

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 250 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg of stiripentol.

Excipient with known effect: 0.16 mg sodium per capsule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Size 2 pink capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Diacomit should only be administered under the supervision of a paediatrician / paediatric neurologist experienced in the diagnosis and management of epilepsy in infants and children.

Posology

Paediatric population

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

The daily dosage may be administered in 2 or 3 divided doses.

The initiation of adjunctive therapy with stiripentol should be undertaken gradually using upwards dose escalation to reach the recommended dose of 50 mg/kg/day administered in conjunction with clobazam and valproate.

Stiripentol dosage escalation should be gradual, starting with 20mg/kg/day for 1 week, then 30mg/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 judgment.

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 section 5.1).

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

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

Children aged less than 3 years

The pivotal clinical evaluation of Diacomit was in children of 3 years of age and over 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 (see section 5.1). Data are limited about the use of Diacomit under 12 months of age. For these children the use of stiripentol will be done under the close supervision of the doctor.

Patients aged ≥ 18 years of age

Long-term data has not been collected in a sufficient number of adults to confirm maintenance of effect in this population. Treatment should be continued for as long as efficacy is observed.

Dose adjustments of other antiepileptics used in combination with stiripentol

Despite the absence of comprehensive pharmacology data on potential drug interactions, the following advice regarding modification of the dose and dosage schedules of other anti-epileptic medicinal products administered in conjunction with stiripentol 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 five fold increases in norclobazam plasma levels respectively have been reported with co-administration of stiripentol in children with Dravet's 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 for continuing use or adjusting the dose of stiripentol 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 (see section 4.4).

Effect of formulation

The sachet formulation has a slightly higher C_{max} than the capsules and thus the formulations are not bioequivalent. It is recommended that if a switch of formulations is required this is done under clinical supervision, in case of problems with tolerability (see section 5.2).

Renal and hepatic impairment

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

Method of administration

Precautions to be taken before handling or administering the medicinal product

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

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

Stiripentol 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients 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

Carbamazepine, phenytoin and phenobarbital

These substances should not be used in conjunction with stiripentol in the management of Dravet's syndrome. The daily dosage of clobazam and/or valproate should be reduced according to the onset of side effects whilst on stiripentol therapy (see section 4.2).

Growth rate of children

Given 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.

Blood count

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

Liver function

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

Hepatic or renal impairment

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

Substances interfering with CYP enzymes

Stiripentol is an inhibitor of the enzymes CYP2C19, CYP3A4 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* studies suggested that stiripentol phase 1 metabolism is catalyzed by CYP1A2, CYP2C19 and CYP3A4 and possibly other enzymes. Caution is advised when combining stiripentol with other substances that inhibit or induce one or more of these enzymes.

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

4.5 Interaction with other medicinal products and other forms of interaction

Potential medicinal product interactions affecting stiripentol

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

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

In vitro studies suggested that stiripentol phase 1 metabolism is catalyzed by CYP1A2, CYP2C19 and CYP3A4 and possibly other enzymes. Caution is advised when combining stiripentol with other substances 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. 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, CYP2D6 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.

Caution must be exercised if clinical circumstances require combining stiripentol with substances metabolised by CYP2C19 (e.g. citalopram, omeprazole) or CYP3A4 (e.g. HIV protease inhibitors, antihistamines such as astemizole, chlorpheniramine, calcium channel blockers, statins, oral contraceptives, codeine) due to the increased risk of adverse 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 stiripentol 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.

As stiripentol inhibited CYP2D6 *in vitro* at concentrations that are achieved clinically in plasma, substances that are metabolized by this isoenzyme like: beta-blockers (propranolol, carvedilol, timolol), antidepressants (fluoxetine, paroxetine, sertraline, imipramine, clomipramine), antipsychotics (haloperidol), analgesics (codeine, dextromethorphan, tramadol) may be subject to metabolic interactions with stiripentol. A dose-adjustment may be necessary for substances metabolised by CYP2D6 and that are individually dose titrated.

Potential for stiripentol to interact with other medicinal products

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

Undesirable combinations (to be avoided unless strictly necessary)

- Rye ergot alkaloids (ergotamine, dihydroergotamine)
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)
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 agent).

Combinations requiring precautions

- Midazolam, triazolam, alprazolam

Increased plasma benzodiazepine levels may occur via decreased hepatic metabolism leading to excessive sedation.

- Chlorpromazine

Stiripentol enhances the central depressant effect of chlorpromazine.

- Effects on other AEDs

Inhibition of CYP450 isoenzyme CYP2C19 and CYP3A4 may provoke pharmacokinetic interactions (inhibition of their hepatic metabolism) with phenobarbital, primidone, phenytoin, carbamazepine, clobazam (see section 4.2), valproate (see section 4.2), diazepam (enhanced myorelaxation), ethosuximide, and tiagabine. The consequences are increased plasma levels of these anticonvulsants with potential risk of overdose. Clinical monitoring of plasma levels of other anticonvulsants when combined with stiripentol with possible dose adjustments is recommended.

- Topiramate

In a French compassionate use program for stiripentol, topiramate was added to stiripentol, clobazam and 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products 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 the rate of approximately 3% 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. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, foetal development, parturition or postnatal development at non-maternotoxic doses (see section 5.3). In view of the indication, administration of stiripentol during pregnancy and in women of childbearing potential would not be expected. The clinical decision for use of stiripentol in pregnancy needs to be made on an individual patient basis taking into consideration the potential clinical benefits and risks. Caution should be exercised when prescribing to pregnant women and use of efficient methods of contraception is advisable.

During pregnancy

Effective anticonvulsant treatment with stiripentol must not be stopped during pregnancy as worsening of the disease is potentially harmful to both mother and foetus.

Breastfeeding

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 during treatment. In case stiripentol therapy is continued during breast-feeding, the breast-fed infant should be carefully observed for potential adverse effects.

Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

4.7 Effects on ability to drive and use machines

Patients with SMEI 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.

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

4.8 Undesirable effects

Summary of the safety profile

The most common side effects with Diacomit (seen in more than 1 in 10 patients) are anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia and dystonia.

Tabulated list of adverse reactions

Adverse reactions encountered most often are as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing severity.

System Organ Class (MedDRA terminology)	Very common	Common	Uncommon	Rare
Blood and lymphatic system disorders		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 disorders	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 γ GT (notably when combined with carbamazepine and valproate).		Liver function test abnormal

Description of selected adverse reactions

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

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

In animal models, stiripentol antagonizes seizures induced by electric shock, pentetrazole and bicuculline. In rodent models, stiripentol appears to increase brain levels of gamma-aminobutyric acid (GABA) - the major inhibitory neurotransmitter in mammalian brain. This could occur by inhibition

of synaptosomal uptake of GABA and/or inhibition of GABA transaminase. Stiripentol has also been shown to enhance GABAA receptor-mediated transmission in the immature rat hippocampus and increase the mean open-duration (but not the frequency) of GABAA receptor chloride channels by a barbiturate-like mechanism. Stiripentol potentiates the efficacy of other anticonvulsants, such as carbamazepine, sodium valproate, phenytoin, phenobarbital and many benzodiazepines, as the result of pharmacokinetic interactions. The second 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 efficacy and safety

The pivotal clinical evaluation of Diacomit was in children of 3 years of age and over with SMEI.

A French compassionate use program included children from 6 months of age because the diagnosis of Dravet's syndrome may be made with confidence at that age in some patients. 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 (see section 4.2).

41 children with SMEI were included in a randomised, placebo-controlled, add-on trial. After a baseline period of 1 month, placebo (n=20) or stiripentol (n=21) was added to valproate and clobazam during a double-blind period of 2 months. Patients then received stiripentol in an open fashion. Responders were defined as having more than 50% reduction in the frequency of clonic (or tonic-clonic) seizures during the second month of the double-blind period compared with baseline. 15 (71%) patients were responders on stiripentol (including nine free of clonic or tonic-clonic seizures), whereas there was only one (5%) on placebo (none was seizure free; stiripentol 95% CI 52.1-90.7 vs. placebo 0-14.6). The 95% CI of the difference was 42.2-85.7. Percentage of change from baseline was higher on stiripentol (-69%) than on placebo (+7%), $p < 0.0001$. 21 patients on stiripentol had moderate side-effects (drowsiness, loss of appetite) compared with eight on placebo, but side-effects disappeared when the dose of comedication was decreased in 12 of the 21 cases (Chiron et al, Lancet, 2000).

5.2 Pharmacokinetic properties

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

Absorption

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.

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. The two formulations were bioequivalent in terms of AUC but not in terms of C_{max} . 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%).

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 was in the range of 4.5 hours to 13 hours, increasing with dose.

Biotransformation

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 principal liver cytochrome P450 isoenzymes involved in phase I metabolism are considered to be CYP1A2, CYP2C19 and CYP3A4.

Excretion

Most stiripentol is excreted 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 faeces as unchanged substance.

Paediatric population pharmacokinetic study

A population pharmacokinetic study was conducted in 35 children with Dravet Syndrome treated with stiripentol and two substances not known to affect stiripentol pharmacokinetics, valproate and clobazam. The median age was 7.3 years (range: 1 to 17.6 years) and the median daily dose of stiripentol was 45.4 mg/kg/day (range: 27.1 to 89.3 mg/kg/day) received in two or three divided doses.

The data were best fitted with a one compartment model with first order absorption and elimination processes. The population estimate for the absorption rate constant K_a was 2.08 hr^{-1} (standard deviation of random effect = 122%). Clearance and volume of distribution were related to body weight by an allometric model with exponents of 0.433 and 1, respectively: as body weight increased from 10 to 60 kg, apparent oral clearance increased from 2.60 to 5.65 L/hr and apparent volume of distribution increased from 32.0 to 191.8 L. As a result, elimination half-life increased from 8.5hr (for 10 kg) to 23.5 hr (for 60 kg).

5.3 Preclinical safety data

Toxicity studies in animals (rat, monkey, mouse) have not revealed any consistent pattern of toxicity apart from liver enlargement associated with hepatocellular hypertrophy, which occurred when high doses of stiripentol were administered to both rodents and non-rodents. This finding is considered to be an adaptive response to a high metabolic burden on the liver.

Stiripentol was not teratogenic when tested in the rat and rabbit; in one study in the mouse, but not in several other similar studies, a low incidence of cleft palate formation was observed at a maternotoxic dose (800 mg/kg/day). These studies in mice and rabbits were undertaken prior to the introduction of Good Laboratory Practice requirements. Studies in the rat on fertility and general reproductive performance and on pre- and postnatal development were uneventful except for a minor reduction in the survival of pups nursed by mothers exhibiting toxic responses to stiripentol at a dose of 800 mg/kg/day (see section 4.6).

Genotoxicity studies have not detected any mutagenic or clastogenic activity.

Carcinogenicity studies gave negative results in the rat. In the mouse there was only a small increase in the incidence of hepatic adenomas and carcinomas in animals treated with 200 or 600 mg/kg/day for 78 weeks but not in those given 60 mg/kg/day. In view of the lack of genotoxicity of stiripentol and the well known, special susceptibility of the mouse liver to tumour formation in the presence of 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 core

Povidone K29/32

Sodium starch glycolate (type A)

Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Erythrosine (E127)
Indigotine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Polypropylene bottle with tamper-evident seal and polyethylene screw cap.
Bottles of 30, 60 and 90 capsules in cardboard cartons.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Biocodex, 7 Avenue Gallieni, 94250 Gentilly, France.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/367/001-3

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 04 January 2007

Date of latest renewal: 8 January 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 500 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 mg of stiripentol.

Excipient with known effect: 0.32 mg sodium per capsule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

Size 0, white capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Diacomit should only be administered under the supervision of a paediatrician / paediatric neurologist experienced in the diagnosis and management of epilepsy in infants and children.

Posology

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

The daily dosage may be administered in 2 or 3 divided doses.

The initiation of adjunctive therapy with stiripentol should be undertaken gradually using upwards dose escalation to reach the recommended dose of 50 mg/kg/day administered in conjunction with clobazam and valproate.

Stiripentol dosage escalation should be gradual, starting with 20mg/kg/day for 1 week, then 30mg/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 judgment.

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 section 5.1).

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

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

Children aged less than 3 years

The pivotal clinical evaluation of Diacomit was in children of 3 years of age and over 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 (see section 5.1). Data are limited about the use of Diacomit under 12 months of age. For these children the use of stiripentol will be done under the close supervision of the doctor.

Patients aged ≥ 18 years of age

Long-term data has not been collected in a sufficient number of adults to confirm maintenance of effect in this population. Treatment should be continued for as long as efficacy is observed.

Dose adjustments of other antiepileptics used in combination with stiripentol

Despite the absence of comprehensive pharmacology data on potential drug interactions, the following advice regarding modification of the dose and dosage schedules of other anti-epileptic medicinal products administered in conjunction with stiripentol 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 five fold increases in norclobazam plasma levels respectively have been reported with co-administration of stiripentol in children with Dravet's 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 for continuing use or adjusting the dose of stiripentol 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 (see section 4.4).

Effect of formulation

The sachet formulation has a slightly higher C_{max} than the capsules and thus the formulations are not bioequivalent. It is recommended that if a switch of formulations is required this is done under clinical supervision, in case of problems with tolerability (see section 5.2).

Renal and hepatic impairment

Stiripentol 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.

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

Stiripentol 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients 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

Carbamazepine, phenytoin and phenobarbital

These substances should not be used in conjunction with stiripentol in the management of Dravet's syndrome. The daily dosage of clobazam and/or valproate should be reduced according to the onset of side effects whilst on stiripentol therapy (see section 4.2).

Growth rate of children

Given 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.

Blood count

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

Liver function

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

Hepatic or renal impairment

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

Substances interfering with CYP enzymes

Stiripentol is an inhibitor of the enzymes CYP2C19, CYP3A4 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* studies suggested that stiripentol phase 1 metabolism is catalyzed by CYP1A2, CYP2C19 and CYP3A4 and possibly other enzymes. Caution is advised when combining stiripentol with other substances that inhibit or induce one or more of these enzymes.

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

4.5 Interaction with other medicinal products and other forms of interaction

Potential medicinal product interactions affecting stiripentol

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

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

In vitro studies suggested that stiripentol phase 1 metabolism is catalyzed by CYP1A2, CYP2C19 and CYP3A4 and possibly other enzymes. Caution is advised when combining stiripentol with other substances 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. 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, CYP2D6 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.

Caution must be exercised if clinical circumstances require combining stiripentol with substances metabolised by CYP2C19 (e.g. citalopram, omeprazole) or CYP3A4 (e.g. HIV protease inhibitors, antihistamines such as astemizole, chlorpheniramine, calcium channel blockers, statins, oral contraceptives, codeine) due to the increased risk of adverse 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 increased plasma levels of theophylline and caffeine which may occur via inhibition of their hepatic metabolism, potentially leading to toxicity. Use in combination with stiripentol 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.

As stiripentol inhibited CYP2D6 *in vitro* at concentrations that are achieved clinically in plasma, substances that are metabolized by this isoenzyme like: beta-blockers (propranolol, carvedilol, timolol), antidepressants (fluoxetine, paroxetine, sertraline, imipramine, clomipramine), antipsychotics (haloperidol), analgesics (codeine, dextromethorphan, tramadol) may be subject to metabolic interactions with stiripentol. A dose-adjustment may be necessary for substances metabolised by CYP2D6 and that are individually dose titrated.

Potential for stiripentol to interact with other medicinal products

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

Undesirable combinations (to be avoided unless strictly necessary)

- Rye ergot alkaloids (ergotamine, dihydroergotamine)

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)

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 agent).

Combinations requiring precautions

- Midazolam, triazolam, alprazolam

Increased plasma benzodiazepine levels may occur via decreased hepatic metabolism leading to excessive sedation.

- Chlorpromazine

Stiripentol enhances the central depressant effect of chlorpromazine.

- Effects on other AEDs

Inhibition of CYP450 isoenzyme CYP2C19 and CYP3A4 may provoke pharmacokinetic interactions (inhibition of their hepatic metabolism) with phenobarbital, primidone, phenytoin, carbamazepine, clobazam (see section 4.2), valproate (see section 4.2), diazepam (enhanced myorelaxation), ethosuximide, and tiagabine. The consequences are increased plasma levels of these anticonvulsants with potential risk of overdose. Clinical monitoring of plasma levels of other anticonvulsants when combined with stiripentol with possible dose adjustments is recommended.

- Topiramate

In a French compassionate use program for stiripentol, topiramate was added to stiripentol, clobazam and 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products 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 the rate of approximately 3% 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. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, foetal development, parturition or postnatal development at non-maternotoxic doses (see section 5.3). In view of the indication, administration of stiripentol during pregnancy and in women of childbearing potential would not be expected. The clinical decision for use of stiripentol in pregnancy needs to be made on an individual patient basis taking into consideration the potential clinical benefits and risks. Caution should be exercised when prescribing to pregnant women and use of efficient methods of contraception is advisable.

During pregnancy

Effective anticonvulsant treatment with stiripentol must not be stopped during pregnancy as worsening of the disease is potentially harmful to both mother and foetus.

Breastfeeding

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 during treatment. In case

stiripentol therapy is continued during breast-feeding, the breast-fed infant should be carefully observed for potential adverse effects.

Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

4.7 Effects on ability to drive and use machines

Patients with SMEI 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.

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

4.8 Undesirable effects

Summary of the safety profile

The most common side effects with Diacomit (seen in more than 1 in 10 patients) are anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia and dystonia.

Tabulated list of adverse reaction

Adverse reactions encountered most often are as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing severity.

System Organ Class (MedDRA terminology)	Very common	Common	Uncommon	Rare
Blood and lymphatic system disorders		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 disorders	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 γ GT (notably when combined with carbamazepine and valproate).		Liver function test abnormal

Description of selected adverse reactions

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

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

In animal models, stiripentol antagonizes seizures induced by electric shock, pentetrazole and bicuculline. In rodent models, stiripentol appears to increase brain levels of gamma-aminobutyric acid (GABA) - the major inhibitory neurotransmitter in mammalian brain. This could occur by inhibition of synaptosomal uptake of GABA and/or inhibition of GABA transaminase. Stiripentol has also been shown to enhance GABAA receptor-mediated transmission in the immature rat hippocampus and increase the mean open-duration (but not the frequency) of GABAA receptor chloride channels by a barbiturate-like mechanism. Stiripentol potentiates the efficacy of other anticonvulsants, such as carbamazepine, sodium valproate, phenytoin, phenobarbital and many benzodiazepines, as the result of pharmacokinetic interactions. The second 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 efficacy and safety

The pivotal clinical evaluation of Diacomit was in children of 3 years of age and over with SMEI.

A French compassionate use program included children from 6 months of age because the diagnosis of Dravet's syndrome may be made with confidence at that age in some patients. 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 (see section 4.2).

41 children with SMEI were included in a randomised, placebo-controlled, add-on trial. After a baseline period of 1 month, placebo (n=20) or stiripentol (n=21) was added to valproate and clobazam during a double-blind period of 2 months. Patients then received stiripentol in an open fashion. Responders were defined as having more than 50% reduction in the frequency of clonic (or tonic-clonic) seizures during the second month of the double-blind period compared with baseline. 15 (71%) patients were responders on stiripentol (including nine free of clonic or tonic-clonic seizures), whereas there was only one (5%) on placebo (none was seizure free; stiripentol 95% CI 52.1-90.7 vs. placebo 0-14.6). The 95% CI of the difference was 42.2-85.7. Percentage of change from baseline was higher on stiripentol (-69%) than on placebo (+7%), $p < 0.0001$. 21 patients on stiripentol had moderate side-effects (drowsiness, loss of appetite) compared with eight on placebo, but side-effects disappeared when the dose of comedication was decreased in 12 of the 21 cases (Chiron et al, Lancet, 2000).

5.2 Pharmacokinetic properties

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

Absorption

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.

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. The two formulations were bioequivalent in terms of AUC but not in terms of C_{max} . 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%).

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 was in the range of 4.5 hours to 13 hours, increasing with dose.

Biotransformation

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 principal liver cytochrome P450 isoenzymes involved in phase 1 metabolism are considered to be CYP1A2, CYP2C19 and CYP3A4.

Excretion

Most stiripentol is excreted 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 faeces as unchanged substance.

Paediatric population pharmacokinetic study

A population pharmacokinetic study was conducted in 35 children with Dravet Syndrome treated with stiripentol and two substances not known to affect stiripentol pharmacokinetics, valproate and clobazam. The median age was 7.3 years (range: 1 to 17.6 years) and the median daily dose of stiripentol was 45.4 mg/kg/day (range: 27.1 to 89.3 mg/kg/day) received in two or three divided doses.

The data were best fitted with a one compartment model with first order absorption and elimination processes. The population estimate for the absorption rate constant K_a was 2.08 hr^{-1} (standard deviation of random effect = 122%). Clearance and volume of distribution were related to body weight by an allometric model with exponents of 0.433 and 1, respectively: as body weight increased from 10 to 60 kg, apparent oral clearance increased from 2.60 to 5.65 L/hr and apparent volume of distribution increased from 32.0 to 191.8 L. As a result, elimination half-life increased from 8.5hr (for 10 kg) to 23.5 hr (for 60 kg).

5.3 Preclinical safety data

Toxicity studies in animals (rat, monkey, mouse) have not revealed any consistent pattern of toxicity apart from liver enlargement associated with hepatocellular hypertrophy, which occurred when high doses of stiripentol were administered to both rodents and nonrodents. This finding is considered to be an adaptive response to a high metabolic burden on the liver.

Stiripentol was not teratogenic when tested in the rat and rabbit; in one study in the mouse, but not in several other similar studies, a low incidence of cleft palate formation was observed at a maternotoxic dose (800 mg/kg/day). These studies in mice and rabbits were undertaken prior to the introduction of Good Laboratory Practice requirements. Studies in the rat on fertility and general reproductive performance and on pre- and postnatal development were uneventful except for a minor reduction in the survival of pups nursed by mothers exhibiting toxic responses to stiripentol at a dose of 800 mg/kg/day (see section 4.6).

Genotoxicity studies have not detected any mutagenic or clastogenic activity.

Carcinogenicity studies gave negative results in the rat. In the mouse there was only a small increase in the incidence of hepatic adenomas and carcinomas in animals treated with 200 or 600 mg/kg/day for 78 weeks but not in those given 60 mg/kg/day. In view of the lack of genotoxicity of stiripentol and the well known, special susceptibility of the mouse liver to tumour formation in the presence of 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 core

Povidone K29/32

Sodium starch glycolate (type A)

Magnesium stearate

Capsule shell

Gelatin

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Polypropylene bottle with tamper-evident seal and polyethylene screw cap.

Bottles of 30, 60 and 90 capsules in cardboard cartons.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Biocodex, 7 Avenue Gallieni, 94250 Gentilly, France.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/367/004-6

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 04 January 2007

Date of latest renewal: 8 January 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 250 mg powder for oral suspension in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 250 mg of stiripentol.

Excipient with known effect: 0.11 mg sodium per sachet.

Each sachet contains 2.5 mg of aspartame, 500 mg of glucose liquid spray and 2.4 mg of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension

Pale pink crystalline powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Diacomit should only be administered under the supervision of a paediatrician / paediatric neurologist experienced in the diagnosis and management of epilepsy in infants and children.

Posology

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

The daily dosage may be administered in 2 or 3 divided doses.

The initiation of adjunctive therapy with stiripentol should be undertaken gradually using upwards dose escalation to reach the recommended dose of 50 mg/kg/day administered in conjunction with clobazam and valproate.

Stiripentol dosage escalation should be gradual, starting with 20mg/kg/day for 1 week, then 30mg/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 judgment.

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 section 5.1).

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

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

Children aged less than 3 years

The pivotal clinical evaluation of Diacomit was in children of 3 years of age and over 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 (see section 5.1). Data are limited about the use of Diacomit under 12 months of age. For these children the use of Diacomit will be done under the close supervision of the doctor.

Patients aged ≥ 18 years of age

Long-term data has not been collected in a sufficient number of adults to confirm maintenance of effect in this population. Treatment should be continued for as long as efficacy is observed.

Dose adjustments of other antiepileptics used in combination with stiripentol

Despite the absence of comprehensive pharmacology data on potential drug interactions, the following advice regarding modification of the dose and dosage schedules of other anti-epileptic medicinal products administered in conjunction with stiripentol 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 five fold increases in norclobazam plasma levels respectively have been reported with co-administration of stiripentol in children with Dravet's 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 for continuing use or adjusting the dose of stiripentol 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 (see section 4.4).

Effect of formulation

The sachet formulation has a slightly higher C_{max} than the capsules and thus the formulations are not bioequivalent. It is recommended that if a switch of formulations is required this is done under clinical supervision, in case of problems with tolerability (see section 5.2).

Renal and hepatic impairment

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

Method of administration

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

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

Stiripentol 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients 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

Carbamazepine, phenytoin and phenobarbital

These substances should not be used in conjunction with stiripentol in the management of Dravet's syndrome. The daily dosage of clobazam and/or valproate should be reduced according to the onset of side effects whilst on stiripentol therapy (see section 4.2).

Growth rate of children

Given 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.

Blood count

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

Liver function

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

Hepatic or renal impairment

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

Substances interfering with CYP enzymes

Stiripentol is an inhibitor of the enzymes CYP2C19, CYP3A4 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* studies suggested that stiripentol phase 1 metabolism is catalyzed by CYP1A2, CYP2C19 and CYP3A4 and possibly other enzymes. Caution is advised when combining stiripentol with other substances that inhibit or induce one or more of these enzymes.

Stiripentol

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

Stiripentol powder for oral suspension in sachet contains aspartame, a source of phenylalanine. Therefore it may be harmful for people with phenylketonuria. Patients with rare glucose-galactose malabsorption should not take this medicine, as the formulation contains glucose. As the flavouring component contains small amount of sorbitol, patients with hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Potential medicinal product interactions affecting stiripentol

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

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

In vitro studies suggested that stiripentol phase 1 metabolism is catalyzed by CYP1A2, CYP2C19 and CYP3A4 and possibly other enzymes. Caution is advised when combining stiripentol with other substances 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. 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, CYP2D6 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.

Caution must be exercised if clinical circumstances require combining stiripentol with substances metabolised by CYP2C19 (e.g. citalopram, omeprazole) or CYP3A4 (e.g. several HIV protease inhibitors, antihistamines, astemizole, 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 increased plasma levels of theophylline and caffeine which may occur via inhibition of their hepatic metabolism, potentially leading to toxicity. Use in combination with stiripentol 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.

As stiripentol inhibited CYP2D6 *in vitro* at concentrations that are achieved clinically in plasma, substances that are metabolized by this isoenzyme like: beta-blockers (propranolol, carvedilol, timolol), antidepressants (fluoxetine, paroxetine, sertraline, imipramine, clomipramine), antipsychotics (haloperidol), analgesics (codeine, dextromethorphan, tramadol) may be subject to metabolic interactions with stiripentol. A dose-adjustment may be necessary for substances metabolised by CYP2D6 and that are individually dose titrated.

Potential for stiripentol to interact with other medicinal products

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

Undesirable combinations (to be avoided unless strictly necessary)

- Rye ergot alkaloids (ergotamine, dihydroergotamine)

Ergotism with possibility of necrosis of the extremities (inhibition of hepatic elimination of rye ergot).

- Cisapride, halofantrine, pimozone, quinidine, bepridil
Increased risk of cardiac arrhythmias and torsades de pointes/wave burst arrhythmia in particular.

- Immunosuppressants (tacrolimus, cyclosporine, 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 agent).

Combinations requiring precautions

- Midazolam, triazolam, alprazolam
Increased plasma benzodiazepine levels may occur via decreased hepatic metabolism leading to excessive sedation.

- Chlorpromazine
Stiripentol enhances the central depressant effect of chlorpromazine.

- Effects on other AEDs
Inhibition of CYP450 isoenzyme CYP2C19 and CYP3A4 may provoke pharmacokinetic interactions (inhibition of their hepatic metabolism) with phenobarbital, primidone, phenytoin, carbamazepine, clobazam (see section 4.2), valproate (see section 4.2), diazepam (enhanced myorelaxation), ethosuximide, and tiagabine. The consequences are increased plasma levels of these anticonvulsants with potential risk of overdose. Clinical monitoring of plasma levels of other anticonvulsants when combined with stiripentol with possible dose adjustments is recommended.

- Topiramate
In a French compassionate use program for stiripentol, topiramate was added to stiripentol, clobazam and 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products 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 the rate of approximately 3% 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. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, foetal development, parturition or postnatal development at non-maternotoxic doses (see section 5.3). In view of the indication, administration of stiripentol during pregnancy and in women of childbearing potential would not be expected. The clinical decision for use of stiripentol in pregnancy needs to be made on an individual patient basis taking into

consideration the potential clinical benefits and risks. Caution should be exercised when prescribing to pregnant women and use of efficient methods of contraception is advisable.

During pregnancy

Effective anticonvulsant treatment with stiripentol must not be stopped during pregnancy as worsening of the disease is potentially harmful to both mother and foetus.

Breastfeeding

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 during treatment. In case stiripentol therapy is continued during breast-feeding, the breast-fed infant should be carefully observed for potential adverse effects.

Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

4.7 Effects on ability to drive and use machines

Patients with SMEI 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.

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

4.8 Undesirable effects

Summary of the safety profile

The most common side effects with Diacomit (seen in more than 1 in 10 patients) are anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia and dystonia.

Tabulated list of adverse reactions

Adverse reactions encountered most often are as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing severity.

System Organ Class (MedDRA terminology)	Very common	Common	Uncommon	Rare
Blood and lymphatic system disorders		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 disorders	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 γ GT (notably when combined with carbamazepine and valproate).		Liver function test abnormal

Description of selected adverse reactions

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

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

In animal models, stiripentol antagonizes seizures induced by electric shock, pentetrazole and bicuculline. In rodent models, stiripentol appears to increase brain levels of gamma-aminobutyric acid (GABA) - the major inhibitory neurotransmitter in mammalian brain. This could occur by inhibition of synaptosomal uptake of GABA and/or inhibition of GABA transaminase. Stiripentol has also been

shown to enhance GABAA receptor-mediated transmission in the immature rat hippocampus and increase the mean open-duration (but not the frequency) of GABAA receptor chloride channels by a barbiturate-like mechanism. Stiripentol potentiates the efficacy of other anticonvulsants, such as carbamazepine, sodium valproate, phenytoin, phenobarbital and many benzodiazepines, as the result of pharmacokinetic interactions. The second 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 efficacy and safety

The pivotal clinical evaluation of Diacomit was in children of 3 years of age and over with SMEI.

A French compassionate use program included children from 6 months of age because the diagnosis of Dravet's syndrome may be made with confidence at that age in some patients. 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 (see section 4.2).

41 children with SMEI were included in a randomised, placebo-controlled, add-on trial. After a baseline period of 1 month, placebo (n=20) or stiripentol (n=21) was added to valproate and clobazam during a double-blind period of 2 months. Patients then received stiripentol in an open fashion. Responders were defined as having more than 50% reduction in the frequency of clonic (or tonic-clonic) seizures during the second month of the double-blind period compared with baseline. 15 (71%) patients were responders on stiripentol (including nine free of clonic or tonic-clonic seizures), whereas there was only one (5%) on placebo (none was seizure free; stiripentol 95% CI 52.1-90.7 vs. placebo 0-14.6). The 95% CI of the difference was 42.2-85.7. Percentage of change from baseline was higher on stiripentol (-69%) than on placebo (+7%), $p < 0.0001$. 21 patients on stiripentol had moderate side-effects (drowsiness, loss of appetite) compared with eight on placebo, but side-effects disappeared when the dose of comedication was decreased in 12 of the 21 cases (Chiron et al, Lancet, 2000).

5.2 Pharmacokinetic properties

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

Absorption

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.

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. The two formulations were bioequivalent in terms of AUC but not in terms of C_{max} . 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%).

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 was in the range of 4.5 hours to 13 hours, increasing with dose.

Biotransformation

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 principal liver cytochrome P450 isoenzymes involved in phase I metabolism are considered to be CYP1A2, CYP2C19 and CYP3A4.

Excretion

Most stiripentol is excreted 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 faeces as unchanged substance.

Paediatric population pharmacokinetic study

A population pharmacokinetic study was conducted in 35 children with Dravet Syndrome treated with stiripentol and two substances not known to affect stiripentol pharmacokinetics, valproate and clobazam. The median age was 7.3 years (range: 1 to 17.6 years) and the median daily dose of stiripentol was 45.4 mg/kg/day (range: 27.1 to 89.3 mg/kg/day) received in two or three divided doses.

The data were best fitted with a one compartment model with first order absorption and elimination processes. The population estimate for the absorption rate constant K_a was 2.08 hr^{-1} (standard deviation of random effect = 122%). Clearance and volume of distribution were related to body weight by an allometric model with exponents of 0.433 and 1, respectively: as body weight increased from 10 to 60 kg, apparent oral clearance increased from 2.60 to 5.65 L/hr and apparent volume of distribution increased from 32.0 to 191.8 L. As a result, elimination half-life increased from 8.5hr (for 10 kg) to 23.5 hr (for 60 kg).

5.3 Preclinical safety data

Toxicity studies in animals (rat, monkey, mouse) have not revealed any consistent pattern of toxicity apart from liver enlargement associated with hepatocellular hypertrophy, which occurred when high doses of stiripentol were administered to both rodents and nonrodents. This finding is considered to be an adaptive response to a high metabolic burden on the liver.

Stiripentol was not teratogenic when tested in the rat and rabbit; in one study in the mouse, but not in several other similar studies, a low incidence of cleft palate formation was observed at a maternotoxic dose (800 mg/kg/day). These studies in mice and rabbits were undertaken prior to the introduction of Good Laboratory Practice requirements. Studies in the rat on fertility and general reproductive performance and on pre- and postnatal development were uneventful except for a minor reduction in the survival of pups nursed by mothers exhibiting toxic responses to stiripentol at a dose of 800 mg/kg/day (see section 4.6).

Genotoxicity studies have not detected any mutagenic or clastogenic activity.

Carcinogenicity studies gave negative results in the rat. In the mouse there was only a small increase in the incidence of hepatic adenomas and carcinomas in animals treated with 200 or 600 mg/kg/day for 78 weeks but not in those given 60 mg/kg/day. In view of the lack of genotoxicity of stiripentol and the well known, special susceptibility of the mouse liver to tumour formation in the presence of hepatic enzyme induction, this finding is not considered to indicate a risk of tumorigenicity in patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K29/32
Sodium starch glycolate type A
Glucose liquid, spray dried
Erythrosine (E127)
Titanium dioxide (E171)
Aspartame (E951)
Tutti frutti flavour (contains sorbitol)
Carmellose sodium
Hydroxyethylcellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Sachets are made with a composite paper/aluminium/polyethylene film.
Boxes of 30, 60 and 90 sachets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Biocodex, 7 Avenue Gallieni, 94250 Gentilly, France.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/367/007-9

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 04 January 2007
Date of latest renewal: 8 January 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 500 mg powder for oral suspension in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 500 mg of stiripentol.

Excipient with known effect: 0.22 mg sodium per sachet.

Each sachet contains 5 mg of aspartame, 1,000 mg of glucose liquid spray and 4.8 mg of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension

Pale pink crystalline powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Diacomit should only be administered under the supervision of a paediatrician / paediatric neurologist experienced in the diagnosis and management of epilepsy in infants and children.

Posology

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

The daily dosage may be administered in 2 or 3 divided doses.

The initiation of adjunctive therapy with stiripentol should be undertaken gradually using upwards dose escalation to reach the recommended dose of 50 mg/kg/day administered in conjunction with clobazam and valproate.

Stiripentol dosage escalation should be gradual, starting with 20mg/kg/day for 1 week, then 30mg/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 judgment.

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 section 5.1).

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

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

Children aged less than 3 years

The pivotal clinical evaluation of Diacomit was in children of 3 years of age and over 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 (see section 5.1). Data are limited about the use of Diacomit under 12 months of age. In these children, the use of Diacomit will be done under the close supervision of the doctor.

Patients aged ≥ 18 years of age

Long-term data has not been collected in a sufficient number of adults to confirm maintenance of effect in this population. Treatment should be continued for as long as efficacy is observed.

Dose adjustments of other antiepileptics used in combination with stiripentol

Despite the absence of comprehensive pharmacology data on potential drug interactions, the following advice regarding modification of the dose and dosage schedules of other anti-epileptic medicinal products administered in conjunction with stiripentol 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 five fold increases in norclobazam plasma levels respectively have been reported with co-administration of stiripentol in children with Dravet's 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 for continuing use or adjusting the dose of stiripentol 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 (see section 4.4).

Effect of formulation

The sachet formulation has a slightly higher C_{max} than the capsules and thus the formulations are not bioequivalent. It is recommended that if a switch of formulations is required this is done under clinical supervision, in case of problems with tolerability (see section 5.2).

Renal and hepatic impairment

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

Method of administration

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

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

Stiripentol 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients 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

Carbamazepine, phenytoin and phenobarbital

These substances should not be used in conjunction with stiripentol in the management of Dravet's syndrome. The daily dosage of clobazam and/or valproate should be reduced according to the onset of side effects whilst on stiripentol therapy (see section 4.2).

Growth rate of children

Given 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.

Blood count

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

Liver function

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

Hepatic or renal impairment

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

Substances interfering with CYP enzymes

Stiripentol is an inhibitor of the enzymes CYP2C19, CYP3A4 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* studies suggested that stiripentol phase 1 metabolism is catalyzed by CYP1A2, CYP2C19 and CYP3A4 and possibly other enzymes. Caution is advised when combining stiripentol with other substances that inhibit or induce one or more of these enzymes.

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

Diacomit powder for oral suspension in sachet contains aspartame, a source of phenylalanine. Therefore it may be harmful for people with phenylketonuria. Patients with rare glucose-galactose malabsorption should not take this medicine, as the formulation contains glucose. As the flavouring component contains small amount of sorbitol, patients with hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Potential medicinal product interactions affecting stiripentol

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

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

In vitro studies suggested that stiripentol phase 1 metabolism is catalyzed by CYP1A2, CYP2C19 and CYP3A4 and possibly other enzymes. Caution is advised when combining stiripentol with other substances 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. 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, CYP2D6 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.

Caution must be exercised if clinical circumstances require combining stiripentol with substances metabolised by CYP2C19 (e.g. citalopram, omeprazole) or CYP3A4 (e.g. several HIV protease inhibitors, antihistamines, astemizole, 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 increased plasma levels of theophylline and caffeine which may occur via inhibition of their hepatic metabolism, potentially leading to toxicity. Use in combination with stiripentol 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.

As stiripentol inhibited CYP2D6 *in vitro* at concentrations that are achieved clinically in plasma, substances that are metabolized by this isoenzyme like: beta-blockers (propranolol, carvedilol, timolol), antidepressants (fluoxetine, paroxetine, sertraline, imipramine, clomipramine), antipsychotics (haloperidol), analgesics (codeine, dextromethorphan, tramadol) may be subject to metabolic interactions with stiripentol. A dose-adjustment may be necessary for substances metabolised by CYP2D6 and that are individually dose titrated.

Potential for stiripentol to interact with other medicinal products

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

Undesirable combinations (to be avoided unless strictly necessary)

- Rye ergot alkaloids (ergotamine, dihydroergotamine)

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)
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 agent).

Combinations requiring precautions

- Midazolam, triazolam, alprazolam
Increased plasma benzodiazepine levels may occur via decreased hepatic metabolism leading to excessive sedation.

- Chlorpromazine
Stiripentol enhances the central depressant effect of chlorpromazine.

- Effects on other AEDs
Inhibition of CYP450 isoenzyme CYP2C19 and CYP3A4 may provoke pharmacokinetic interactions (inhibition of their hepatic metabolism) with phenobarbital, primidone, phenytoin, carbamazepine, clobazam (see section 4.2), valproate (see section 4.2), diazepam (enhanced myorelaxation), ethosuximide, and tiagabine. The consequences are increased plasma levels of these anticonvulsants with potential risk of overdose. Clinical monitoring of plasma levels of other anticonvulsants when combined with stiripentol with possible dose adjustments is recommended.

- Topiramate
In a French compassionate use program for stiripentol, topiramate was added to stiripentol, clobazam and 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products 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 the rate of approximately 3% 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. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, foetal development, parturition or postnatal development at non-maternotoxic doses (see section 5.3). In view of the indication, administration of stiripentol during pregnancy and in women of childbearing potential would not be expected. The clinical decision for use of stiripentol in pregnancy needs to be made on an individual patient basis taking into

consideration the potential clinical benefits and risks. Caution should be exercised when prescribing to pregnant women and use of efficient methods of contraception is advisable.

During pregnancy

Effective anticonvulsant treatment with stiripentol must not be stopped during pregnancy as worsening of the disease is potentially harmful to both mother and foetus.

Breastfeeding

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 during treatment. In case stiripentol therapy is continued during breast-feeding, the breast-fed infant should be carefully observed for potential adverse effects.

Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

4.7 Effects on ability to drive and use machines

Patients with SMEI 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.

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

4.8 Undesirable effects

Summary of adverse reactions

The most common side effects with Diacomit (seen in more than 1 in 10 patients) are anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia and dystonia.

Tabulated list of adverse reactions

Adverse reactions encountered most often are as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing severity.

System Organ Class (MedDRA terminology)	Very common	Common	Uncommon	Rare
Blood and lymphatic system disorders		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 disorders	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 γ GT (notably when combined with carbamazepine and valproate).		Liver function test abnormal

Description of selected adverse reactions

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

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

In animal models, stiripentol antagonizes seizures induced by electric shock, pentetrazole and bicuculline. In rodent models, stiripentol appears to increase brain levels of gamma-aminobutyric acid (GABA) - the major inhibitory neurotransmitter in mammalian brain. This could occur by inhibition

of synaptosomal uptake of GABA and/or inhibition of GABA transaminase. Stiripentol has also been shown to enhance GABAA receptor-mediated transmission in the immature rat hippocampus and increase the mean open-duration (but not the frequency) of GABAA receptor chloride channels by a barbiturate-like mechanism. Stiripentol potentiates the efficacy of other anticonvulsants, such as carbamazepine, sodium valproate, phenytoin, phenobarbital and many benzodiazepines, as the result of pharmacokinetic interactions. The second 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 efficacy and safety

The pivotal clinical evaluation of Diacomit was in children of 3 years of age and over with SMEI.

A French compassionate use program included children from 6 months of age because the diagnosis of Dravet's syndrome may be made with confidence at that age in some patients. 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 (see section 4.2).

41 children with SMEI were included in a randomised, placebo-controlled, add-on trial. After a baseline period of 1 month, placebo (n=20) or stiripentol (n=21) was added to valproate and clobazam during a double-blind period of 2 months. Patients then received stiripentol in an open fashion. Responders were defined as having more than 50% reduction in the frequency of clonic (or tonic-clonic) seizures during the second month of the double-blind period compared with baseline. 15 (71%) patients were responders on stiripentol (including nine free of clonic or tonic-clonic seizures), whereas there was only one (5%) on placebo (none was seizure free; stiripentol 95% CI 52.1-90.7 vs. placebo 0-14.6). The 95% CI of the difference was 42.2-85.7. Percentage of change from baseline was higher on stiripentol (-69%) than on placebo (+7%), $p < 0.0001$. 21 patients on stiripentol had moderate side-effects (drowsiness, loss of appetite) compared with eight on placebo, but side-effects disappeared when the dose of comedication was decreased in 12 of the 21 cases (Chiron et al, Lancet, 2000).

5.2 Pharmacokinetic properties

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

Absorption

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.

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. The two formulations were bioequivalent in terms of AUC but not in terms of C_{max} . 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%).

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 was in the range of 4.5 hours to 13 hours, increasing with dose.

Biotransformation

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 principal liver cytochrome P450 isoenzymes involved in phase I metabolism are considered to be CYP1A2, CYP2C19 and CYP3A4.

Excretion

Most stiripentol is excreted 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 faeces as unchanged substance.

Paediatric population pharmacokinetic study

A population pharmacokinetic study was conducted in 35 children with Dravet Syndrome treated with stiripentol and two substances not known to affect stiripentol pharmacokinetics, valproate and clobazam. The median age was 7.3 years (range: 1 to 17.6 years) and the median daily dose of stiripentol was 45.4 mg/kg/day (range: 27.1 to 89.3 mg/kg/day) received in two or three divided doses.

The data were best fitted with a one compartment model with first order absorption and elimination processes. The population estimate for the absorption rate constant K_a was 2.08 hr^{-1} (standard deviation of random effect = 122%). Clearance and volume of distribution were related to body weight by an allometric model with exponents of 0.433 and 1, respectively: as body weight increased from 10 to 60 kg, apparent oral clearance increased from 2.60 to 5.65 L/hr and apparent volume of distribution increased from 32.0 to 191.8 L. As a result, elimination half-life increased from 8.5hr (for 10 kg) to 23.5 hr (for 60 kg).

5.3 Preclinical safety data

Toxicity studies in animals (rat, monkey, mouse) have not revealed any consistent pattern of toxicity apart from liver enlargement associated with hepatocellular hypertrophy, which occurred when high doses of stiripentol were administered to both rodents and nonrodents. This finding is considered to be an adaptive response to a high metabolic burden on the liver.

Stiripentol was not teratogenic when tested in the rat and rabbit; in one study in the mouse, but not in several other similar studies, a low incidence of cleft palate formation was observed at a maternotoxic dose (800 mg/kg/day). These studies in mice and rabbits were undertaken prior to the introduction of Good Laboratory Practice requirements. Studies in the rat on fertility and general reproductive performance and on pre- and postnatal development were uneventful except for a minor reduction in the survival of pups nursed by mothers exhibiting toxic responses to stiripentol at a dose of 800 mg/kg/day (see section 4.6).

Genotoxicity studies have not detected any mutagenic or clastogenic activity.

Carcinogenicity studies gave negative results in the rat. In the mouse there was only a small increase in the incidence of hepatic adenomas and carcinomas in animals treated with 200 or 600 mg/kg/day for 78 weeks but not in those given 60 mg/kg/day. In view of the lack of genotoxicity of stiripentol and the well known, special susceptibility of the mouse liver to tumour formation in the presence of hepatic enzyme induction, this finding is not considered to indicate a risk of tumorigenicity in patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K29/32
Sodium starch glycolate type A
Glucose liquid, spray dried
Erythrosine (E127)
Titanium dioxide (E171)
Aspartame (E951)
Tutti frutti flavour (contains sorbitol)
Carmellose sodium
Hydroxyethylcellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Sachets are made with a composite paper/aluminium/polyethylene film.
Boxes of 30, 60 and 90 sachets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Biocodex, 7 Avenue Gallieni, 94250 Gentilly, France.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/367/010-12

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 04 January 2007
Date of latest renewal: 8 January 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Laboratoires BIOCOCODEX
1 avenue Blaise Pascal,
60000 Beauvais
FRANCE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 250 mg hard capsules
Stiripentol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains 250 mg stiripentol.

3. LIST OF EXCIPIENTS

Contains sodium.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules
60 hard capsules
90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use.

These capsules should be swallowed whole with water. The capsules should not be chewed.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIOCODEX
7 avenue Gallieni
94250 Gentilly
France
Tel: + 33 1 41 24 30 00
e-mail: webar@biocodex.fr

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/367/001 30 hard capsules
EU/1/06/367/002 60 hard capsules
EU/1/06/367/003 90 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Diacomit 250 mg hard capsules

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 250 mg hard capsules
Stiripentol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains 250 mg stiripentol.

3. LIST OF EXCIPIENTS

Contains sodium

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules
60 hard capsules
90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use.

These capsules should be swallowed whole with water. The capsules should not be chewed.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIOCODEX
7 avenue Gallieni
94250 Gentilly
France
Tel: + 33 1 41 24 30 00
e-mail: webar@biocodex.fr

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/367/001 30 hard capsules
EU/1/06/367/002 60 hard capsules
EU/1/06/367/003 90 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 500 mg hard capsules
Stiripentol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains 500 mg stiripentol.

3. LIST OF EXCIPIENTS

Contains sodium.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules
60 hard capsules
90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use.

These capsules should be swallowed whole with water. The capsules should not be chewed.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIOCODEX
7 avenue Gallieni
94250 Gentilly
France
Tel: + 33 1 41 24 30 00
e-mail: webar@biocodex.fr

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/367/004 30 hard capsules
EU/1/06/367/005 60 hard capsules
EU/1/06/367/006 90 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Diacomit 500 mg hard capsules

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 500 mg hard capsules
Stiripentol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains 500 mg stiripentol.

3. LIST OF EXCIPIENTS

Contains sodium.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules
60 hard capsules
90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use.

These capsules should be swallowed whole with water. The capsules should not be chewed.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIOCODEX
7 avenue Gallieni
94250 Gentilly
France
Tel: + 33 1 41 24 30 00
e-mail: webar@biocodex.fr

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/367/004 30 hard capsules
EU/1/06/367/005 60 hard capsules
EU/1/06/367/006 90 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 250 mg powder for oral suspension in sachet
Stiripentol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 sachet contains 250 mg stiripentol.

3. LIST OF EXCIPIENTS

Aspartame (E951)
Sorbitol
Glucose liquid spray dried
Sodium

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 sachets, powder for oral suspension in sachet
60 sachets, powder for oral suspension in sachet
90 sachets, powder for oral suspension in sachet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use.

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

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

BIOCODEX
7 avenue Gallieni
94250 Gentilly
France
Tel: + 33 1 41 24 30 00
e-mail: webar@biocodex.fr

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/367/007 30 sachets
EU/1/06/367/008 60 sachets
EU/1/06/367/009 90 sachets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Diacomit 250 mg powder for oral suspension

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Diacomit 250 mg powder for oral suspension in sachet
Stiripentol
For oral use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 mg

6. OTHER

Store in the original package in order to protect from light.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 500 mg powder for oral suspension in sachet
stiripentol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 sachet contains 500 mg stiripentol.

3. LIST OF EXCIPIENTS

Aspartame (E951)
Sorbitol
Glucose liquid spray dried
Sodium

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 sachets, powder for oral suspension in sachet
60 sachets, powder for oral suspension in sachet
90 sachets, powder for oral suspension in sachet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use.

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

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

BIOCODEX
7 avenue Gallieni
94250 Gentilly
France
Tel: + 33 1 41 24 30 00
e-mail: webar@biocodex

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/367/010 30 sachets
EU/1/06/367/011 60 sachets
EU/1/06/367/012 90 sachets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Diacomit 500 mg powder for oral suspension

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Diacomit 500 mg powder for oral suspension in sachet
Stiripentol
For oral use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 mg

6. OTHER

Store in the original package in order to protect from light.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Diacomit 250 mg hard capsule Diacomit 500 mg hard capsule Stiripentol

Read all of this leaflet carefully before your child starts taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their symptoms are the same as your child's.
- If your child gets any side effects, talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See Section 4.

What is in this leaflet

1. What Diacomit is and what it is used for
2. What you need to know before your child takes Diacomit
3. How to take Diacomit
4. Possible side effects
5. How to store Diacomit
6. Contents of the pack and other information

1. What Diacomit is and what it is used for

Stiripentol, the active ingredient of Diacomit, belongs to a group of medicines called antiepileptics.

It is used in conjunction with clobazam and valproate to treat a certain form of epilepsy called severe myoclonic epilepsy in infancy (Dravet's syndrome), which affects children. Your child's doctor has prescribed this medicine to help treat your child's epilepsy. It should always be taken in combination with other prescribed antiepileptic medicines under the direction of a doctor.

2. What you need to know before your child takes Diacomit

Your child must NOT take Diacomit

- if your child is allergic to stiripentol or to any of the other ingredients of Diacomit (listed in section 6).
- if your child has ever experienced attacks of delirium (a mental state with confusion, excitement, restlessness and hallucinations).

Warnings and precautions

Talk to your child's doctor or pharmacist before taking Diacomit

- if your child has kidney or liver problems.
- Your child's liver function should be assessed prior to starting Diacomit and checked every 6 months.
- Your child's blood count should be assessed prior to starting Diacomit and checked every 6 months.
- Because the frequency of gastrointestinal side effect with Diacomit, clobazam and valproate, such as anorexia, loss of appetite, vomiting, your child's growth rate should be carefully monitored.

Other medicines and Diacomit

Tell your doctor if your child is taking any of the following medicines:

- medicines containing:
 - cisapride (used to treat symptoms of night time heartburn);
 - 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 treatment);
 - quinidine (used to treat abnormal heart rhythms);
 - 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).
- antiepileptic medicines containing:
phenobarbital, primidone, phenytoin, carbamazepine, diazepam.
- medicines containing:
midazolam or triazolam (medicines 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).
- If your child takes medicines containing:
caffeine (this substance helps restore mental alertness) or theophylline (this substance is used in case of asthma). The combination with Diacomit should be avoided as it may increase their blood levels, leading to digestive disorders, racing heart and insomnia.
- If your child takes medicines metabolized by certain liver enzymes:
 - citalopram (used in the treatment of depressive episodes),
 - omeprazole (used in case of gastric ulcer)
 - HIV protease inhibitors (used in the treatment of HIV)
 - astemizole, chlorpheniramine (antihistamines)
 - calcium channel blockers (used in the treatment of anger or troubles of heart rhythm),
 - oral contraceptives,
 - propranolol, carvedilol, timolol (used in the treatment of high blood pressure),
 - fluoxetine, paroxetine, sertraline, imipramine, clomipramine (antidepressants),
 - haloperidol (antipsychotics),
 - codeine, dextromethorphan, tramadol (used in the treatment of pain)

Please tell your child's doctor or pharmacist if your child is using or has recently used any other medicines, including medicines obtained without a prescription, dietary supplements and herbal medicines.

Diacomit with food and drink

Do NOT take Diacomit with milk or dairy products (yoghurt, soft cream cheeses, etc), fruit juice, fizzy drinks or food and drinks that contain caffeine or theophylline (for example cola, chocolate, coffee, tea and energy drinks).

Pregnancy

During pregnancy, effective antiepileptic treatment must NOT be stopped. If your child may be or is pregnant, please ask your child's doctor for advice.

Ask your child's doctor or pharmacist for advice before taking any medicine.

Breast-feeding

Breast-feeding is not recommended during treatment with this medicine.

Ask your child's doctor or pharmacist for advice before taking any medicine.

Driving and using machines

This medicine may make your child feel sleepy.

Your child should not use any tools, machines, ride or drive if affected in this way. Check with your child's doctor.

This medicine contains 0.16 mg sodium per 250 mg capsule and 0.32 mg sodium per 500 mg capsule. To be taken into consideration by patients on a controlled sodium diet

3. How to take Diacomit

Your child should always take these capsules exactly as your child's doctor has told you. You should check with your child's doctor or pharmacist if you are not sure.

Dosage

The dose is adjusted by the doctor according to your child's age, weight and condition, generally 50 mg per kg bodyweight and per day.

When to take Diacomit

Your child should take this medicine two or three times a day at regular intervals as directed by your child's doctor: it is recommended to take the medicine at regular intervals in 2 or 3 intakes, for example morning - noon - bed-time to cover the night-and-day period.

Dose adjustment

Dose increases should be gradual, taking place over a few weeks while the dose(s) of the other antiepileptic medicine(s) is (are) reduced at the same time. Your child's doctor will tell you the new dose of the other antiepileptic medicine(s).

If you have the impression that the effect of this medicine is too strong or too weak, talk to your child's doctor or pharmacist. The dose will be adjusted by the doctor according to your child's condition.

Please consult your child's doctor in the event of any side effects as the doctor may have to adjust the dose of this medicine and the other antiepileptic medicine(s).

There are slight differences between the Diacomit capsules and powder for oral suspension. If your child experiences any problems when switching from taking the capsules to the powder for oral suspension or vice versa please inform your doctor. In case of switch between capsule and powder formulations it should be done under the close supervision of the doctor.

In case of vomiting within the first few minutes of intake it is assumed that no medicine has been absorbed and a new dose should be given.

However, the situation is different if the vomiting occurs more than one hour after medicine intake because stiripentol is quickly absorbed.

In such a case, it is assumed that a significant fraction of the administered dose has been absorbed systemically from the digestive tract. Thus, there would be no need for a new intake or for an adjustment of the next dose.

How to take the Diacomit capsules

These capsules should be swallowed whole with water. The capsules should not be chewed. Your child should take Diacomit with food, it should NOT be taken on an empty stomach. For food and drinks to be avoided, see the section "*Diacomit with food and drink*" above.

If your child takes more Diacomit than he or she should

Contact your child's doctor if you know or think your child has taken more medicine than he or she should have.

If your child forgets to take Diacomit

It is important that your child takes this medicine regularly at the same time each day. If your child forgets to take a dose, he or she should 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. Your child should not take a double dose to make up for a forgotten individual dose.

If your child stops taking Diacomit

Your child must not stop taking this medicine unless the doctor tells you to. Stopping treatment suddenly can lead to an outbreak of seizures.

If you have any further questions on the use of this product, ask your child's doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects (may affect more than one in 10 people):

- loss of appetite, weight loss (especially when combined with the antiepileptic medicine sodium valproate);
- insomnia (sleeplessness), drowsiness;
- ataxia (inability to coordinate muscle movements), hypotonia (low muscle strength), dystonia (involuntary muscle contractions).

Common side effects (may affect up to 1 in 10 people):

- raised levels of liver enzymes, especially when given with either of the antiepileptic medicines carbamazepine and sodium valproate;
- aggressiveness, irritability, agitation, hyperexcitability (state of being unusually excitable);
- sleep disorders (abnormal sleeping);
- hyperkinesia (exaggerated movements);
- nausea, vomiting;
- a low number of a type of white blood cells.

Uncommon side effects (may affect up to 1 in 100 people):

- double vision when used in combination with the antiepileptic medicine carbamazepine;
- sensitivity to light;
- rash, skin allergy, urticaria (pinkish, itchy swellings on the skin);
- fatigue (tiredness).

Rare side effects (may affect up to 1 in 1,000 people)

- decrease of platelet level in the blood;

To eliminate these side effects, your child's doctor may have to change the dose of Diacomit or one of the other medicines prescribed for your child.

If your child gets any side effects talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#).

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Diacomit

- Keep this medicine out of the sight and reach of children.
- Your child should not take Diacomit after the expiry date, which is stated on the label. The expiry date refers to the last day of that month.
- Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Diacomit 250 mg contains

- The active substance is stiripentol. Each hard capsule contains 250 mg of stiripentol.
- The other ingredients in this medicine are povidone K29/32, sodium starch glycolate type A and magnesium stearate.
- The capsule shell is made of gelatin, titanium dioxide (E171), erythrosine (E127), indigotin (E132).

What Diacomit 500 mg contains

- The active substance is stiripentol. Each hard capsule contains 500 mg of stiripentol.
- The other ingredients in this medicine are povidone K29/32, sodium starch glycolate type A and magnesium stearate.
- The capsule shell is made of gelatin, titanium dioxide (E171).

What Diacomit 250 mg looks like and contents of the pack

Diacomit 250 mg hard capsule is pink.

The hard capsules are supplied in plastic bottles containing 30, 60 or 90 capsules in cardboard cartons. Not all pack sizes may be marketed.

What Diacomit 500 mg looks like and contents of the pack

Diacomit 500 mg hard capsules are white.

The hard capsules are supplied in plastic bottles containing 30, 60 or 90 capsules in cardboard cartons. Not all pack sizes may be marketed.

Diacomit is also available as 250 mg and 500 mg powder for oral suspension in sachets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Biocodex, 7 avenue Gallieni - F-94250 Gentilly - France

Tel: + 33 1 41 24 30 00 - e-mail: webar@biocodex.fr

Manufacturer: Biocodex, 1 avenue Blaise Pascal - F-60000 Beauvais - France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

AT/BE/BG/CY/EE/EL/ES/FR/HR/HU/IE/IS/IT/LT/LU/LV/MT/NL/PL/PT/SI/UK

Biocodex

7 avenue Gallieni - F-94250 Gentilly

Франция/ Francie/ Frankrig/ Frankreich/ Γαλλία/ France/ Francia/ Prantsusmaa/ Ranska/

Franciaország/ Frakkland/France/ Prancūzija/ Francija/ Franza/ Frankrijk/ Frankrike/ Francja/ Franța/ Francúzsko

Tél/Tel/Тел/Τηλ/Sími: + 33 (0)1 41 24 30 00

e-mail: webar@biocodex.fr

DE

Desitin Arzneimittel GmbH
Weg beim Jäger 214
D-22335 Hamburg
Germany
Tel: +49 (0)40 59101 525
e-mail: epi.info@desitin.de

DK

Desitin Pharma AS
Havnegade 55, st. tv.
1058 Kopenhagen K
Denmark
Tel: +45 33 73 00 73
e-mail: desitin@desitin.dk

NO

Desitin Pharma AS
Niels Leuchs vei 99
1359 Eiksmarka
Norway
Tel: +47 67 15 92 30
e-mail: firmapost@desitin.no

FI/SE

Desitin Pharma AB
Krokslätts Torg 5
43137 Mölndal
Sweden
Tel: +46 31 20 23 10
e-mail: info@desitin.se

RO

Desitin Pharma s.r.l
Sevastopol street, no 13-17
Diplomat Business Centre, office 102
Sector 1, 010991 Bucharest
Romania
Tel: 004021-252-3481
e-mail: office@desitin.ro

SK

Desitin Pharma s.r.o.
Trojicné námestie 13
82106 Bratislava
Slovakia
Tel: 00421-2-5556 38 10
e-mail: desitin@desitin.sk

CZ

Desitin Pharma spol. s r.o
Opletalova 25
11121 Prague 1
Czech Republic
Tel: 00420-2-222 45 375
e-mail: desitin@desitin.cz

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicine Agency website:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.

Package leaflet: information for the user

Diacomit 250 mg powder for oral suspension in sachet **Diacomit 500 mg powder for oral suspension in sachet** Stiripentol

Read all of this leaflet carefully before your child starts taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their symptoms are the same as your child's.
- If your child gets any side effects, talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See Section 4.

What is in this leaflet:

1. What Diacomit is and what it is used for
2. What you need to know before your child takes Diacomit
3. How to take Diacomit
4. Possible side effects
5. How to store Diacomit
6. Contents of the pack and other information

1. What Diacomit is and what it is used for

Stiripentol, the active ingredient of Diacomit, belongs to a group of medicines called antiepileptics.

It is used in conjunction with clobazam and valproate to treat a certain form of epilepsy called severe myoclonic epilepsy in infancy (Dravet's syndrome), which affects children. Your child's doctor has prescribed this medicine to help treat your child's epilepsy. It should always be taken in combination with other prescribed antiepileptic medicines under the direction of a doctor.

2. What you need to know before your child takes Diacomit

Your child must NOT take Diacomit

- if your child is allergic to stiripentol or to any of the other ingredients of Diacomit.
- if your child has ever experienced attacks of delirium (a mental state with confusion, excitement, restlessness and hallucinations).

Warnings and precautions

Talk to your child's doctor or pharmacist before taking Diacomit

- if your child has kidney or liver problems.
- Your child's liver function should be assessed prior to starting Diacomit and checked every 6 months.
- Your child's blood count should be assessed prior to starting Diacomit and checked every 6 months.
- Because of the frequency of gastrointestinal side effects with Diacomit, clobazam and valproate, such as anorexia, loss of appetite, vomiting, your child's growth rate should be carefully monitored.

If your child has problems with certain ingredients of Diacomit (e.g. aspartame, glucose, sorbitol). In this case, please see below: "*Important information about some of the ingredients of Diacomit*".

Other medicines and Diacomit

Tell your doctor if your child is taking any of the following medicines:

- medicines containing:
 - cisapride (used to treat symptoms of night time heartburn);
 - 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 treatment);
 - quinidine (used to treat abnormal heart rhythms);
 - 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).
- antiepileptic medicines containing:
phenobarbital, primidone, phenytoin, carbamazepine, diazepam.
- medicines containing:
midazolam or triazolam (medicines 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).

- If your child takes medicines containing:
Caffeine (this substance helps restore mental alertness) or theophylline (this substance is used in case of asthma). The combination with Diacomit should be avoided as it may increase their blood levels, leading to digestive disorders, racing heart and insomnia.

- If your child takes medicines metabolized by certain liver enzymes:
 - citalopram (used in the treatment of depressive episodes),
 - omeprazole (used in case of gastric ulcer)
 - HIV protease inhibitors (used in the treatment of HIV)
 - astemizole, chlorpheniramine (antihistamines)
 - calcium channel blockers (used in the treatment of anger or troubles of heart rhythm),
 - oral contraceptives,
 - propranolol, carvedilol, timolol (used in the treatment of high blood pressure),
 - fluoxetine, paroxetine, sertraline, imipramine, clomipramine (antidepressants),
 - haloperidol (antipsychotics),
 - codeine, dextromethorphan, tramadol (used in the treatment of pain)

Please tell your child's doctor or pharmacist if your child is using or has recently used any other medicines, including medicines obtained without a prescription, dietary supplements and herbal medicines.

Diacomit with food and drink

Do NOT take Diacomit with milk or dairy products (yoghurt, soft cream cheeses, etc), fruit juice, fizzy drinks or food and drinks that contain caffeine or theophylline (for example cola, chocolate, coffee, tea and energy drinks).

Pregnancy

During pregnancy, effective antiepileptic treatment must NOT be stopped. If your child may be or is pregnant, please ask your child's doctor for advice.

Ask your child's doctor or pharmacist for advice before taking any medicine.

Breast-feeding

Breast-feeding is not recommended during treatment with this medicine.

Ask your child's doctor or pharmacist for advice before taking any medicine.

Driving and using machines

This medicine may make your child feel sleepy.

Your child should not use any tools, machines, ride or drive if affected in this way. Check with your child's doctor.

Important information about some of the ingredients of Diacomit

Contains a source of phenylalanine. May be harmful for people with phenylketonuria.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

This medicine contains 0.11 mg sodium per 250 mg sachet and 0.22 mg sodium per 500 mg sachet. To be taken into consideration by patients on a controlled sodium diet

3. How to take Diacomit

Your child should always take the contents of each sachet exactly as your child's doctor has told you. You should check with your child's doctor or pharmacist if you are not sure.

Dosage

The dose is adjusted by the doctor according to your child's age, weight and condition, generally 50 mg per kg bodyweight and per day.

When to take Diacomit

Your child should take this medicine two or three times a day at regular intervals as directed by your child's doctor: it is recommended to take the medicine at regular intervals in 2 or 3 intakes, for example morning - noon - bed-time to cover the night-and-day period.

Dose adjustment

Dose increases should be gradual, taking place over a few weeks while the dose(s) of the other antiepileptic medicine(s) is (are) reduced at the same time. Your child's doctor will tell you the new dose of the other antiepileptic medicine(s).

If you have the impression that the effect of this medicine is too strong or too weak, talk to your child's doctor or pharmacist. The dose will be adjusted by the doctor according to your child's condition.

Please consult your child's doctor in the event of any side effects as the doctor may have to adjust the dose of this medicine and the other antiepileptic medicine(s).

There are slight differences between the Diacomit capsules and powder for oral suspension. If your child experiences any problems when switching from taking the capsules to the powder for oral suspension or vice versa please inform your doctor. In case of switch between capsule and powder formulation it should be done under the close supervision of the doctor.

In case of vomiting within the first few minutes of intake it is assumed that no medicine has been absorbed and a new dose should be given.

However, the situation is different if the vomiting occurs more than one hour after medicine intake because stiripentol is quickly absorbed. In such a case, it is assumed that a significant fraction of the administered dose has been absorbed systemically from the digestive tract. Thus, there would be no need for a new intake or for an adjustment of the next dose.

How to take the Diacomit powder for oral suspension

The powder should be mixed in a glass of water and should be taken immediately after mixing during the meal. Your child should take Diacomit with food, it should NOT be taken on an empty stomach. For food and drinks to be avoided, see the section "*Diacomit with food and drink*" above.

If your child takes more Diacomit than he or she should

Contact your child's doctor if you know or think your child has taken more medicine than he or she should have.

If your child forgets to take Diacomit

It is important that your child takes this medicine regularly at the same time each day. If your child forgets to take a dose, he or she should 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. Your child should not take a double dose to make up for a forgotten individual dose.

If your child stops taking Diacomit

Your child must not stop taking this medicine unless the doctor tells you to. Stopping treatment suddenly can lead to an outbreak of seizures.

If you have any further questions on the use of this product, ask your child's doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects (may affect more than one in 10 people):

- loss of appetite, weight loss (especially when combined with the antiepileptic medicine sodium valproate);
- insomnia (sleeplessness), drowsiness;
- ataxia (inability to coordinate muscle movements), hypotonia (low muscle strength), dystonia (involuntary muscle contractions).

Common side effects (may affect up to 1 in 10 people):

- raised levels of liver enzymes, especially when given with either of the antiepileptic medicines carbamazepine and sodium valproate;
- aggressiveness, irritability, agitation, hyperexcitability (state of being unusually excitable);
- sleep disorders (abnormal sleeping);
- hyperkinesia (exaggerated movements);
- nausea, vomiting;
- a low number of a type of white blood cells.

Uncommon side effects (may affect up to 1 in 100 people):

- double vision when used in combination with the antiepileptic medicine carbamazepine;
- sensitivity to light;
- rash, skin allergy, urticaria (pinkish, itchy swellings on the skin);
- fatigue (tiredness).

Rare side effects (may affect up to 1 in 1,000 people)

- decrease of platelet level in the blood;

To eliminate these side effects, your child's doctor may have to change the dose of Diacomit or one of the other medicines prescribed for your child.

If your child gets any side effects talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#).

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Diacomit

- Keep this medicine out of the sight and reach of children.
- Your child should not take Diacomit after the expiry date, which is stated on the label. The expiry date refers to the last day of that month.
- Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Diacomit 250 mg contains

- The active substance is stiripentol. Each sachet contains 250 mg of stiripentol.
- The other ingredients in this medicine are povidone K29/32, sodium starch glycolate type A, glucose liquid (spray dried), erythrosine (E127), titanium dioxide (E171), aspartame (E951), tutti frutti flavour (contains sorbitol), carmellose sodium, hydroxyethylcellulose.

What Diacomit 500 mg contains

- The active substance is stiripentol. Each sachet contains 500 mg of stiripentol.
- The other ingredients in this medicine are povidone K29/32, sodium starch glycolate type A, glucose liquid (spray dried), erythrosine (E127), titanium dioxide (E171), aspartame (E951), tutti frutti flavour (contains sorbitol), carmellose sodium, hydroxyethylcellulose.

What Diacomit 250 mg looks like and contents of the pack

This medicine is a pale pink powder supplied in sachets.

Cartons contain either 30, 60 or 90 sachets. Not all pack sizes may be marketed.

What Diacomit 500 mg looks like and contents of the pack

This medicine is a pale pink powder supplied in sachets.

Cartons contain either 30, 60 or 90 sachets. Not all pack sizes may be marketed.

Diacomit is also available as 250 mg and 500 mg capsules for oral use

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Biocodex, 7 avenue Gallieni – F-94250 Gentilly - France

Tel: + 33 1 41 24 30 00 - e-mail: webar@biocodex.fr

Manufacturer : Biocodex, 1 avenue Blaise Pascal - F-60000 Beauvais - France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

AT/BE/BG/CY/EE/EL/ES/FR/HR/HU/IE/IS/IT/LT/LU/LV/MT/NL/PL/PT/SI/UK

Biocodex

7 avenue Gallieni - F-94250 Gentilly

Франция/ Francie/ Frankrig/ Frankreich/ Γαλλία/ France/ Francia/ Prantsusmaa/ Ranska/

Franciaország/ Frakkland/France/ Prancūzija/ Francija/ Franza/ Frankrijk/ Frankrike/ Francja/ Franța/ Francúzsko

Tél/Tel/Тел/Τηλ/Σίμι: + 33 (0)1 41 24 30 00

e-mail: webar@biocodex.fr

DE

Desitin Arzneimittel GmbH
Weg beim Jäger 214
D-22335 Hamburg
Germany
Tel: +49 (0)40 59101 525
e-mail: epi.info@desitin.de

DK

Desitin Pharma AS
Havnegade 55, st. tv.
1058 Kopenhagen K
Denmark
Tel: +45 33 73 00 73
e-mail: desitin@desitin.dk

NO

Desitin Pharma AS
Niels Leuchs vei 99
1359 Eiksmarka
Norway
Tel: +47 67 15 92 30
e-mail: firmapost@desitin.no

FI/SE

Desitin Pharma AB
Kroksläatts Torg 5
43137 Mölndal
Sweden
Tel: +46 31 20 23 10
e-mail: info@desitin.se

RO

Desitin Pharma s.r.l
Sevastopol street, no 13-17
Diplomat Business Centre, office 102
Sector 1, 010991 Bucharest
Romania
Tel: 004021-252-3481
e-mail: office@desitin.ro

SK

Desitin Pharma s.r.o.
Trojicné námestie 13
82106 Bratislava
Slovakia
Tel: 00421-2-5556 38 10
e-mail: desitin@desitin.sk

CZ

Desitin Pharma spol. s r.o
Opletalova 25
11121 Prague 1
Czech Republic
Tel: 00420-2-222 45 375
e-mail: desitin@desitin.cz

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicine Agency website:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.