1. NAME OF THE MEDICINAL PRODUCT

Diacomit 250 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg of stiripentol

Excipients
Each capsule contains sodium starch glycolate (type A) Ph. Eur. 3.946mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

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.

The dose of Diacomit 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 Diacomit should be undertaken over 3 days using upwards dose escalation to reach the recommended dose of 50 mg/kg/day administered in conjunction with clobazam and valproate. This recommended dose 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 Diacomit administered at daily doses greater than 50mg/kg/day.
There are no clinical study data to support the use of Diacomit as monotherapy in Dravet's syndrome.

Dose adjustments of other antiepileptics used in combination with Diacomit
Despite the absence of comprehensive pharmacology data on potential drug interactions, the following advice regarding modification of the dose and dosage schedules of other anti-epileptic medicinal products administered in conjunction with Diacomit is provided based on clinical experience.

- Clobazam

In the pivotal studies, when the use of Diacomit was initiated, the daily dose of clobazam was 0.5 mg/kg/day usually administered in divided doses, twice daily. In the event of clinical signs of side effects or overdosage of clobazam (i.e., drowsiness, hypotonia, and irritability in young children), this daily dose was reduced by 25% every week. Approximately two to three fold increases in clobazam and five fold increases in norclobazam plasma levels respectively have been reported with co-administration of Diacomit in children with Dravet's syndrome.

- Valproate
The potential for metabolic interaction between Diacomit and valproate is considered modest and thus, no modification of valproate dosage should be needed when Diacomit is added, except for clinical safety reasons. In the pivotal studies in the event of gastrointestinal adverse reactions such as loss of appetite, loss of weight, the daily dose of valproate was reduced by around 30% every week.

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 Diacomit in conjunction with adjusting the doses of clobazam and valproate needs to be made on an individual patient basis taking into consideration the potential clinical benefits and risks (See, section 4.4).

Effects of food
Diacomit must always be taken with food as it degrades rapidly in an acidic environment (e.g. exposure to gastric acid in an empty stomach).
The capsule should be swallowed whole with a glass of water.
Diacomit should not be taken with milk or dairy products (yoghurt, soft cream cheese, etc.), carbonated drinks, fruit juice or food and drinks that contain caffeine or theophylline.

Effect of formulation
Bioequivalence between the capsules and oral suspension formulations has not been established. Clinical supervision is recommended if changing stiripentol formulation.

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.

Patients with renal and hepatic impairment
Diacomit is not recommended for use in patients with impaired hepatic and/or renal function (See, section 4.4)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
A past history of psychoses in the form of episodes of delirium.

4.4 Special warnings and precautions for use

Carbamazepine, iphenytoin and phenobarbital should not be used in conjunction with Diacomit 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 Diacomit therapy (See, section 4.2).

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

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

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

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

Stiripentol is an inhibitor of the enzymes CYP2C19, CYP3A4 and CYP2D6 and may markedly increase the plasma concentrations of drugs metabolised by these enzymes and increase the risk of adverse effects (See, section 4.5.). Caution is also advised when combining stiripentol with other drugs that may inhibit stiripentol phase 1 metabolism which is thought to be metabolised by CYP1A2, CYP2D6, CYP3A4 and possibly other isoenzymes.

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.

This medicinal product contains 0.007 mmol (0.16 mg) sodium per 250 mg capsule. This should be taken into consideration by patients on a controlled sodium diet.

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.

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 Diacomit, 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 side effects and adverse reactions.
Caution must be exercised if clinical circumstances require combining stiripentol with drugs metabolised by CYP2C19 (e.g. citalopram, omeprazole) or CYP3A4 (e.g. HIV protease inhibitors,

antinistamines such as astemizole, chlorpheniramine, calcium channel blockers, statins, oral contraceptives, codeine) due to the increased risk of adverse events (see further in this section for antiepileptic drugs). Monitoring of plasma concentrations or adverse effects is recommended. A dose adjustment may be necessary.

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

Data on the potential for inhibition of CYP1A2 are limited, and therefore, interactions with theophylline and caffeine cannot be excluded. Use in combination with stiripentol is not recommended. This warning is not only restricted to medicinal products but also to a considerable number of foods and nutritional products aimed at children, such as cola drinks, which contain significant quantities of caffeine or chocolate, which contains trace amounts of theophylline.

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

Potential for stiripentol to interact with other medicinal products

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

Undesirable combinations (to be avoided unless strictly necessary)
- Rye ergot alkaloids (ergotamine, dihydroergotamine)
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.

- Theophylline, caffeine
Increased plasma levels of theophylline and caffeine may occur via inhibition of their hepatic metabolism, potentially leading to toxicity. These combinations should be avoided.

- Chlorpromazine
Stiripentol enhances the central depressant effect of chlorpromazine.

- Effects on other AEDs
Inhibition of CYP450 isoenzyme CYP2C19 and CYP3A4 may provoke pharmacokinetic interactions (inhibition of their hepatic metabolism) with phenobarbital, primidone, phenytoin, carbamazepine, clobazam (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 Diacomit, topiramate was added to Diacomit, 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 Pregnancy and lactation

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 Diacomit:
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 Diacomit during pregnancy and in women of childbearing potential would not be expected. The clinical decision for use of Diacomit in pregnancy needs to be made on an individual patient basis 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 Diacomit must not be stopped during pregnancy as worsening of the disease is potentially harmful to both mother and foetus.

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

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

4.8 Undesirable effects

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

System/organ classes

System Organ Class (MedDRA terminology)	**Very Common**	**Common**	**Uncommon**
Blood and lymphatic system disorders		Neutropenia Persistent severe neutropenia usually resolves spontaneously when Diacomit is stopped.	
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			Fatigue
Investigations		Raised γGT (notably when combined with carbamazepine and valproate).	

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.

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: Other Antiepileptics, ATC code: N03AX17
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 drugs.

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).

This medicinal product has been authorised under a "conditional approval" scheme. This means that further evidence on this medicinal product is awaited, in particular about the efficacy of stiripentol in combination with the maximum safe dose of the add-on therapy. A study is being conducted to investigate this. The European Medicines Agency (EMEA) will review new information on the product every year and this SPC will be updated as necessary.

5.2 Pharmacokinetic properties

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

Absorption / Bioavailability:
Stiripentol is quickly absorbed, with a time to peak plasma concentration of about 1.5 hours. The absolute bioavailability of stiripentol is not known since an intravenous formulation is not available for testing. It is well absorbed by the oral route since the majority of an oral dose is excreted in urine.

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

Elimination:
Systemic exposure to stiripentol increases markedly compared to dose proportionality. Plasma clearance decreases markedly at high doses; it falls from approximately 40 l/kg/day at the dose of 600 mg/day to about 8 l/kg/day at the dose of 2400 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.

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

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 drug.

Bioequivalence:
Bioequivalence between the capsules and oral suspension formulations has not been established. Clinical supervision is recommended if changing stiripentol formulation.

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 600mg/kg/day for 78 weeks but not in those given 60mg/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)
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

In order to protect from light, store in the original package.

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 and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Biocodex, 7 Avenue Gallieni, 94250 Gentilly, France.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Laboratoires BIOCODEX
1 avenue Blaise Pascal,
60000 Beauvais
FRANCE

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

Risk Management plan

The Marketing Authorisation Holder commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

An updated Risk Management Plan should be provided as per the CHMP Guideline on Risk Management Systems for medicinal products for human use.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame. The results of which shall be taken into account in the risk benefit balance during the assessment of the application for a renewal:

1. A randomised controlled clinical trial with stiripentol in the add-on therapy using maximally safe doses of clobazam+valproate by 2009 (STP 165).
2. A bioavailability study in 24 subjects to determine the relative bioavailability of the stiripentol sachet versus stiripentol capsule by 2007 (STP 166).

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 250 mg capsules
Stiripentol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains 250 mg stiripentol.

3. LIST OF EXCIPIENTS

0.16 mg sodium per capsule

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

For oral use.
These capsules should be swallowed whole with water. The capsules should not be chewed.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

In order to protect from light, store in the original package.

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/0/00/000/00W 30 capsules
EU/0/00/000/00X 60 capsules
EU/0/00/000/00Y 90 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 capsules

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT

Diacomit 250 mg capsules
Stiripentol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains 250 mg stiripentol.

3. LIST OF EXCIPIENTS

0.16 mg sodium per capsule

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

For oral use.
These capsules should be swallowed whole with water. The capsules should not be chewed.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

In order to protect from light, store in the original package.

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/0/00/000/00W 30 capsules
EU/0/00/000/00X 60 capsules
EU/0/00/000/00Y 90 capsules

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PACKAGE LEAFLET: INFORMATION FOR THE USER

Diacomit 250 mg hard capsules
Stiripentol

Read all of this leaflet carefully before your child starts taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as your child's.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your child's doctor or pharmacist.

In this leaflet:

1. WHAT DIACOMIT IS AND WHAT IT IS USED FOR

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. BEFORE YOUR CHILD TAKES DIACOMIT

Your child must NOT take Diacomit
- if your child is allergic (hypersensitive) to stiripentol or to any of the other ingredients of Diacomit
- if your child has ever experienced attacks of delirium

Take special care with Diacomit
- if your child has kidney or liver problems
- if your child is using 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 drug);
  - 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).
- if your child uses one of the following products:

- antiepileptic medicines containing:
  phenobarbital, primidone, phenytoin, carbamazepine, diazepam.
- medicines containing:
  midazolam or triazolam (drugs used to reduce anxiety and sleeplessness – in combination with Diacomit they may make your child very sleepy);
  chlorpromazine (used for mental illness such as psychosis).
- medicines, beverages and foods containing:
  caffeine or theophylline (these substances help restore mental alertness). The combination with Diacomit should be avoided as it may increase their blood levels, leading to digestive disorders, racing heart and insomnia.

Using other medicines
If your child needs to use other medicines, please see above *"Take special care with Diacomit"*.

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.

Taking Diacomit with food and drink
Your child should take Diacomit with food, it should NOT be taken on an empty stomach. 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.

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 condition, generally 50 mg per kg bodyweight and per day.

How to take the Diacomit capsules

These capsules should be swallowed whole with water. The capsules should not be chewed. For food and drinks to be avoided, see the section *"Taking Diacomit with food and drink"* above.

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.

Dose adjustment

Any increase in dose should be gradual over 3 days while the dose of the other antiepileptic medicine(s) is 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).

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, Diacomit can cause side effects, although not everybody gets them.

Very common side effects (more than one in 10 patients)
- 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 (muscle disorders)

Common side effects (between one in 100 patients and one in 10 patients)
- 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)
- hyperkinesis (exaggerated movements)
- nausea, vomiting
- a low number of a type of white blood cells

Uncommon side effects (between one in 1,000 patients and one in 100 patients)
- 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)

To eliminate these side effects, your child's doctor may have to change the dose of concomitant medicines, or the dosage of Diacomit.

If any of these side effects persists or gets serious, or if you notice any side effects not listed in this leaflet, please tell your child's doctor or pharmacist.

5. HOW TO STORE DIACOMIT

- Keep out of the reach and sight 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.
- In order to protect from light, store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Diacomit contains
- The active substance is stiripentol. Each 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 looks like and contents of the pack
Diacomit 250mg capsules are pink.
The capsules are supplied in plastic bottles containing 30, 60 and 90 capsules in cardboard cartons.
Not all pack sizes may be marketed.
Diacomit is also available as 500 mg capsules for oral use and 250 mg and 500 mg powder for oral suspension in sachets.

Marketing Authorisation Holder

Biocodex
7 avenue Gallieni
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

This leaflet was last approved in {MM/YYYY}.

This medicine has been given "conditional approval". This means that there is more definitive evidence to come about this medicine for the treatment of this form of epilepsy when stiripentol is used in conjunction with clobazam and valproate. The European Medicines Agency (EMEA) will review new information on the medicine every year and this leaflet will be updated as necessary.

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