DIACOMIT

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.

Active ingredient: stiripentol.

Excipients: Povidone, Sodium starch glycolate, Glucose liquid, spray dried Erythrosine (E127), Titanium dioxide (E171), Aspartame (E951), Tutti frutti flavour (contains sorbitol), Carmellose sodium, Hydroxyethylcellulose.

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

3. PRODUCT DESCRIPTION

Sachets are made with a composite paper/aluminium/polyethylene film.
Boxes of 60 sachets.

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 Pharmacodynamic properties).

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

Children aged less than 3 years
The pivotal clinical evaluation of stiripentol was in children of 3 years of age and over with SMEI. The clinical decision for use of stiripentol 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 Pharmacodynamic properties). Data are limited about the use of stiripentol 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 Special warnings and precautions for use).

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 Pharmacokinetic properties).

Renal and hepatic impairment
Stiripentol is not recommended for use in patients with impaired hepatic and/or renal function (see section Special warnings and precautions for use).

Method of administration

Oral use
The powder should be mixed in a glass of water and should be taken immediately after mixing.
For the interaction of stiripentol with food, please see section Interaction with other medicinal products and other forms of interaction.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients of the medicinal product.
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 Posology and method of administration).

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 (see section Posology and method of administration).

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 Interaction with other medicinal products and other forms of interaction). *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.

Paediatric population

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.
Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age. 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.
This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially ‘sodium-free’.

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

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

Data on the potential for inhibition of CYP1A2 are limited, and therefore, interactions with theophylline and caffeine cannot be excluded because of 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 (for example: cola, chocolate, coffee, tea, and energy drinks) and nutritional products aimed at children: Patient should not drink cola drinks, which contain significant quantities of caffeine or chocolate, which contains trace amounts of theophylline (see section Posology and method of administration).

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 medicinal product).

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 antiepileptic drugs (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 Posology and method of administration), valproate (see section Posology and method of administration), 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 Preclinical safety data). 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.

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 Preclinical safety data). No clinical data are available, potential risk for human is unknown.

4.7. Effects on ability to drive and use machines

Stiripentol has major influence on the ability to drive and use machines because it may cause dizziness and ataxia. Patients should be advised not to drive or use machines until they have gained sufficient experience to gauge whether it adversely affects their abilities (see section Undesirable effects).

4.8. Undesirable effects

Summary of the safety profile

The most common side effects with stiripentol 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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**	**Not known**
Blood and lymphatic system disorders		Neutropenia		Thrombocytopenia *	
Metabolism and nutrition disorders	Anorexia, loss of appetite, weight loss				
Psychiatric disorders	Insomnia	Aggressiveness, irritability, behaviour disorders, opposing behaviour, hyperexcitability, sleep disorders			
Nervous system disorders	Drowsiness, ataxia, hypotonia, dystonia	Hyperkinesias			
Eye disorders			Diplopia		
Gastrointestinal disorders		Nausea, vomiting			
Skin and subcutaneous tissue disorders			Photosensitivity, rash, cutaneous allergy, urticaria		
General disorders and administration site conditions			Fatigue		
Investigations		Raised γGT		Liver function test abnormal	
Infections and infestations					Pneumonia, aspiration pneumonia

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

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 Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction) 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: 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 stiripentol 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 Posology and method of administration).

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).

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.

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 Ka 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 Fertility, pregnancy and lactation).
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
Sodium starch glycolate
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 below 30ºC in the original package in order to protect from light.

6.5. Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

NAME AND ADDRESS OF MANUFACTURER/MARKETING AUTHORIZATION HOLDER
ASIAKARE MALAYSIA SDN. BHD.
Level 3A, Sunway Visio Tower, Lingkaran SV,
Sunway Velocity 55100 Kuala Lumpur,
W.P. Kuala Lumpur, Malaysia

Name and address of the Manufacturer
Biocodex
1 Avenue Blaise Pascal, Beauvais, 60000, France

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