ± 0.752 N=17	p <0.001	3.97 ± 1.83 N=11	0.687 ± 0.483 N=9	p <0.002

* Missing data for 1 patient
NS = not significant

As expected, the plasma concentrations of valproate were not significantly affected by concomitant DIACOMIT. By contrast, the plasma concentrations of clobazam and its metabolite norclobazam were significantly increased with DIACOMIT.

Comparative Bioavailability Studies

Relative bioavailability between the capsules and powder for suspension formulations has been studied in healthy male volunteers after a 1,000 mg single oral administration. The powder for suspension formulation has a higher C_{max} than the capsule. Clinical supervision is recommended if switching between the DIACOMIT capsule and powder for suspension formulations.

Table 8. Comparative Bioavailability for DIACOMIT Powder for Suspension (2 x 500 mg) and Capsules (2 x 500 mg) (Uncorrected for Potency)

Parameter	DIACOMIT powder for suspension*	DIACOMIT capsules*	% Ratio of Geometric Means	90% Confidence Interval
AUC_{τ} (h·µg/mL)	31.28	28.54	109.6	104-116
$AUC_{0-\infty}$ (h·µg/mL)	35.20	32.93	106.9	98.0-115
C_{max} (µg/mL)	7.04	5.72	123.1	110-137
T_{max} † (h)	3.50 (1.50-4.00)	3.00 (1.00-4.00)		
$T_{½}$ ‡ (h)	14.38 (53)	17.41 (65)		

† Expressed as the median (range)
‡ Expressed as the arithmetic mean (CV%)

DETAILED ANIMAL PHARMACOLOGY

Primary Pharmacodynamics

Stiripentol antagonizes electrical shock and chemically induced seizures in animal models.

Anticonvulsant Activity in Mice and Rats

The profile of anticonvulsant activity of orally administered stiripentol was studied in mice and rats in well-established seizure models. The activity of stiripentol was compared to that of phenytoin, phenobarbital, ethosuximide, and valproate.

Orally administered stiripentol antagonized maximal electroshock-induced seizures with an ED_{50} of 812 mg/kg and 411 mg/kg in mice and rats respectively. In rats, stiripentol antagonized metrazol-induced seizures with an ED_{50} of 375 mg/kg. In both mice and rats, stiripentol had anticonvulsant activity in doses that did not affect rotarod, a test viewed as indicating sedation and cerebellar motor incoordination. Note that when the anticonvulsant potency of stiripentol is compared to that of other antiepileptic drugs using only nominal doses (in mg/kg), stiripentol appears to be a weaker anticonvulsant.

Results are summarized in the following Table 9 (mice) and Table 10 (rats) au-dessous.

Table 9. Profile in Mice of the Anticonvulsant Activity of Orally-Administered Stiripentol Compared to Reference Antiepileptic Drugs

Test Drug	Rotarod TD_{50} (CI) mg/kg p.o.	Anticonvulsant ED_{50} (CI) mg/kg p.o.	
		MES	s.c. MET
Stiripentol	No effect up to 2,500	812 (745-984)	No protection up to 2,500
Phenytoin	86.71 (80-96)	9 (7-11)	No protection up to 300
Phenobarbital	96.78 (80-115)	20 (15-32)	13 (8-19)
Ethosuximide	879 (840-933)	No protection up to 2,000	192 (159-218)
Valproate	1,264.39 (800-2,250)	665 (605-718)	388 (349-439)

Experiments in groups of 8 animals.
TD_{50} = the dose eliciting evidence of minimal sedation and motor incoordination in 50% of animals; CI = 95% confidence limits; mg = milligram; kg = kilogram; ED_{50} = the dose at which 50% of animals were completely protected from seizures; MES = maximal electroshock seizure pattern test; MET = Metrazol seizure test; s.c. = subcutaneous

Table 10. Profile in Rats of the Anticonvulsant Activity of Orally-Administered Stiripentol Compared to Reference Antiepileptic Drugs

Test Drug	Rotarod TD_{50} (CI) mg/kg p.o.	Anticonvulsant ED_{50} (CI) mg/kg p.o.	
		MES	s.c. MET
Stiripentol	No ataxia up to 2,000	411 (370-462)	375 (251-516)
Phenytoin	No ataxia up to 3,000	30 (22-39)	No protection up to 800
Phenobarbital	61 (44-96)	9 (8-12)	11 (8-15)
Ethosuximide	1012 (902-1,109)	No protection up to 1,200	54 (46-61)
Valproate	280 (191-353)	489 (351-728)	180 (147-210)

Experiments in groups of 8 animals.
TD_{50} = the dose eliciting evidence of minimal sedation and motor incoordination in 50% of animals; CI = 95% confidence limits; mg = milligram; kg = kilogram; ED_{50} = the dose at which 50% of animals were completely protected from seizures; MES = maximal electroshock seizure pattern test; MET = Metrazol seizure test; s.c. = subcutaneous

When the anticonvulsant potency of stiripentol is compared to that of other antiepileptic drugs using nominal doses (in mg/kg), stiripentol appears to be a weaker anticonvulsant. As shown in Table 11 au-dessous, in rats, an oral dose of 600 mg/kg demonstrated anticonvulsant activity and resulted in plasma concentrations that were within the same range as those observed in patients treated with stiripentol (6-81 µg/mL).

Table 11. Stiripentol Plasma Concentrations in Rats

Time Post-Stiripentol Administration	Stiripentol Dose po (mg/kg)	Mean Stiripentol Concentrations	
		Plasma (mg/L)	Brain (mg/kg)
4 hours	600	16.9	0.9-8.8
6 hours	600	29.8	8.4-21.6

In this study stiripentol was dissolved in polyethylene glycol (PEG).
mg/kg = milligram per kilogram; mg/L = milligram per liter

Comparison of the anticonvulsant activities of the two enantiomers and the racemate in a pentylenetetrazol infusion seizure rat model suggested that the (+) enantiomer was slightly more potent.

Antiepileptic Activity of Stiripentol in Various Seizure Models

Stiripentol (125 to 500 mg/kg i.p.) antagonized seizures in rats in a genetic model of petit mal seizures in a dose-dependent manner.

In mice susceptible to audiogenic-induced seizures, a genetic model for partial seizures, i.p. stiripentol antagonized clonic and tonic seizures with an ED_{50} value of 72 mg/kg/i.p.

Chronic (4-week) treatment with stiripentol also reduced interictal spike activity in a primate model of partial seizures (the alumina gel model) in plasma concentrations of 24-28 mg/L.

Anticonvulsant Activity of Stiripentol When Co-Administered with Other Antiepileptic Drugs

In mice, when stiripentol (200 mg/kg i.p.), valproate (37 mg/kg i.p.) and a benzodiazepine (diazepam 0.25 mg/kg i.p.) were administered together, supra-additive synergy was observed.

Mechanism of Action Studies

In vitro, stiripentol at concentrations up to 10^{-4} M (0.1 mM or 23.4 mg/L) did not bind to the gamma-aminobutyric acid (GABA), GABA-B, strychnine, or benzodiazepine receptors. In the recent publication by Fisher (2009), stiripentol at 1 mM (234 mg/L) can directly activate the GABA-A receptor, as a weak partial agonist. When Swiss EOPS mice were treated with stiripentol or valproate (300 mg/kg IP), there was an increase GABA levels in the brain 30 minutes following administration. Patch clamp experiments conducted ex vivo on rat hippocampal slices showed that stiripentol at 30 to 300 µM (7-70 mg/L) gradually and concentration dependently increased duration and frequency of miniature GABA-A receptor-mediated currents (mIPSCs) without modifying amplitude or rise time. These effects persisted in the presence of inhibitors of the benzodiazepine or neurosteroid binding sites. Saturating barbiturate sites antagonized the effect of stiripentol indicating a barbiturate-like mechanism.

In rats, stiripentol increased brain levels of gamma-aminobutyric acid (GABA). *In vitro* studies reported by Fisher (2009) using patch-clamp recordings, showed that the drug acts as a positive allosteric modulator of the GABA-A receptor, and potentiates GABA currents at several types of GABA-A receptors, with greatest potentiation occurring in α3-containing receptors. In

mammalian cells transfected with recombinant GABA-A receptors, stiripentol at EC_{50} of 24.6 µM (5.8 mg/L) caused a shift in the GABA concentration-response curve to the left, without increasing maximal response, indicating allosteric modulation of GABA-A receptors. Stiripentol was shown not to act on the neurosteroid modulatory site or on the loreclezole modulatory site. These findings suggest that stiripentol acts as a direct allosteric modulator of the GABA-A receptor at a site distinct from many commonly used anti-convulsant, sedative and anxiolytic drugs. Fisher also showed that when maximally effective concentrations of stiripentol (100 µM or 23.4mg/L) and diazepam (1 µM) were applied together, the drugs act synergistically to further increase channel activity (Fisher, 2009).

Secondary Pharmacodynamics

In mice, stiripentol (ranging from 50 to 200 mg/kg i.p.) decreased basal motor activity and higher doses (600 to 1,800 mg/kg i.p.) induced sedation, muscle relaxation, and decreased respiration with cyanosis.

In mice, single doses of stiripentol of 200 and 400 mg/kg i.p. dose-dependently potentiated alcohol-induced sedation and was found to both increase the percentage of animals affected by narcosis and to prolong ethanol-induced sleeping time. Oral administration of stiripentol for 5 days at a dose of 400 mg/kg potentiated sedation induced by ethanol.

In mice, stiripentol potentiated sedation induced by other sedative drugs, such as benzodiazepines, neuroleptics, and barbiturates.

Safety Pharmacology

In dogs, stiripentol (2.5 and 5.0 mg/kg i.v.) induced a slight decrease in blood pressure and heart rate. Stiripentol (2.5 mg/kg i.v.) did not significantly affect respiration rate or amplitude.

In mice, stiripentol (200 mg/kg i.p. or 400 mg/kg p.o.) did not modify intestinal transit.

Stiripentol (200 mg/kg p.o. for 4 days) was administered to prepubertal rats. Animals were sacrificed on Day 5. No significant effects were observed on the weight of thyroid, adrenals, ovaries or seminal vesicles and testes.

Effects on hERG channels have not been evaluated.

Other Pharmacodynamic Drug Interactions

Concomitant administration of stiripentol (300 mg/kg/day p.o. for 5 days) reduced prothrombin time in rats given acenocumarol or phenindione alone. The mechanism for this is unknown.

Stiripentol (300 mg/kg/day po for 5 days) also enhanced the plasma glucose-lowering effects of glibenclamine (INN), also known as glyburide (USAN), in rats.

Pharmacokinetics

The kinetic parameters of stiripentol have not been comprehensively characterized in experimental animals. There is no data in the mouse and limited data in rats and monkeys. Of the limited data available, oral administration in monkeys indicate bioavailability of 25-28%. The volume of distribution was larger in rats than monkeys (5.6 L/kg in rats and ~1 L/kg in monkeys) with faster clearance in monkeys (~1 L/h/kg) than in rats (0.28 L/h/kg). After i.v. administration, stiripentol is rapidly distributed to tissues with maximum concentrations 30 min postdose. The highest concentrations were liver>lung>cerebellum>total brain>spinal cord. Stiripentol crosses the placenta in rat. Brain concentrations of stiripentol were determined in rats and depending on the study, plasma and brain ratios range from 0.37 to 1.2. In a study that included evaluation of stiripentol effects on seizures induced by infused pentylenetetrazol, the plasma and brain EC50 was 54.1 and 20.0 mg/L, respectively. The kinetics of enantiomers have been evaluated in rats only. R(+) stiripentol was eliminated faster than the S(-) enantiomer.

Stiripentol is extensively metabolized by cytochrome P450 in rats, monkeys and human. Glucuronidation is a route of elimination in monkeys and humans but not significant in rats. Metabolism is the major route of elimination in all species and in both rats and monkeys, urinary concentration of the parent drug is <1%. Using labeled stiripentol, no radioactivity was noted in exhaled breath and after oral dosing in the rat, 22% of the label was excreted in urine and ~69% in feces. After i.v. dosing, high concentrations were noted in bile suggesting biliary elimination. Stiripentol was excreted in milk of lactating goats.

TOXICOLOGY

The toxicity of stiripentol was examined in acute, subacute, and chronic toxicology studies in mice, rats, and monkeys.

Acute Toxicity

The acute toxicity of stiripentol was assessed in mice and rats (Table 12).

Table 12. Median Lethal Dose (LD_{50}) Values for Stiripentol in Mice and Rats

Route of Administration	Species	LD_{50} (mg/kg)
Oral	Mice	>3000
	Rats	
Intraperitoneal	Mice	~1500
	Rats	1000-1685
Intravenous	Mice	72-78

LD_{50} = median lethal dose; mg=milligram; kg=kilogram

The acute oral toxicity of the drug was low with a maximal non-lethal dose of 3000 and 5000 mg/kg for rats and mice respectively. After i.p. administration, the acute toxicity of stiripentol was still low with LD_{50} values of about 1,500 mg/kg bw in almost all studies in mice and rats. In contrast, stiripentol was more toxic by the i.v. route with LD_{50} values of 72-78 mg/kg bw in mice and rats. After i.p. administration, clinical signs observed included

convulsions, agitation, sedation, ptosis, stretching and respiratory disturbances in both mice and rats.

Subacute and Chronic Toxicity

Stiripentol was tested for repeated-dose toxicity in mice, rats and monkeys. The key findings are shown in Table 13.

Table 13. Overview of Findings in Subacute and Chronic Toxicity Studies

Species, Strain	Route	Duration	Doses (mg/kg/day)	Main Effects
Mouse, Swiss (CD-1, ICR)	Oral	13 weeks	0, 60, 800	Slightly increased cholesterol levels in high-dose males, markedly increased liver-weights with histologically visible centrilobular hepatocellular hypertrophy in high-dose animals. No elevation of plasma AST or ALT. Two animals died at 800 mg/kg.
Rat, Sprague-Dawley	Oral	21 days	0, 80 220, 800	Dose-related increase of liver weight that reached statistical significance at 220 mg/kg/day.
Rat, Wistar	Oral	6 months	0, 30, 60, 300	Slightly reduced body weight gains in 60 and 300 mg/kg/day females, increased liver weights in low- and high-dose females and in high-dose males without histological correlate.
Rat, Sprague-Dawley	Oral	26 weeks	0, 80, 220, 800	Poor clinical condition, reduced body weight gains, and single mortalities at 220 and 800 mg/kg/day, increased protein excretion in urine in all treated groups, increased liver weight at 220 and 800 mg/kg/day, increased kidney weight at 800 mg/kg/day, marked centrilobular hepatocyte hypertrophy and renal tubular nephrosis at 220/800 mg/kg/day. No elevation of plasma AST or ALT.
Cynomolgus monkey	Oral	4 weeks	0, 100, 300, 900	Hypotonia, sedation, reduced bodyweight and food consumption, and a single mortality at high dose, increased blood urea, increased liver weight without histological changes, focal tubular nephrosis, and thymus involution at high dose.
Cynomolgus monkey	Oral	26 weeks (+ 4-week recovery)	0, 100, 250, 600	Slight anemic changes at high-dose; reversible slight increase of liver weight in males without histological correlate at the two higher dose levels.

Reproductive and Development Toxicity

There were no effects of stiripentol on fertility in male and female rats at doses up to 800 mg/kg. At 800 mg/kg, stiripentol caused clinical signs and a low incidence of mortality in the dosed female dams (the F0 generation), delayed ossification of F1 fetuses, and decreased pup viability. There were no effects on the F2 generation of treatment with stiripentol of the F0 generation. The NOEL for maternal and embryo-fetal toxicity was determined at 200 mg/kg.

Embryo-fetal development was assessed in mice and rabbits. In the rabbit, doses of 200 and 800 mg/kg were toxic to the dam and there was an increase in the number of abortions and resorptions resulting in a reduced number of live fetuses. In the mouse, there were no effects on

fetal weight, number of live and dead fetuses, or the number of implantations, whereas the number of resorptions was dose-dependently increased at 200 and 800 mg/kg. Stiripentol at doses up to 800 mg/kg was not associated with major external, visceral and skeletal variations in mice and rabbits.

In the peri- and post-natal development, treatment of dams during gestation and lactation had no effect on dams or pups at 200 mg/kg. At 800 mg/kg, stiripentol adversely affected pup survival, growth, and the reflex development.

Carcinogenicity

Stiripentol was tested for carcinogenic potential in rats and mice. In mice, an increased incidence of hepatocellular hypertrophy with stiripentol doses of 200 mg/kg and 600 mg/kg was observed and was not considered due to genotoxicity, but rather to massive enzyme induction in the liver. Hepatocellular adenomas and carcinomas are a well-known effect of drugs that, like stiripentol, cause enzyme induction in liver cells. In rats, stiripentol was not carcinogenic.

Mutagenicity

Stiripentol was not a bacterial mutagen. The assays conducted as a follow up strategy to address the equivocal positive clastogenicity response in CHO hamster cells are consistent with the suggestion that the clastogenicity may be related to cytotoxicity at high doses and stiripentol is not a mammalian cell mutagen. Stiripentol was not genotoxic *in vivo*.

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PART III: CONSUMER INFORMATION

PrDIACOMIT™*
stiripentol capsules
stiripentol powder for suspension

This leaflet is Part III of a three-part "Product Monograph" published when DIACOMIT was approved for sale in Canada, and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DIACOMIT. Contact your doctor or your pharmacist if you have any questions about the drug.

This consumer information is directed to adults and children where applicable.

ABOUT THIS MEDICATION

What the medication is used for:
In patients 3 years and older DIACOMIT is used with clobazam and valproate to control tonic-clonic seizures associated only with Dravet Syndrome (also known as severe myoclonic epilepsy in infancy or SMEI) when clobazam and valproate did not control seizures on their own.

DIACOMIT is not effective on other forms of epilepsy.

What it does:
DIACOMIT
- affects chemicals in the brain that are involved in sending signals to the nerves
- interacts with the break down (metabolism) of other drugs

When it should not be used:
If you are allergic to any of the ingredients in the product.

What the medicinal ingredient is:
Stiripentol

What the nonmedicinal ingredients are:
Capsules: erythrosine (250 mg capsule only), gelatin, indigotine (250 mg capsule only), magnesium stearate, povidone, sodium starch glycolate, titanium dioxide.

Powder for suspension: aspartame, carmellose sodium, erythrosine, glucose, hydroxyethylcellulose, povidone, sodium starch glycolate, sorbitol, titanium dioxide, tutti frutti flavour.

What dosage forms it comes in:
Capsules: 250 mg, 500 mg
Powder for suspension: 250 mg, 500 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
When you take DIACOMIT for Dravet syndrome, you should not take carbamazepine, phenytoin and phenobarbital

You can expect your doctor to adjust the dosages of clobazam and/or valproate that you are taking.

Tell your doctor if you have a history of delirium or hallucinations (see or hear things that are not there). These have happened to adults taking DIACOMIT.

BEFORE you use DIACOMIT, talk to your doctor or pharmacist if you have or have had:
- liver or kidney disease;
- any allergies;
- other medicines (see list of medicines in "Interactions with This Medication");
- a growth problem
- medicines that slow down the nervous system (CNS depressants);
- problems with certain ingredients of DIACOMIT (e.g. aspartame, glucose, sorbitol, erythrosine, indigotine);
- a plan to be pregnant;
- you are breastfeeding a baby.

DIACOMIT may cause drowsiness, sleepiness, dizziness, confusion and difficulty concentrating. Wait until you know how you response to DIACOMIT before you perform tasks which require special attention, such as:
- activities requiring mental alertness
- activities requiring physical coordination

While taking DIACOMIT, you should be alert to new or worsened symptoms of depression or any unusual changes in mood or behaviour.

Some people have thoughts of suicide or hurting themselves while taking medications to prevent seizures such as DIACOMIT. Talk to your doctor right away if this happens to you.

DIACOMIT can cause some people to have:
- a severe loss of appetite, nausea and vomiting and therefore loss of weight
- growth problems

Measure and record your child's height and tell you doctor if you have concerns about their growth.

Before having surgery, tell your doctor that you are taking DIACOMIT.

Do not discontinue this medication without talking to your doctor first.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, mineral, natural supplements, or alternative medicines.

DIACOMIT may increase the concentrations of other drugs (such as clobazam) in your blood stream. This makes you at greater risk of having side effects from other drugs.

The following may interact with DIACOMIT:

- Antiepileptic medicines containing: phenobarbital, primidone, phenytoin, carbamazepine, clobazam, diazepam, ethosuximide, tiagabine;
- Pimozide (used to treat the symptoms of Tourette's syndrome e.g. vocal outbursts and uncontrolled, repeated movements of the body);
- Ergotamine (used to treat migraine);
- Dihydroergotamine (used to relieve the signs and symptoms of decreased mental capacity due to the aging process);
- Halofantrine (an antimalarial drug);
- Quinidine and beta-blockers (propranolol, carvedilol, timolol) (used to treat abnormal heart rhythms);
- Cisapride and omeprazole (used to treat gastric reflux);
- Bepridil (used to control chest pain);
- Cyclosporine, tacrolimus, sirolimus (all three used to prevent rejections of liver, kidney and heart transplants);
- Statins (simvastatin and atorvastatin, both used to reduce the amount of cholesterol in blood);
- Medicines containing midazolam, alprazolam or triazolam (drugs used to reduce anxiety and sleeplessness) - in combination with DIACOMIT they may make your child very sleepy);
- Chlorpromazine (used for mental illness such as psychosis);
- HIV protease inhibitors;
- Chlorpheniramine and antihistamines such as astemizole (used to treat allergic reactions);
- Calcium channel blockers (used to decrease blood pressure);
- Oral contraceptives;
- Fluoxetine, paroxetine, sertraline, imipramine, clomipramine, citalopram (used as antidepressants);
- Haloperidol (used as antipsychotics);
- Macrolide antibiotics, such as erythromycin, clarithromycin or azithromycin;
- Fentanyl, codeine, dextromethorphan and tramadol (used for pain).

Avoid medicines, foods and beverages that contain alcohol, caffeine or theophylline, such as:

- Medicines that contain caffeine (read the labels to verify the ingredients in each product);
- Medicines that contain theophylline (use to treat asthma, bronchitis and emphysema);
- Beverages that contain caffeine such as cola, coffee, tea and energy drinks;
- Foods that contain caffeine or theophylline such as chocolate;
- Alcoholic beverages such as beer, wine and spirits.

PROPER USE OF THIS MEDICATION

DIACOMIT must be taken with food. It is important that you take DIACOMIT regularly at the same times each day.

DIACOMIT capsules: should be swallowed whole with a glass of water during a meal. The capsules should not be opened, broken or chewed.

DIACOMIT powder for suspension: should be mixed in a glass of water and should be taken immediately after mixing during a meal.

DIACOMIT should not be taken:

- on an empty stomach;
- with milk or dairy products (yogurt, cream cheese, etc.);
- with fruit juice or fizzy drinks;
- with food and drinks that contain caffeine or theophylline (for example cola, chocolate, coffee, tea and energy drinks);
- with alcoholic beverages such as wine, beer or spirits.

Always check that you have enough DIACOMIT (capsules or powder for suspension) and that you do not run out.

Do not switch between powder and capsules without first checking with your doctor.

Usual Dose in Patients 3 Years Old and Older:
DIACOMIT is usually taken 2 to 3 times per day, at regular intervals, or as directed by the doctor.

The dosage is usually 50 mg per kg body weight per day, but your doctor may tell you to take a higher or a lower dose, depending on your condition.

Any increase in dose should be gradual over 3 days while the dose of other antiepileptic medicine(s) may be reduced at the same time. Your doctor will tell you the new dose of the other antiepileptic medicine(s).

Never stop taking, increase or decrease the amount of DIACOMIT you are taking unless your doctor tells you to.

If you have the impression that the effect of DIACOMIT is too strong or too weak, talk to your doctor or pharmacist. The dose may be adjusted by your doctor according to your condition.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take a dose, take it as soon as you remember unless it is time for the next dose. In that case carry on with the next dose as normal. You should not take a double dose to make up for a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Dry, red, itchy or swollen skin;
- Trouble sleeping, nightmares;
- Abdominal or back pain;
- Weight loss or weight gain;
- Excessive secretion of saliva;
- Intellectual slowing;
- Loss of Appetite;
- Nausea or vomiting;
- Feeling tired, drowsy or sleepy.

If any of these affects you severely, tell your doctor or pharmacist.

DIACOMIT can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Very Common	**Changes in Behavior:** agitation, nervousness or aggressiveness		√	
	Movement Disorders	√		
	Hypotonia: low muscle tone	√		
	Ataxia: inability to coordinate muscle movements	√		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Movement Disorders**	√		
	Dystonia: abnormal, weak or involuntary muscle contractions	√		
	Tremor Hyperkinesia: increased muscle activity, excessive abnormal movements	√		
	Dysarthria: difficulty with speech (slow, slurred) or difficulty pronouncing words	√		
	Equilibrium disorders: Trouble with balance or coordination	√		
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√	
	Decreased Platelets: bruising, bleeding, fatigue and weakness		√	
	Liver Disorder/ Abnormal Blood Tests Related to Liver Enzymes: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
Un-common	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
	Thoughts of suicide or of hurting yourself		√	

This is not a complete list of side effects. If you/your child have any unexpected effects while taking DIACOMIT, contact your doctor or pharmacist

HOW TO STORE DIACOMIT

- Do not use this product after the expiry date written on the package. The expiry date refers to the last day of the month.
- Store in the original package, in order to protect from light.
- Store at room temperature between 15 and 30°C in a dry place.
- Keep this and all medicines out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found at: http://www.biocodex.com or by contacting the sponsor, Biocodex SA at: 011-800-3728-3800

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