DIACOMIT®

(stiripentol) *250 mg, 500 mg*

capsules or powder for oral suspension

Product Monograph

DIACOMIT® (stiripentol) in the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam

BIOCODEX

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I. Introduction

A. Dravet syndrome

Dravet syndrome (DS), previously known as Severe Myoclonic Epilepsy in Infancy (SMEI), was first described in 1978 by Dr. Charlotte Dravet (Dravet, 1992, 2005). Dravet syndrome is a devastating condition and is considered one of the most medically intractable forms of epilepsy. Its characteristics include the following:

- Initial seizures triggered by fever during the first year of life in the form of generalized (tonic-)clonic seizures or hemiclonic seizures;
- Then, additional types of seizure appear in early childhood, such as myoclonic seizures, atypical absences or focal seizures;
- Psychomotor development, while normal at seizure onset, ultimately slows. Essentially, all patients have variable degrees of intellectual disability. Ataxia and pyramidal signs occur;
- Highly pharmacoresistant to most antiepileptic drugs;
- No causal lesion on brain MRI.

Various factors are suspected of contributing to the intellectual disability:

- Genetic mutations in the SCN1A gene are detected in approximately 85% of the patients. The SCN1A gene encodes for a type I voltage-gated sodium channel (Nav1.1), and mutations may lead to interneuron dysfunction responsible for both seizure activity and cognitive dysfunction (Bender *et al*, 2012).
- Recurrent, prolonged seizures also likely have a developmental cost. Both status epilepticus (Sheppard *et al*, 2012), as well as high seizure frequency at diagnosis and persisting over time predict cognitive impairment (O'Reilly *et al*, 2018). It is therefore crucial to reduce the frequency of seizures in DS patients to maximize developmental potential.

Additionally, DS is associated with a high premature mortality rate, especially between 3 and 11 years of age, often due to sudden unexpected death in epilepsy or status epilepticus. Early diagnosis allows avoidance of specific antiepileptic drugs (carbamazepine, phenytoin, vigabatrin and lamotrigine) which exacerbate seizures in Dravet syndrome.

B. DIACOMIT® (stiripentol)

Stiripentol belongs to a family of α-ethylene alcohols with an effect on the central nervous system. The chemical formula for stiripentol is 4.4-dimethyl-1-[3.4-(methylenedioxy)-phenyl]-1-penten-3-ol. It is a chiral molecule with a central asymmetric carbon atom C3. Both enantiomers are active, and the pharmaceutical substance is an equimolar racemate which has been used in all studies on humans.

The product was first identified in 1978 and developed further in the 1980s. Stiripentol was studied in various forms of epilepsy and an exploratory study demonstrated its unique efficacy in DS. Additional studies then confirmed the benefit of stiripentol in combination with valproate and clobazam in Dravet syndrome.

II. Product Information

A. Indication

DIACOMIT® is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam. There are no clinical data to support the use of DIACOMIT® as monotherapy in Dravet syndrome.

B. Approaches to treatment

Dravet syndrome is one of the most drug-resistant forms of epilepsy and complete seizure control is typically not achievable. The major treatment goal is to reduce the frequency and/or duration of seizures with the highest morbidity. Thus, elimination or significant reduction of prolonged convulsive seizures and status epilepticus is the highest priority in treatment.

Table 1 presents the current therapeutic approaches in the treatment of Dravet syndrome, according to the recently published North America Consensus Panel recommendations (Wirrell *et al*, 2017).

Table 1. Current treatment algorithm for Dravet syndrome (based on the North America Consensus Panel)

First-line treatment				
Valproic acid OR clobazam (if first choice not effective, add the other) *Agreed upon by strong consensus*				
Second-line treatment				
Addition of **stiripentol** (in combination with valproic acid and clobazam) *Agreed upon by strong consensus*	or	**Topiramate** *Agreed upon by strong consensus*	or	**Ketogenic diet** (High fat, adequate-protein, low-carbohydrate diet increasing production of ketone bodies suspected of anticonvulsant activity) *Agreed upon by strong consensus*
Third-line treatment				
Addition of an AED: **Clonazepam** (strong consensus) **Levetiracetam** (strong consensus) **Zonisamide** (strong consensus) **Ethosuximide** (moderate consensus) **Phenobarbital** (moderate consensus)	or	Consider **Vagus Nerve Stimulation** *Agreed upon by moderate consensus*		

AED: antiepileptic drug

Clobazam and valproic acid are the recommended first-line medications in Dravet syndrome (Wirrell *et al*, 2017). Treatment should be initiated with one of these agents, with the other added if seizure control remains suboptimal.

In the case of inadequate seizure control with the combination of first-line therapies, which can be seen in 52% to 78% of patients treated with valproic acid and in approximately 72% of patients treated with clobazam (Knupp *et al*, 2018), the North America Consensus Panel recommends stiripentol as a second-line medication (Wirrell *et al*, 2017).

Management strategies published by American pediatric neurologists in a recent review indicated that stiripentol (in combination with valproic acid and clobazam) should be considered as the second-line treatment for Dravet syndrome, while topiramate or a ketogenic diet should be considered as the third-line treatment (Ziobro *et al*, 2018). Their review also emphasized the unique efficacy of the combination of valproic acid and clobazam with stiripentol in the treatment of Dravet syndrome.

Besides drug treatment, the ketogenic diet is indicated as the alternative second- or third-line therapeutic approach (Ziobro *et al*, 2018). It is a high-fat diet with a low intake of carbohydrates, suspected to yield therapeutic effects resulting from the direct anticonvulsant activity of ketone bodies (acetoacetate, acetone, and beta-hydroxybutyrate), created in the liver from long and medium-chain fatty acids. This diet may not be feasible for all Dravet syndrome patients. Additionally, patients who suffer from metabolic disorders (including disorders of fatty acid transport, β-oxidation, and some mitochondrial cytopathies) must be excluded.

The response rate for topiramate ranges from 35% to 78%, based on small, open-label, prospective and retrospective studies. Similarly, the ketogenic diet is reported to yield response rates of 53-70%, based on non-randomized studies (Knupp *et al*, 2018).

Stiripentol should be used in combination with valproate and clobazam (Wirrell *et al*, 2017). In this combination, stiripentol shows consistent responder rates of 67-71% and is the only recommended therapy that has evidence derived from well conducted randomized, placebo-controlled trials (Knupp *et al*, 2018).

In patients with suboptimal responses to first- and second-line therapies, third-line therapies, such as clonazepam, levetiracetam, and zonisamide should be considered. Also, ethosuximide (for atypical absences) and phenobarbital may be considered, but the panel consensus regarding the use of these therapies is weaker compared to other third-line therapies as no randomized controlled trials have been conducted (Knupp *et al*, 2018; Wirrell *et al*, 2017). Epidiolex® (cannabidiol) has been recently approved by the US FDA for the treatment of Dravet syndrome (June 2018). The efficacy and tolerability of add-on cannabidiol in DS have been demonstrated in a placebo-controlled, randomized trial, and a recent expert opinion considered it as a third-line therapy (Brigo *et al*, 2018).

Additionally, agents such as carbamazepine, oxcarbazepine, lamotrigine, phenytoin, and vigabatrin are not indicated in treatment of Dravet syndrome due to a risk of worsening seizures (Knupp *et al*, 2018).

C. Dosage and administration

The recommended oral dosage of DIACOMIT® is 50 mg/kg/day, administered in 2 or 3 divided doses (ie, 16.67 mg/kg three times daily or 25 mg/kg twice daily). If the exact dosage is not achievable given the available strengths, round to the nearest possible dosage, which is usually within 50 mg to 150 mg of the recommended 50 mg/kg/day. A combination of the two DIACOMIT® strengths can be used to achieve this dosage. The maximum recommended total dosage is 3,000 mg/day.

Hematologic testing should be obtained prior to starting treatment with DIACOMIT®.

As DIACOMIT® markedly inhibits metabolism of clobazam and its active metabolic norclobazam, clobazam doses should be reduced by 25% as stiripentol is started. If somnolence persists, further clobazam reduction by an additional 25% should be considered, as should adjustment of the dosage of other concomitant anticonvulsant drugs with sedating properties.

DIACOMIT® capsules must be swallowed whole with a glass of water during a meal. Capsules should not be broken or opened.

DIACOMIT® powder for oral suspension should be mixed in a glass of water (100 mL) and should be taken immediately after mixing during a meal. To be sure there is no medicine left in the glass, add a small amount of water (25 mL) to the drinking cup and drink all of the mixture.

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

Overdosage

There are no data concerning overdose in humans. Treatment of an overdose should be supportive (symptomatic measures in intensive care units).

Regional Poison Control Center should be contacted for management of a suspected drug overdose (call 24/7 hotline 1-800-222-1222).

D. Contraindications

Treatment with stiripentol is not associated with any specific contraindications.

E. Special warnings

Special warnings are listed in **Table 2**.

Table 2. Special Warnings for DIACOMIT® (stiripentol)

	Special warnings	Incidence in patients with Dravet syndrome in controlled studies	Adaptation of co-medication
Somnolence	DIACOMIT® can cause somnolence. Co-administration of DIACOMIT® with clobazam results in increased levels of clobazam and its active metabolite norclobazam, both of which are also known to cause somnolence. Other central nervous system (CNS) depressants, including alcohol, could potentiate the somnolence effect of DIACOMIT®. Prescribers should monitor patients for somnolence. Prescribers should caution patients against engaging in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles, until the effect of DIACOMIT® on mental alertness is known.	67% compared to 23% on placebo	Clobazam doses should be reduced by 25% as stiripentol is started. If somnolence persists, further clobazam reduction by an additional 25% should be considered, as should adjustment of the dosage of other concomitant anticonvulsant drugs with sedating properties.
Decreased Appetite and Decreased Weight	DIACOMIT® can cause decreases in appetite and weight. Nausea and vomiting also occurred more frequently in DIACOMIT®-treated patients. Given the frequency of these adverse reactions, the growth of pediatric patients treated with DIACOMIT® should be carefully monitored.	Decreased appetite: 46% compared to 10% on placebo Decreased weight: 27% compared to 6% on placebo	In some cases, decreasing the dose of concomitant valproate by 30% per week can reduce the decrease in appetite and weight.
Neutropenia and Thrombocytopenia	DIACOMIT® can cause a significant decline in neutrophil count. Hematologic testing should be obtained prior to starting treatment with DIACOMIT®, and then every 6 months. DIACOMIT® can cause a significant decline in platelet count. Hematologic testing should be obtained prior to starting treatment with DIACOMIT®, and then every 6 months.	In controlled studies in patients with Dravet syndrome, 31 patients treated with DIACOMIT® had both a baseline and end-of-study neutrophil count. A decrease in neutrophil count from normal at baseline to less than 1,500 cells/mm^3 during the trial was observed in 13% of these DIACOMIT®-treated patients, but not in any placebo-treated patients. In controlled studies in patients with Dravet syndrome, 31 patients treated with DIACOMIT® had both a baseline and end-of-study platelet count. A decrease in platelet count from normal at baseline to less than 150,000/µL during the trial was observed in 13% of these DIACOMIT®-treated patients, but not in any placebo-treated patients.	

	Special warnings
Withdrawal Symptoms	As with most antiepileptic drugs, DIACOMIT® should generally be withdrawn gradually to minimize the risk of increased seizure frequency and status epilepticus. In situations where rapid withdrawal of DIACOMIT® is required (e.g., in the setting of a serious adverse reaction), appropriate monitoring is recommended.
Risks in Patients with Phenylketonuria	Phenylalanine can be harmful to patients with phenylketonuria (PKU). DIACOMIT® Powder for Suspension contains phenylalanine, a component of aspartame. Each 250 mg packet contains 1.40 mg phenylalanine; each 500 mg packet contains 2.80 mg phenylalanine. Before prescribing DIACOMIT® Powder for Suspension to a patient with PKU, the combined daily amount of phenylalanine from all sources, including DIACOMIT® Powder for Suspension, should be considered. DIACOMIT® Capsules do not contain phenylalanine.
Suicidal Behavior and Ideation	Anti-Epileptic Drugs (AEDs), including DIACOMIT®, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

F. Adverse reactions

Table 8 (*see section IV.A.2*) lists the adverse reactions which occurred in ≥ 5% of DIACOMIT®-treated patients in the pivotal STICLO France and STICLO Italy studies.

G. Drug interactions

Effect of DIACOMIT® (stiripentol) on other drugs

In vitro data show that stiripentol is both an inhibitor and inducer of CYP1A2, CYP2B6, and CYP3A4. Because of potential drug-drug interactions, dose adjustment of CYP1A2 substrates (e.g., theophylline, caffeine), CYP2B6 substrates (e.g., sertraline, thiotepa), and CYP3A4 substrates (e.g., midazolam, triazolam, quinidine), as clinically appropriate, should be considered when they are administered concomitantly with DIACOMIT®.

Because of potential inhibition of enzyme/transporter activity, a reduction in dosage of substrates of CYP2C8, CYP2C19 (e.g., diazepam, clopidogrel), P-gp (e.g., carbamazepine), and breast cancer resistance protein (BCRP) (e.g., methotrexate, prazosin, glyburide), should be considered if adverse reactions are experienced when they are administered concomitantly with DIACOMIT®.

Interaction with clobazam

Co-administration of DIACOMIT® (which inhibits CYP 3A4 and 2C19) with clobazam results in increased plasma concentrations of clobazam (a substrate of CYP3A4) and norclobazam, the active metabolite of clobazam (a substrate of CYP2C19). This may increase the risk of clobazam-related adverse reactions. A reduction in dosage of clobazam is recommended when DIACOMIT® therapy is started.

Effect of other drugs on DIACOMIT® (stiripentol)

Induction-based interactions leading to decreases in DIACOMIT® concentrations are possible when co-administered with a potent CYP1A2, CYP3A4, or CYP2C19 inducer, such as rifampin, phenytoin, phenobarbital and carbamazepine, as these enzymes all metabolize stiripentol. Concomitant use of strong inducers with DIACOMIT® should be avoided, or dosage adjustments should be made.

Central nervous system (CNS) depressants and alcohol

Concomitant use of DIACOMIT® with other CNS depressants, including alcohol, may increase the risk of sedation and somnolence.

H. Use in specific populations

Table 3. Use of DIACOMIT® (stiripentol) in specific populations

Specific population	Use
Pregnancy	There is inadequate data on the developmental risks associated with the use of stiripentol in pregnant women. Studies on animals provided evidence of developmental toxicity, including increased incidence of fetal malformations, increased embryofetal and pup mortality, and decreased embryofetal and pup growth, following administration of stiripentol to pregnant animals. Physicians are advised to recommend that pregnant patients taking stiripentol enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry.
Lactation	There are no data on the presence of stiripentol in human milk, the effects on the breastfed infant, or the effects on milk production. Benefits of breastfeeding should be considered along with the mother's clinical need for DIACOMIT® and any potential adverse effects on the breastfed infant from DIACOMIT® or from the underlying maternal condition.
Pediatric use	The safety and effectiveness of stiripentol for the treatment of seizures associated with Dravet syndrome in patients taking clobazam have been established in patients 2 to 18 years of age. Use of stiripentol in this pediatric population is supported by 2 multicenter, placebo-controlled, double-blind randomized studies. Limited information on safety was reported from non-pivotal trials in patients 6 months and older.
Geriatric use	DIACOMIT® was not studied in patients ≥ 65 years of age. Possible age-associated hepatic and renal function abnormalities should be considered when using DIACOMIT® in patients ≥ 65 years of age.
Renal/hepatic impairment	Because stiripentol is mainly metabolized by the liver and its metabolites eliminated mainly through the kidney, administration to patients with moderate or severe liver impairment or renal impairment is not recommended.

II. Product Information

I. Mechanism of action

The precise anticonvulsant mechanism of stiripentol is not fully known. However, stiripentol acts as a positive allosteric modulator of the GABA(A) receptor, by enhancing the inhibiting effect of GABA (Quilichini *et al*, 2006). Stiripentol preferentially binds to both benzodiazepine-sensitive γ-containing GABA(A) receptors and the benzodiazepine-insensitive δ-containing GABA(A) receptors, which are predominantly peri- and extrasynaptic in location and responsible for mediating tonic inhibition. Thus, the combination of stiripentol and benzodiazepines enhances GABAergic neurotransmission beyond the effect of each compound administered alone (Fisher *et al*, 2011). Stiripentol has also been shown to have a particular affinity for and a highest activity at α3 subunit-containing GABA(A) receptors, which are found at the highest level in the immature brain (Fisher *et al*, 2011).*

Furthermore, in status epilepticus, stiripentol continues to be efficacious, both by maintaining phasic inhibition, due to its action on α4-containing GABA(A) receptors (which are not internalized), and tonic inhibition, by its action on δ-containing GABA(A) receptors (which are also not internalized) (Grosenbaugh *et al*, 2013). In contrast, pharmacoresistance to benzodiazepines develops due to an internalization of the GABA(A) receptors containing the γ2 subunit.

In addition, DIACOMIT® exerts indirect effects involving inhibition of cytochrome P450 activity with resulting increase in blood levels of clobazam and its active metabolite norclobazam.

Recent experimental data also suggest a secondary mechanism of non-competitive inhibition of lactate dehydrogenase (LDH), which has been shown to suppress neural activity and seizures and involving the potassium (K) ATP channels (Sada *et al*, 2015).*

In vitro models of neuronal injury in rat neuron-astrocyte cultures deprived of glucose and oxygen or exposed to excess glutamate mimic key events associated with seizures. The presence of stiripentol prior to neuronal injury resulted in reduced cytoskeleton alteration and reduction of associated cell dysfunction. This effect was also seen when stiripentol exposure occurred after neuronal injury induced by excess glutamate. It is proposed that the neuroprotective properties of stiripentol may involve calcium and sodium channels (Verleye *et al*, 2016).*

J. Pharmacokinetics

The following pharmacokinetic properties of stiripentol have been found in studies in adult healthy volunteers and adult patients. Systemic exposure of stiripentol increases in a greater than dose proportional manner from 500 mg to 2,000 mg.

Absorption

The median time to stiripentol peak plasma concentration is 2 to 3 hours.

Distribution

Protein binding of stiripentol is 99%.

Elimination

The elimination half-life of stiripentol ranges from 4.5 to 13 hours, increasing with doses of 500 mg, 1,000 mg and 2,000 mg.

Metabolism

Based on in vitro studies, the main liver cytochrome P450 (CYP) isoenzymes involved in metabolism are considered to be CYP1A2, CYP2C19, and CYP3A4.

Specific populations

The effect of age (≥ 65 years), race, and renal and hepatic impairment on stiripentol pharmacokinetics is unknown. Sex does not have a clinically significant effect on the pharmacokinetics of DIACOMIT®.

**Additional supporting data that are not presented in the current DIACOMIT® prescribing information*

Pediatric patients

In a study of children (median age 7.3 years) with Dravet syndrome treated with DIACOMIT®, valproate, and clobazam, the apparent clearance and volume of distribution of stiripentol were related to body weight. Elimination half-life increased from 8.5 hr (for 10 kg) to 23.5 hr (for 60 kg).

Drug interaction studies

The metabolic pathway for stiripentol has not been clearly elucidated. Stiripentol is a substrate of several CYP enzymes, including CYP1A2, CYP2C19, and CYP3A4. Stiripentol inhibits and induces CYP1A2, CYP2B6, and CYP3A4. Stiripentol also inhibits CYP2C8, CYP2C19, and drug transporters, including P-gp and BCRP, at clinically relevant concentrations.

Clinical studies have evidenced that co-administration of clobazam with stiripentol increased concentrations of clobazam by approximately 2-fold and norclobazam (clobazam active metabolite) by 5-fold.

K. Regulatory status

In the United States, stiripentol has been available under special access program since 2000 for compassionate use. DIACOMIT® was granted orphan designation for the treatment of Dravet syndrome by the FDA (orphan designation number 08-2661) on October 30, 2008 and was approved on August 20, 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam (NDA 206709 and 207223).

The recent approval of stiripentol addresses key unmet medical needs in this population. DIACOMIT® is not registered under the Controlled Substances Act (US regulation of the use of drugs considered as having potential for abuse). There is no evidence of potential abuse associated with stiripentol.

In the European Union, DIACOMIT® was granted orphan drug status by the European Medicines Agency in 2001. In January 2007 DIACOMIT® received a marketing authorization for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with Dravet syndrome.

In 2012, DIACOMIT® was approved in Canada and in Japan with the same indication as in Europe.

In 2018, DIACOMIT® was registered in Switzerland with the same indication.

III. Preclinical Data

A. Animal data

Oral administration of stiripentol (0, 50, 200, or 800 mg/kg/day) to pregnant mice throughout the period of organogenesis resulted in increased embryofetal mortality and decreased fetal body weights at all doses and an increased incidence of malformations at the high dose, with no evidence of maternal toxicity. The lowest effective dose for developmental toxicity in mice (50 mg/kg/day) was less than the recommended human dose (RHD) of 50 mg/kg/day on a body surface area (mg/m^2) basis.

Oral administration of stiripentol (0, 50, 200, or 800 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in increased embryofetal mortality at the mid and high dose and decreased fetal body weights at all doses. The mid and high doses were associated with maternal toxicity. The lowest effect dose for developmental toxicity in rabbits (50 mg/kg/day) was less than the RHD on a mg/m^2 basis.

Oral administration of stiripentol (0, 50, 200, or 800 mg/kg/day) to rats throughout pregnancy and lactation resulted in decreased pup survival, decreased pup body weights at birth and throughout lactation, and deficits in pup reflex development at the high dose, which was also associated with maternal toxicity. The no-effect dose for pre- and postnatal developmental toxicity in rats (200 mg/kg) was less than the RHD on a mg/m^2 basis.

B. Carcinogenesis

In mice, oral administration of stiripentol (0, 60, 200, or 600 mg/kg/day) for 78 weeks increased the incidences of liver tumors (hepatocellular adenoma and carcinoma) at the mid and high dose. The dose not associated with an increase in liver tumors (60 mg/kg/day) is less than the recommended human dose (RHD) of 50 mg/kg/day, based on body surface area (mg/m^2). In rats, oral administration of stiripentol at doses of up to 800 mg/kg/day (approximately 2.5 times the RHD on a mg/m^2 basis) for 102 weeks did not result in an increase in tumors.

C. Mutagenesis

Stiripentol was negative for genotoxicity in in vitro (Ames, HPRT gene mutation in V79 Chinese hamster cells, and chromosomal aberration in human lymphocytes) and in vivo (mouse bone marrow micronucleus) assays. Stiripentol was clastogenic in CHO cells in vitro, but only at cytotoxic concentrations.

D. Impairment of fertility

Oral administration of stiripentol (0, 50, 200, or 800 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females throughout organogenesis produced no adverse effects on fertility. The highest dose tested is approximately 2.5 times the RHD on a mg/m^2 basis.

IV. Clinical Data

Clinical effectiveness of stiripentol for the treatment of seizures associated with Dravet syndrome was established in 2 multicenter, placebo-controlled, double-blind, randomized studies (STICLO France and STICLO Italy trials) conducted according to similar protocols. In both trials, stiripentol versus placebo was added on to stable doses of clobazam and valproic acid in patients with inadequately controlled seizures (Chiron *et al*, 2000; Kassaï *et al*, 2008).

Efficacy results of the pooled STICLO France and STICLO Italy trials showed an outstanding efficacy:

- A response rate of 69.7% with stiripentol versus 6.5% with placebo (response rate being defined as ≥ 50% reduction in generalized clonic or tonic-clonic seizure frequency) ($P < 0.0001$).
- A mean percent reduction in seizure frequency of 66% with stiripentol versus an increase of 4% with placebo ($P < 0.0001$).
- 36% of children on stiripentol versus none on placebo became completely seizure-free (generalized clonic or tonic-clonic seizures) after 8 weeks of treatment ($P = 0.0002$).

Several supportive studies (open-label, short and long-term design trials) with over 25 years of clinical evidence associated with extensive data collection and analyses confirmed the sustained efficacy of stiripentol. The efficacy to stiripentol was demonstrated to be maintained over several years, including very long-term into adulthood (up to 24 years) (Chiron *et al*, 2018).

Overall, a total of 628 Dravet syndrome patients were enrolled in Biocodex-sponsored pivotal and non-pivotal clinical trials. Of these 628 patients, 529 received stiripentol.

Stiripentol is a safe and well-tolerated treatment option:

- Most adverse events with stiripentol could be categorized as either neurological (sleepiness/drowsiness/somnolence) or gastrointestinal (loss of appetite, nausea, and loss of weight) in origin. These observations are consistent within and across multiple studies; adverse events are often due to associated antiepileptic drugs, particularly clobazam, which are easily managed through their dose reduction, with no impact on efficacy.
- These findings are consistent across all studies and clinical practice experience.
- Stiripentol was first launched in 2007, with more than 2,300 exposed patients, and no significant safety signal has been reported to date.

An overview of all individual trials evaluating stiripentol in Dravet Syndrome patients is presented in **Table 20**.

A. Pivotal randomized clinical trials studies: STICLO France and STICLO Italy

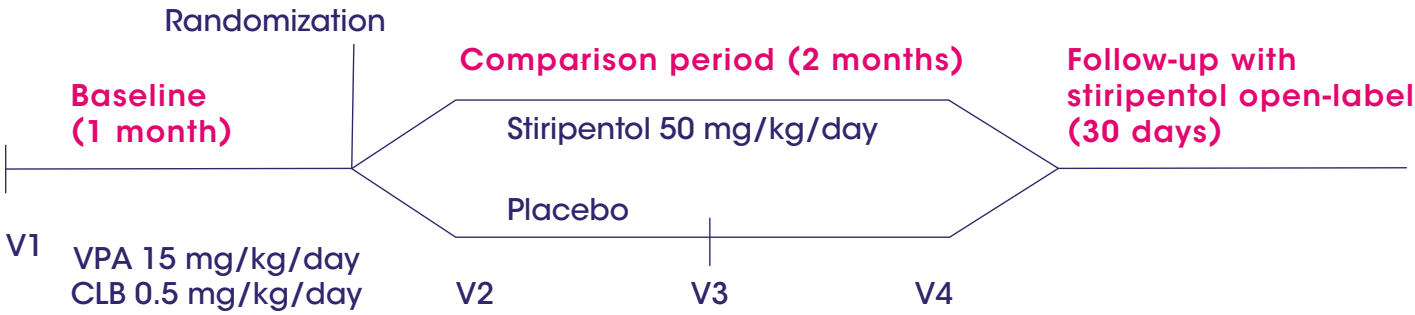
1. Study design

The efficacy of stiripentol, as an add-on therapy to optimized treatment with valproic acid and clobazam in patients with Dravet syndrome, was demonstrated in two randomized, double-blind, placebo-controlled, phase III, pivotal clinical trials (STICLO France and STICLO Italy). These trials had identical protocol designs, enabling for comparisons and the pooling of data. Both trials were conducted according to Good Clinical Practice principles.

These studies were divided into two parts: a one-month baseline period followed by a two-month comparison period. Eligible patients were initially enrolled in a 1-month baseline period during which they continued to receive their optimized antiepileptic treatment with valproic acid (VPA) and clobazam (CLB). Following this 1-month baseline, patients who continued to have at least 4 generalized tonic-clonic or clonic seizures per month were randomly allocated to receive either stiripentol or placebo added on to their antiepileptic treatment for 2 months. During the 2-month double-blind period, the dose of stiripentol was fixed at 50 mg/kg/day and administered in 2 or 3 doses (**Figure 1**).

The selection of the permitted AEDs (valproic acid & clobazam) was in line with the usual clinical management of this condition. Other AEDs were prohibited, except for rescue progabide or per-rectal diazepam.

Figure 1. Study design of STICLO studies (France and Italy)



After the end of the comparison period, children received stiripentol under the open-label extension trial for 30 days, and possible subsequent prescription of stiripentol was left to the discretion of the investigators.

The numbers of patients who participated in the STICLO France and STICLO Italy clinical trials totaled 42 and 23, respectively.

The STICLO France study was stopped after inclusion of only 42 patients, when preliminary results demonstrated a significant benefit regarding the primary endpoint criterion in the stiripentol cohort. It was followed by the STICLO Italy study, which included 23 patients.

Table 4 provides a tabulated summary of design of STICLO studies.

Table 4. Summary of design of STICLO France and STICLO Italy studies

	STICLO France	STICLO Italy
Design	A multicenter, randomized, double blind, comparative, parallel group, phase III study of stiripentol vs placebo, as add-on treatment to clobazam and valproate sodium therapy. The study involved 2 phases: 1-month baseline period followed by a 2-month comparison period.	
Location	14 centers in France	6 centers in Italy
Study participants (n)	42	23
Key objectives	The key objectives were: • To demonstrate efficacy of stiripentol as add-on therapy to CLB and VPA in children with Dravet syndrome and refractory seizures • To study the safety profile of the combinations (or acceptability of stiripentol) • To document steady state concentrations of stiripentol and concomitant medications	
Start and completion dates	From October 1996 to August 1998	From 1999 to 2000
Randomization and blinding procedures	Randomized, double-blind, placebo-controlled trial. Randomization by computer-generated list. The stiripentol and placebo were identical in their presentation and were not identifiable.	
Inclusion criteria	**Pre-inclusion criteria for entering 1-month baseline period:** • Children 3–18 years of age • Diagnosed with Dravet syndrome • ≥ 4 generalized clonic or tonic-clonic seizures/month • Receiving concomitant CLB 0.5 mg/kg/day + VPA ≤ 30 mg/kg/day • Weight ≤ 60 kg **Final inclusion criteria for entering double-blind period:** • Children who met the pre-inclusion criteria and participated in the baseline period • ≥ 4 generalized clonic or tonic-clonic seizures/month during the baseline period • Normal lab test assessments (CBS, platelets, serum creatinine, and ASAT and ALAT < 3 times the upper limit of normal)	
Exclusion criteria	• Children receiving other AEDs (except for CLB, VPA, and rescue medications *pro re nata*) • Asthma patients treated with theophylline • Parents could not accurately record the number of seizures • Enrolled in another ongoing clinical study	

Table 4. Summary of design of STICLO France and STICLO Italy studies (cont'd)

	STICLO France	STICLO Italy
Intervention	**Baseline period:** • CLB 0.5 mg/kg/day, maximum 20 mg/day • VPA 30 mg/kg/day or less **Double-blind period:** Stiripentol capsules (250 mg or 500 mg) 50 mg/kg/day as 2 or 3 daily divided doses, PO, in addition to CLB+VPA (at the same doses adopted in baseline).	
Comparator(s)	**Double-blind period:** Matching placebo in addition to CLB+VPA	
Primary endpoint	Percentage of responders measured at the end of the double-blind period ("responder" was defined as ≥ 50% reduction in clonic or tonic-clonic seizure frequency during the second month of DB period compared with baseline).	
Secondary endpoints	• Mean percent change from baseline in frequency of generalized tonic-clonic or clonic seizures • Change in number of seizures during the DB period (month 1 and month 2) compared with baseline • Percentage of children withdrawn from the study • Time elapsed until the same number of seizures as that in the 1-month baseline period was experienced • Safety	
Sample size	• STICLO France: since no numerical data were available to calculate the sample size, a preliminary analysis was planned after an enrollment of 20 patients in each group. In case of a demonstration of a significant difference regarding the primary endpoint criterion considered as clinically relevant between the 2 treatment groups (at the reduced level of significance $\alpha = 2.5\%$) the study had to be stopped. • STICLO Italy: the number of patients included was based on the results of STICLO France.	
Statistical analysis	Statistical analyses were done on an ITT basis. The primary endpoint was analyzed using the chi-squared test. The number of seizures and percentage change from baseline in the number of seizures were analyzed non-parametrically using the Mann-Whitney test. No replacement technique was used for missing data. The analyses were performed on available data.	

CBS: complete blood screening; ASAT: aspartate amino transferase; ALAT: alanine amino transferase; AEDs: antiepileptic drugs; PO: per os (oral administration); DB: double-blind; ITT: intention-to-treat

2. Study results

Patient disposition

The patient disposition is presented in **Figure 2** for STICLO France study and in **Figure 3** for STICLO Italy.

In the STICLO France study, 41 subjects (of 47 screened) were analyzed (intention-to-treat (ITT) population); 21 in stiripentol group and 20 in placebo group:

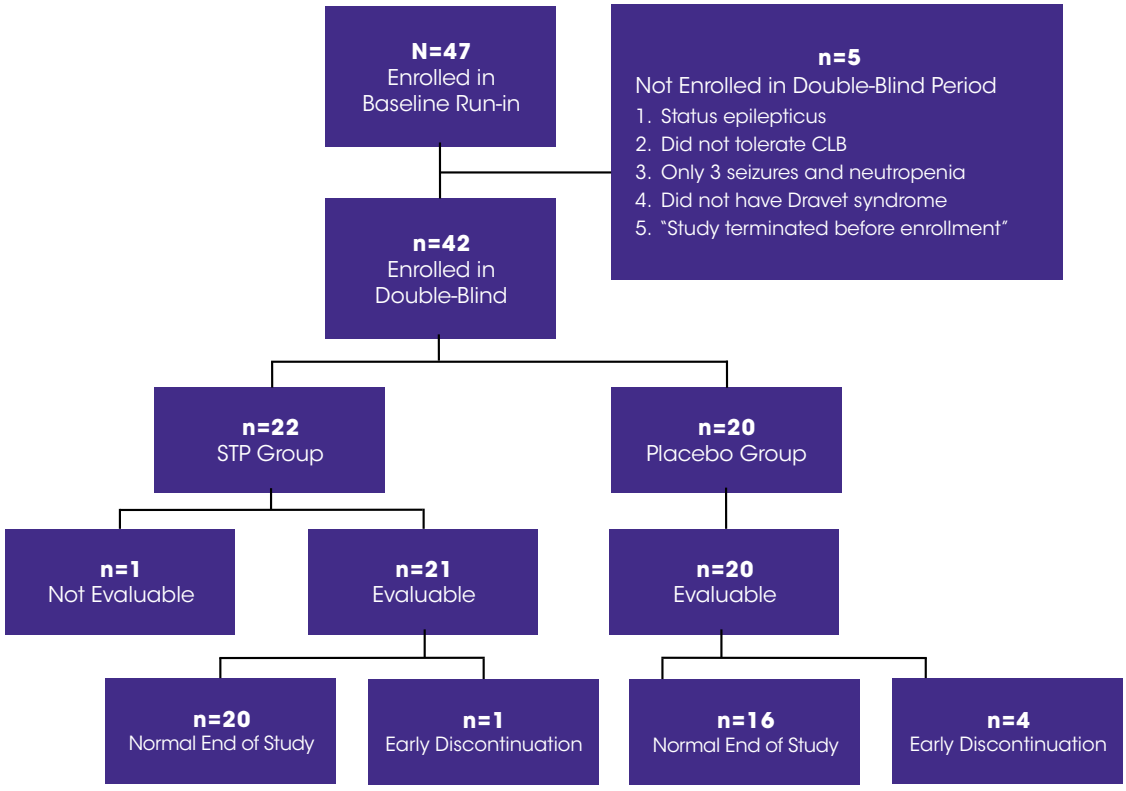
- Five patients did not enter the baseline period for the following reasons (1 patient per reason): status epilepticus, did not tolerate clobazam, fewer than 4 seizures per month plus neutropenia, did not have Dravet syndrome, and study terminated before enrollment.
- During the double-blind period, 1 patient in the stiripentol group was considered not evaluable because the treatment was taken irregularly and because the seizures were not recorded in the patient's diary; therefore, this patient was excluded from efficacy and safety analysis.
- One child (5%) was withdrawn from the study in the stiripentol group, versus 4 (20%) in the placebo group as reported in **Figure 2**, which was not statistically different ($P = 0.184$).

In STICLO Italy study, 23 subjects (of 24 screened) were analyzed (ITT population); 12 in stiripentol group and 11 in placebo group:

- One patient included in the baseline period did not enter the double-blind period, however, the reason for this exclusion was not provided in the clinical study report.
- One patient (9%) was withdrawn from the study in the stiripentol group, versus 2 (18%) in the placebo group as reported in **Figure 3**.

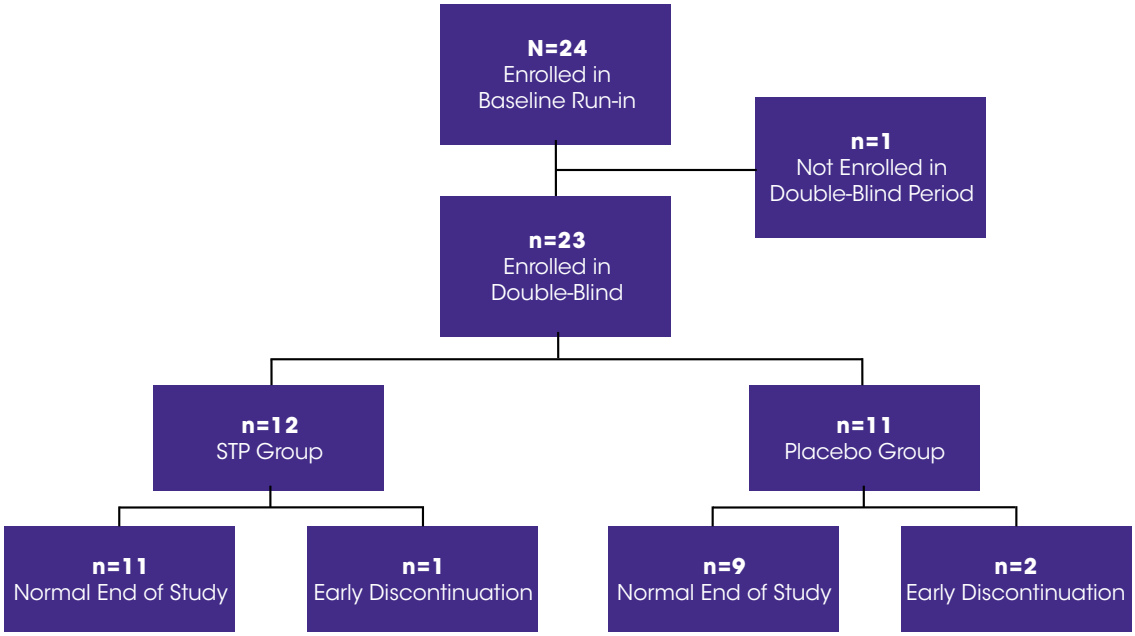
No patient was lost to follow-up in either study.

Figure 2. STICLO France study – patient disposition



Early discontinuation in the stiripentol arm: Status epilepticus (1) - Early discontinuation in the placebo arm: Status epilepticus (1), No improvement (2), Drowsiness, motor deficiency (1)

Figure 3. STICLO Italy study – patient disposition



Early discontinuation in the stiripentol arm: Adverse events (drowsiness, balance symptoms) (1) - Early discontinuation in the placebo arm: Worsening (1), Patient's request because of lack of improvement (1)

Baseline demographic data

Table 5 depicts the selected, important baseline characteristics.

Table 5. Baseline demographic across the STICLO France and STICLO Italy studies (DIACOMIT®: EPAR – Scientific Discussion EMA 2007)

	STICLO France		STICLO Italy	
	STP n = 21	Placebo n = 20	STP n = 12	Placebo n = 11
Gender (M/F)	6/15	11/9	8/4	5/6
Age (mean ± SD)	9.4 ± 4	9.29 ± 4.86	9.17 ± 3.63	8.72 ± 4.43
Weight	31.8 ± 12.7	30.5 ± 14.4	31.9 ± 11.7	29.2 ± 9.04
Number of seizures/month	17.9 ± 17.3 (3.9 – 72.9)	18.5 ± 17.0 (4.1 – 76.2)	33.6 ± 28.2 (2.14 – 86.1)	27.4 ± 28.6 (3.75 – 101.0)
No. of previous treatments	6.6 ± 2.5 (3 – 11)	7.5 ± 2.9 (3 – 13)	NA	NA
AED doses (preinclusion) (mg/kg/day) Sodium Valproate Clobazam	 23.6 ± 9.47 0.532 ± 0.247	 24.04 ± 8.53 0.55 ± 0.27	 28.2 ± 7.98 0.575 ± 0.21	 25.3 ± 7.0 0.538 ± 0.18

M: male; F: female; SD: standard deviation; STP: stiripentol

Clinical efficacy results

STICLO France and STICLO Italy demonstrated the antiepileptic efficacy of stiripentol added to valproate and clobazam in the treatment of Dravet syndrome.

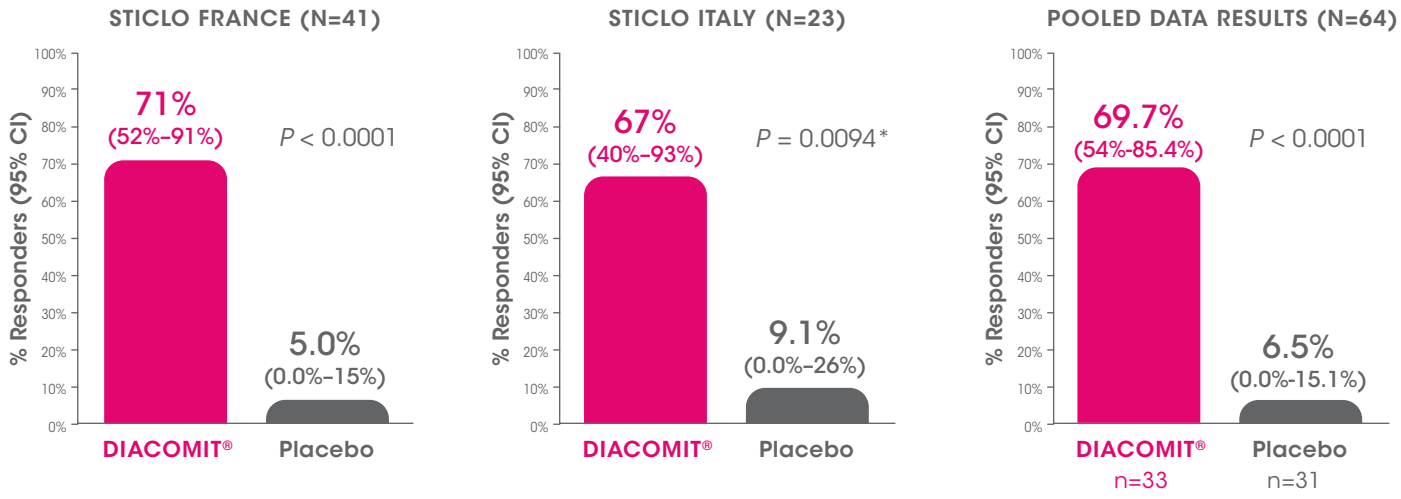
Primary endpoint

Results of the primary endpoint (number of responders) of both STICLO studies are given in **Table 6**. The percentage of responders in the stiripentol group was significantly higher than in the placebo group in both studies. **When efficacy results of both STICLO trials were pooled, 69.7% of patients on stiripentol versus 6.5% of patients on placebo significantly met the criterion for response.**

Table 6. Number of responders in STICLO studies

Study	Study arm	Responders		95% confidence interval	*P*-value
		Numbers	Frequency		
STICLO France[a]	Stiripentol	15/21	**71%**	52–91%	$P < 0.0001$
	Placebo	1/20	5%	0.0–15%	
STICLO Italy[a]	Stiripentol	8/12	**67%**	40–93%	$P = 0.0094$
	Placebo	1/11	9.1%	0.0–26%	
STICLO pooled (France & Italy)[b]	Stiripentol	23/33	**69.7%**	54.0–85.4%	$P < 0.0001$
	Placebo	2/31	6.5%	0.0–15.1%	

Figure 4. STICLO France and STICLO Italy studies results[a,b]



*Frequency of generalized tonic-clonic or clonic seizures during month 2

a. DIACOMIT® (stiripentol) prescribing information. Beauvais, France: BIOCODEX. 2018

b. Food and Drug Administration. CDER Clinical Review. August 2018

Secondary endpoints

- **Variations in the number of seizures during the 2nd month**

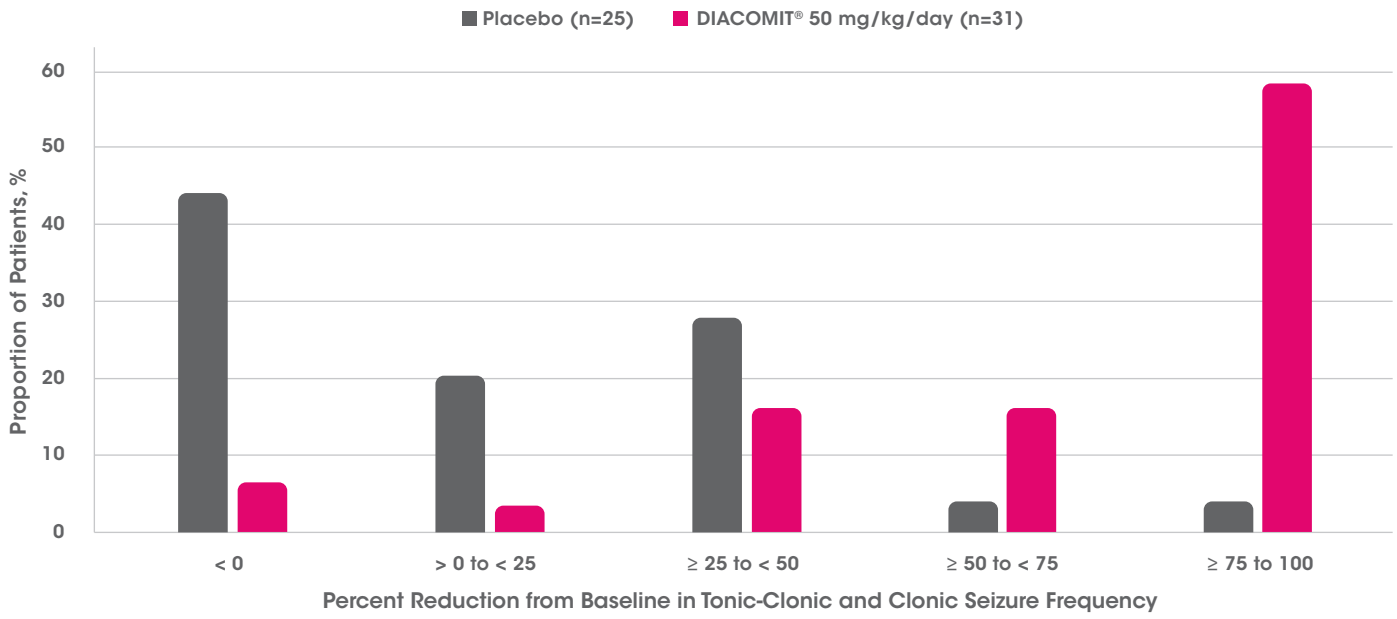
  The secondary endpoints in both STICLO trials showed variations in the number of seizures (presented in **Table 7**). In STICLO France, 9 patients in the stiripentol group (45%) were seizure-free during the second month and in STICLO Italy, 3 patients of the stiripentol group (27%) were seizure-free during the second month versus none in the placebo group.

Figure 7. Variation in seizures with treatment in STICLO studies between baseline and the end of the second month (DIACOMIT®: EPAR – Scientific Discussion EMA 2007)

	STICLO France (PP* population)			STICLO Italy (PP* population)		
	STP n = 20	Placebo n = 16	*P* value	STP n = 11	Placebo n = 9	*P* value
No seizures (100%)	9 (45%)	0		3 (27%)	0	
Decrease > 50 < 100%	6 (30%)	1 (6%)		5 (45%)	1 (11%)	
Decrease < 50%	3 (15%)	5 (31%)	*P* < 0.01	3 (27%)	7 (78%)	*P* ~ 0.05
Increase < 50%	2 (10%)	8 (50%)		0	0	
Increase > 50%	0	2 (13%)		0	1 (11%)	

*PP: per protocol analysis

Figure 5. Proportion of patients by category of seizure response for DIACOMIT® and placebo in STICLO France and STICLO Italy pooled, baseline to 2nd month of treatment (per 30 days) (DIACOMIT® (stiripentol) prescribing information. Beauvais, France: BIOCODEX; 2018)



- Percentage change of seizure frequency from baseline

  Primarily, tonic-clonic seizures were assessed. Evidence was provided that other types of seizures did not worsen, albeit data were very limited.

  In STICLO France, there was a mean decrease in seizures of (-) 69±42% in the stiripentol group at the end of the second month compared with an increase of (+) 7.6±38% in the placebo group.

  Similarly, in STICLO Italy, there was a mean decrease in seizures of (-) 74±27% in the stiripentol group at the end of the second month and a decrease of (-) 13±62% in the placebo group.

Clinical safety and tolerability

In the 2 studies, the percentage of patients reporting adverse events (AEs) was higher in the stiripentol group compared with the placebo group (**Table 8**). AEs were reported as being mild or moderate in severity.

In STICLO France, the most commonly reported AEs with stiripentol included drowsiness, decreased appetite, and weight loss. In the placebo group, the most commonly reported AEs were drowsiness and weight gain.

In STICLO Italy, the most commonly reported AEs in the stiripentol group were sleepiness, behavior disorders, and loss of appetite. In the placebo groups, sleepiness, ataxia, hyperexcitability, irritability, tremors, hyperkinesia, and loss of appetite were reported.

In STICLO France, 2 patients (9.5%) reported 3 serious AEs in the stiripentol group and 3 patients (15%) in the placebo group reported 5 serious AEs. In STICLO Italy, no serious AEs were reported during the study.

In STICLO France, 1 patient in the stiripentol group withdrew due to an AE (status epilepticus) compared with 4 patients in the placebo group (status epilepticus, major drowsiness, and repeated seizures). In STICLO Italy, 1 patient in the stiripentol group withdrew due to symptoms of drowsiness. No patients in the placebo group withdrew from the study due to AEs. No deaths occurred during the STICLO studies.

Table 8. Adverse reactions that occurred in at least 5% of stiripentol-treated patients and were more frequent than in placebo-treated patients in the STICLO studies

Adverse reactions	STICLO studies - pooled total	
	STP (N = 33) %	Placebo (N = 31) %
Gastrointestinal disorders		
Nausea	15	3
Vomiting	9	0
Salivary hypersecretion	6	0
General disorders and administration site conditions		
Fatigue	9	3
Pyrexia	6	3
Infections and infestations		
Bronchitis	6	0
Nasopharyngitis	6	0
Investigations		
Weight decreased	27	6
Weight increased	6	3
Metabolism and nutrition disorders		
Decreased appetite	46	10
Nervous system disorders		
Somnolence	67	23
Ataxia	27	23
Hypotonia	18	13
Tremor	15	10
Dysarthria	12	0
Psychiatric disorders		
Agitation	27	16
Insomnia	12	7
Aggression	9	0

Study limitations

Both STICLO France and STICLO Italy were short-term studies with a treatment duration of two months; long-term studies have been performed after the completion of STICLO studies confirming that the long-term efficacy and safety profile of stiripentol is maintained over long-term treatment, up to several years. (De Liso *et al*, 2016; Myers *et al*, 2018; Chiron *et al*, 2018)

B. Post-marketing safety information: DIAVEY study (2007–2012)

1. Study design

The DIAVEY study* is a post-marketing safety study, international, multicenter and non-interventional. The study was conducted in 11 countries in Europe: Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, and United Kingdom (UK), between January 2007 and May 2012 **(Table 9)**.

The primary objective was to proactively collect adverse drug reactions (ADRs) and safety information in patients newly prescribed DIACOMIT® for the treatment of Dravet syndrome. The secondary objective was to proactively collect ADRs and safety information in patients newly prescribed DIACOMIT® for the treatment of any other type of epilepsy.

Patients were newly prescribed DIACOMIT® which was initiated at the first visit. They were included for a minimum of 1 year and a maximum of 5 years. Physicians could stop treatment based on clinical judgment.

**Additional supporting data (internal source) that are not presented in the current DIACOMIT® prescribing information*

Table 9. Summary of DIAVEY study

	DIAVEY Study
Design	Post-marketing safety study
Location	11 countries in Europe: Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, and UK
Study participants (n)	227 patients analyzed 152 Dravet syndrome patients
Study objectives	To evaluate safety of STP (stiripentol) treatment
Start and completion dates	The study was conducted between January 2007 and May 2012
Key inclusion criteria	Patients newly prescribed DIACOMIT® who had given written consent or for whom written consent had been received from the parent(s) or appropriate guardian were eligible. All patients starting treatment with DIACOMIT®, whatever the dose and the formulation, at any participating site over the study period, were included in the survey.
Intervention	The initial median dose of stiripentol was 28 mg/kg/day, ranging from 20 mg/kg/day (25th percentile) to 43 mg/kg/day (75th percentile)
Key endpoints	**Primary endpoint:** to proactively collect ADRs and safety information in patients newly prescribed DIACOMIT® (stiripentol) for the treatment of Dravet syndrome **Secondary endpoint:** to proactively collect ADRs and safety information in patients newly prescribed DIACOMIT® for the treatment of any other type of epilepsy

2. Study results

230 patients were included and 227 were analyzed. The mean DIACOMIT® exposure was 20.3 months (±14.1 months) and the mean initial dose was 37 mg/kg/day for all patients included. The mean patient age at inclusion was 7.2 (± 5.8) years.

67% of patients (n=152) analyzed in the study were diagnosed with Dravet syndrome, 52% were female and 48% male. Dravet patients were generally younger than patients with other types of epilepsy, with a mean age of 6 (±6) years at inclusion, and 77% (n=117) had a SCN1A mutation.

Safety results

During the treatment period, 130 in 227 patients experienced 387 ADRs and the most frequently reported ADRs (incidence ≥ 10 patients, 4%) for all patients were:

- Raised GGT (38 patients, 17%)
- Raised AST (31 patients, 14%)
- Loss of appetite (30 patients, 13%)
- Somnolence (20 patients, 9%)
- Fatigue (19 patients, 8%)
- Neutropenia (16 patients, 7%)
- Aggression (15 patients, 7%)
- Ataxia (11 patients, 5%)
- Raised ALT (10 patients, 4%)

A total of 83 patients discontinued DIACOMIT®, mostly due to lack of efficacy.

34 patients (15.0%) experienced at least one ADR leading to DIACOMIT® discontinuation. Most of these ADRs were reported in the system organ class (SOC) "Nervous system disorders," including ataxia and somnolence (3 patients each).

Other frequent ADRs leading to discontinuation were:

- Loss of appetite (8 patients)
- Fatigue and/or asthenia (6 patients)
- AST increased (4 patients)
- Aggression (3 patients)
- Insomnia (3 patients)
- Neutropenia (3 patients)

Overall, 28 patients (12.3%) experienced 58 serious ADRs during the treatment period, including 6 deaths. The most frequent serious ADRs other than death were:

- Status epilepticus (7 patients)
- Loss of appetite (5 patients)
- Convulsions (3 patients)
- Thrombocytopenia (3 patients)
- Febrile convulsion
- Hypotonia
- Pneumonia (2 patients each)

Six deaths were reported during the treatment period and 3 after discontinuation of DIACOMIT®, and none were considered related to DIACOMIT® treatment.

In the DIAVEY study, investigators were asked to perform a complete blood count (CBC) and liver enzyme studies at the onset of DIACOMIT® treatment and then every six months. Increased liver enzymes was reported as an ADR for 52 patients during the treatment period. The most frequent was raised GGT (73%) and raised AST (60%). In most cases, these were considered possibly or probably related to treatment with DIACOMIT®.

Conclusion of DIAVEY

During the 5-year period of the DIAVEY survey, through annual interim reports and routine pharmacovigilance PSURs, the DIACOMIT® European SmPC, Section 4.8 – Undesirable Effects was amended to include additional ADRs:

- Blood and Lymphatic System Disorders: Thrombocytopenia – rare.
- Investigations: Liver function test abnormal – rare.

Therefore, during the DIAVEY survey, **no relevant ADRs have been identified** that would raise major safety concerns regarding treatment with DIACOMIT®, since the ADRs that have been reported are already listed in the DIACOMIT® SmPC (with the exception of sedation, which is more likely related to antiepileptic co-medications.)

C. Stiripentol in the USA: Wirrell *et al*, 2013

1. Study design

Wirrell *et al*, 2013* conducted a retrospective survey of the efficacy and safety of stiripentol in the treatment of Dravet patients in the United States. This retrospective review included US clinicians who had treated 2 or more Dravet patients with stiripentol between March 2005 and 2012. The Wirrell *et al*, 2013 study design summary is presented in **Table 10**.

**Additional supporting data that are not presented in the current DIACOMIT® prescribing information*

Table 10. Summary of Wirrell *et al*, 2013 study design

	Wirrell *et al*, 2013
Design	Retrospective chart review
Location	13 epilepsy reference centers in USA
Study participants (n)	82 Dravet syndrome patients treated with stiripentol
Objective	To analyze the efficacy and safety of stiripentol (STP) in Dravet syndrome patients
Start and completion dates	Retrospective review included US clinicians who had treated 2 or more Dravet patients with stiripentol between March 2005 and 2012
Key inclusion criteria	Participating physicians were requested to provide data for all children clinically diagnosed with Dravet syndrome who were treated with stiripentol anytime in the 3 years prior to study onset
Key endpoints	Data collected included stiripentol dosage, concomitant AEDs, overall seizure frequency, frequency of prolonged seizures, use of rescue medication, emergency room visits in the year preceding stiripentol treatment and during stiripentol therapy, as well as AEs during stiripentol treatment. The frequencies of convulsive, absence, myoclonic and total seizures, as well as prolonged seizures, use of rescue medication, and emergency room/hospital visits during the one-year period prior to starting stiripentol (baseline period) were compared to each of the following subgroups: • Group A: stiripentol without CLB or VPA (N=6); • Group B: stiripentol with CLB but without VPA (N=35); • Group C: stiripentol with VPA but without CLB (N=15); • Group D: stiripentol with CLB and VPA (N=48). Note that patients could move from one group to the other. For example, a patient could be counted as part of Group A, and then again as part of Group C or D. Antiepileptic response to treatment was scored according to a 5-point scale: • Reduction in overall seizure frequency marked • Reduction in overall seizure frequency mild • Unchanged overall seizure frequency • Worsening overall seizure frequency mild • Worsening overall seizure frequency marked

N/A: Not Available; AEs: Adverse Events

2. Key study results

Median age at stiripentol initiation was 6.9 years, median age at diagnosis was 5.4 years and 90% of patients had tested positive for an SCN1A mutation. The initial median target dose of stiripentol in these patients was 28 mg/kg/day, ranging from 20 mg/kg/day (25th percentile) to 43 mg/kg/day (75th percentile). The maximal median dose of stiripentol was 42 mg/kg/day (30 to 56 mg/kg/day), and the median stiripentol dose at last follow-up was 30 mg/kg/day (22 to 43 mg/kg/day). Mean duration of stiripentol treatment was 28.5 ± 20.3 months (**Table 11**).

Table 11. Demographic and clinical data of US patients included in Wirrell *et al*, 2013 study

Variable	Data
Sex (male)	38 (46%)
Median age at first seizure	6.0 months
Median age at diagnosis of Dravet syndrome	5.4 years
Median age at stiripentol initiation	6.9 years
Duration of stiripentol therapy in months Median (25th and 75th percentile) Mean (standard deviation)	 22.3 months 28.5 (20.3)
SCN1A mutation present	90.2%
Median number of antiepileptic drugs tried prior to stiripentol initiation	7.0 (25th and 75th percentile, 6.0 and 9.0)
Number with vagus nerve stimulator placed prior to stiripentol	21 (25.6%)
Number treated with dietary therapy (ketogenic diet, modified Atkins diet, low glycemic diet) prior to stiripentol	46 (56.1%)
Number undergoing epilepsy surgery prior to stiripentol	6 (7.3%)
Developmental status prior to stiripentol* (%) Normal/borderline delay Mild delay Moderate/severe delay	 11 (13.6) 24 (29.6) 46 (57.0)
Median initial target dose of stiripentol in mg/kg/day	28
Median maximal dose of stiripentol over treatment course in mg/kg/day	42
Median stiripentol dose at last follow-up in mg/kg/day	30

(N = 82)
*1 Unknown

Table 12 summarizes efficacy results based on the reduction in overall seizure frequency following initiation of stiripentol treatment. Marked and mild reduction in overall seizure frequency ranged from 33% (Group A: stiripentol alone) to 80% (Group B: stiripentol + CLB) of patients. In this study the authors found that efficacy of STP + CLB and STP + CLB + VPA were not different. These results seem to be comparable to results obtained in other clinical trials.

Moreover, 2/4 patients in group A, 25/25 in group B, 5/10 in group C, and 26/33 in group D experienced reduction in frequency of rescue medication use and 1/1 in group A, 12/12 in group B, 3/5 in group C, and 18/19 in group D experienced a reduction in frequency of emergency room/hospital visits.

Table 12. Reduction in overall seizure frequency by treatment group in 82 Dravet syndrome patients treated in the US with stiripentol (Wirrell *et al*, 2013)

Overall Seizure Frequency	**Group A** STP alone **(n=6)**	**Group B** STP + CLB **(n=35)**	**Group C** STP + VPA **(n=14*)**	**Group D** STP + CLB + VPA **(n=48)**	**Overall (n=103)****
Marked reduction	**0 (0%)**	11 (31%)	4 (29%)	17 (35%)	32 (31%)
Mild reduction	**2 (33%)**	17 (49%)	4 (29%)	13 (27%)	36 (35%)
No change	3 (50%)	7 (20%)	6 (43%)	16 (33%)	32 (31%)
Mild worsening	1 (17%)	0 (0%)	0 (0%)	2 (4%)	3 (3%)
Marked worsening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Group A: stiripentol alone without CLB or VPA; Group B: stiripentol with CLB but without VPA; Group C: stiripentol with VPA but without CLB; and Group D: stiripentol with CLB and VPA. *Excluded one subject whose treatment duration was too brief to assess response. **Note that some patients may have been in one group and then moved into another group. These patients were counted more than once

Adverse effects were reported in 31 patients (38%), most commonly sedation and reduced appetite, which were mild and did not require stiripentol discontinuation in the majority. There was no significant difference in maximal doses of stiripentol in patients with and without adverse effects (43.5 versus 46.1 mg/kg/day). Only four (5%) discontinued stiripentol for adverse effects (2 reduced appetite/weight loss and 2 worsening behavior). In addition, two children stopped for lack of efficacy and one for financial reasons.

D. Very long-term outcome: Chiron *et al*, 2018

1. Study design

Chiron *et al*, 2018* conducted a cross-sectional study of patients with Dravet syndrome recruited at pediatric age at the Reference Center of Epilepsies in Paris (Necker Hospital) since 1992 to evaluate both long-term stiripentol efficacy and safety (**Table 13**).

**Additional supporting data that are not presented in the current DIACOMIT® prescribing information*

Table 13. Summary of Chiron *et al*, 2018 study design

	Chiron *et al*, 2018
Design	Single center cohort study
Location	Necker Hospital in Paris, France
Study participants (n)	40 patients treated with STP
Objective	To evaluate continuing STP treatment in adulthood in Dravet syndrome
Start and completion dates	Patients treated since 1992 have been recruited to the study
Inclusion criteria	Patients who fulfilled the following criteria: • STP initiated in childhood or adolescence, • STP continued in adulthood, • At least 1 visit while on STP during childhood or adolescence, • At least 1 visit during adulthood 21 years was considered as the upper limit of adolescence
Intervention	STP treatment
Primary endpoint	Comparison of patient clinical characteristics across three visits: • Last visit before age 15 years • Last visit before adulthood (<21 years) • Last visit in adulthood (>21 years) Which included: • Characteristics of generalized tonic–clonic seizures (frequency, duration, severity, provoking factors) • Other seizure types (myoclonic, absences, focal, tonic) • Neurological/intellectual/behavioral • Status • Antiepileptic drugs • Other central nervous system drugs, standard • Electroencephalographic (EEG) reports • Socio-medical care status

2. Study results

At the last visit in adulthood (18-40 years, median age 23 years), all 40 patients were still receiving stiripentol (exposure: 3-24 years, median age 18 years), along with clobazam (40/40), valproate (39/40), and topiramate (21/40) co-therapy. Between the last visit before 15 years and the last visit in adulthood, stiripentol was interrupted in 5 patients (2 for AEs), but reintroduced following seizure aggravation.

At the last visit in adulthood, 37 of 40 patients still had generalized tonic-clonic seizures, but none still had status epilepticus (versus 3 at the last visit before 15 years) and only 1 had myoclonia. During adulthood, generalized tonic-clonic seizure frequency and duration continued to decrease ($P = 0.02$, $P = 0.008$) and 10 patients experienced seizure-free periods ≥ 1 year (up to 5 years) (**Table 14**).

All patients already had intellectual disability at the last visit before 15 years, but impairment was more severe at the last visit in adulthood ($P = 0.03$). Furthermore, neurological status and gait had declined (2 patients became bedridden) and behavior had worsened ($P < 0.0002$). Nevertheless, the 33 patients who had commenced on stiripentol prior to age 15 years tended to have better seizure outcomes in mid-adulthood than the 7 who started stiripentol at age 15 years or later, or stiripentol-naïve subjects reported in the literature.

Table 14. Clinical outcomes (Chiron *et al,* 2018)

Endpoint	Last visit before age 15 years n = 33	Last visit before adulthood (A) n = 40	Last visit in adulthood (B) n = 40	Significant changes at adulthood (A vs B)*
STP treatment: n; median dose (Q1-Q3), mg/kg/d	n = 33; 39 (33 - 43)	n = 40; 34 (24 - 42)	n = 40; 25 (15 - 33)	$P = 0.0002$
STP duration, y, median (range)	9.4 (0.2 - 14)	10.9 (0.2 - 17)	18.2 (2.8 - 23.5)	$P < 0.0001$
Generalized tonic–clonic seizures, median past month seizure frequency (Q1-Q3)	3 (1 - 8)	4 (1.5 - 12)	3.5 (1 - 7)	$P = 0.0173$
Convulsive status epilepticus	3/31	4/37	0/37	N/A

N/A: Not Available. *Paired comparisons between last visit before adulthood and last visit at adulthood (40 patients) using Wilcoxon signed-rank test for continuous variables and exact McNemar paired test for discrete variables. Changes are statistically significant if $P < 0.05$.

Conclusions

- The efficacy and safety of the stiripentol/valproate/clobazam combination was maintained very long term into adulthood.
- Patients who started stiripentol at a younger age had better seizure outcomes in adulthood than those starting it later.
- Prolonged stiripentol therapy tends to positively impact the late prognosis of epilepsy, especially when initiated before adolescence.

E. Other supportive studies

One exploratory clinical trial (STEV) conducted in the 1990s suggested that stiripentol may have major efficacy in Dravet syndrome, which justified the initiation of a clinical development program in Dravet syndrome.

Following the STEV trial, two randomized, double-blind clinical trials in patients with Dravet syndrome were conducted: STICLO France and STICLO Italy.

Thereafter, 4 open-label studies were established to analyze real-life outcomes of stiripentol: STP-1, STILON, TAU-EAP (ATU de COHORTE), and DIAVEY.

Additional studies assessing the efficacy and safety of stiripentol have been published, including one open-label interventional trial (Inoue *et al,* 2009), several cohort retrospective analyses (Thanh *et al,* 2002; Wirrell *et al,* 2013; De Liso *et al,* 2016; Chiron *et al,* 2018; and Yildiz *et al,* 2018), and one long-term prospective, observational open-label study (2003–2015) (Myers *et al,* 2018).

The supportive studies consistently demonstrate the maintenance of stiripentol efficacy over time (when combined with valproic acid and clobazam), and even into adulthood. Prolonged stiripentol therapy tends to positively impact the late prognosis of epilepsy, especially when initiated before adolescence.

Similarly, in terms of safety and tolerability, supportive studies showed similar findings compared with pivotal studies.

An overview of all individual trials evaluating stiripentol in Dravet syndrome patients is presented in **Table 15.**

Table 15. Overview of several clinical studies on stiripentol

Study	Design	Treatments	Sample size and length of follow-up	Primary endpoints	Secondary endpoints	Main efficacy results
Single-blind, exploratory trial in patients with Dravet syndrome and other epilepsies (*Discovery of STP efficacy in Dravet syndrome*)						
STEV 1992*	Multicenter (2 centers in France), single-blind, add-on therapy	**First treatment period (4 weeks):** STP administered at a dose of 60 mg/kg/day from Day 1 to Day 28 given in 2 to 3 divided doses **Second treatment period (8 weeks):** On Day 29 the dose of STP could be increased up to 90 mg/kg/day Median STP dose: 62.9 mg/kg/day	STP: 24 (with DS) STP: 202 (non-DS) Follow up: 4-week placebo run-in followed by STP treatment for 12 weeks	Responder rate (responders defined as patients with at least 50% decrease in seizure frequency or who became seizure-free)	• Percentage change from baseline in seizure frequency • Number of Dravet syndrome patients judged to be seizure-free	**First trial in which STP was found effective in Dravet syndrome** Dravet Syndrome responders: 16/20 (80.0%) [95% CI 62.5 – 97.5] Other epilepsies: marginal response (25-30%)
Open-label, short- and long-term trials in patients with Dravet syndrome and other epilepsies						
STILON 1999*	Multicenter (39 centers in France), open-label, add-on to other AEDs Conducted between June 1999 and November 2003 In January 2003, STILON was closed, and patients with Dravet syndrome were transferred to a TAU-EAP trial (see below)	STP was administered orally at a flexible dose depending on efficacy and safety as judged by the investigator, but could not exceed 4,000 mg/day Median STP dose: 41.8 mg/kg/day	STP: 45 (with DS) STP: 110 (non-DS) (27 had been enrolled in STICLO France, 14 had been enrolled in STEV, and 4 had received STP on a compassionate basis) Follow up: Up to several years	Long-term safety of STP	• Frequency of monthly seizure at study end • Evolution of epileptic status • Qualitative efficacy assessment at each visit	17.8% (8/45) of DS patients were found to be seizure-free at the end of study Efficacy was maintained over 3 years of treatment: mean (±SD) generalized clonic or tonic-clonic seizure frequency was 5.9 ± 8.05 at enrollment in STILON and 6.8 ± 11.6 at end of treatment
TAU-EAP (ATU de COHORTE) 2007*	Multicenter (77 sites in France), open-label, add-on to other AEDs	STP 50 mg/kg/day divided into 2 or 3 doses per day (dosage could be increased to 75 mg/kg/day and further to a maximum of 100 mg/kg/day) Median STP dose: 54.6 mg/kg/day	STP: 272 (with DS) (210* analyzed of whom 103 previously treated with STP and 34 participated in other STP trials such as STEV, STICLO, STILON) Follow up: Up to several years (patients evaluated at least once per year) *Sixty-two patients in TAU-EAP completed only the baseline visit and did not receive study drug	Safety of STP treatment	• Change in the total frequency of seizures from baseline to the end of treatment	Efficacy was maintained over 3 years of treatment. Patients who had ≥4 seizures per month (N=53) experienced a 54% decrease in seizure frequency from start to end of STP treatment 15 of 210 (7.1%) patients were prematurely withdrawn from the trial, including 7 for lack of efficacy

**Additional supporting data (internal source) that are not presented in the current DIACOMIT® prescribing information*

Table 15. Overview of several clinical studies on stiripentol (cont'd)

Study	Design	Treatments	Sample size and length of follow-up	Primary endpoints	Secondary endpoints	Main efficacy results
STP-1 2010*	Multicenter (11 centers in Japan), open-label, add-on to other AEDs **Group 1** (N=20): STP-naïve, ≤ 18 years of age **Group 2** (N=4): STP naïve, > 19-30 years of age **Group 3:** (N=6): Treated with STP, 1-30 years of age	**Dose adjustment period:** STP was administered (oral route) at the initial dose of 20 mg/kg/day, gradually increased by 10 mg/kg/day every week up to a maximally tolerated dose or up to 50 mg/kg/day **Maintenance period:** STP was administrated at best dose for 12 weeks **Long-term administration period:** for those whom STP was judged to be effective. STP dose can be increased/reduced Median STP dose: 48.9 mg/kg/day	STP: 30 (with DS) Trial comprised of 5 periods: • Baseline (4 weeks) • Dose adjustment (4 weeks) • Dose maintenance (12 weeks) • Long-term administration (40 weeks), a period of up to 52 weeks of treatment, including the fixed-dose period • Continuous evaluation	The percentage of responders for clonic or tonic-clonic seizures during the 3rd period of the STP dose-maintenance period (a responder = subject who showed a ≥50% decrease in the total frequency of seizures per 30 days compared to the seizure frequency at baseline)	• The percentage of subjects who discontinued the study • Total number (per 30 days) of clonic seizures or tonic-clonic seizures during the dose-maintenance period (1st, 2nd and 3rd periods) and long-term administration period • The rate of change, dose change and responder rate compared to the baseline period	Group 1 & 2: 66.7% responders Mean percent change from baseline: Group 1 & 2: -57 ± 30.9% In addition to clonic and tonic-clonic, other types of seizures (myoclonic; partial complex; absences) also responded to STP (80% decreases in other seizure frequency) Response maintained over ≥ 52 weeks
**Additional supporting data (internal source) that are not presented in the current DIACOMIT® prescribing information*						
Additional published studies of STP in patients with Dravet syndrome						
Thanh *et al*, 2002	Single-center, open-label, add-on to other AEDs Conducted between May 1996 and March 2000 (retrospective cohort analysis)	STP was an orally administered add-on to other AEDs. The dose of STP ranged from 50 to 100 mg/kg/day, administered in 2 or 3 divided doses using 250 mg or 500 mg capsules STP dose: 50-100 mg/kg/day	STP: 46 (24 participated in previous STP clinical trials) Follow up: Up to several years (median 3-years)	Response to treatment (defined as marked efficacy if, between the last 3 months before the start of STP and the last 3 months before the final visit, the 3 following criteria were met: • >50% decrease in frequency of seizures; • >50% decrease in duration of seizures; • disappearance of status epilepticus	• Seizure duration • Number of status epilepticus • Percentage of patients who became free of status epilepticus	Efficacy results showed a significant (P<0.001) reduction of seizure frequency and duration compared to baseline (P<0.001) The number of status epilepticus was reduced by 54% 10/46 (22%) of patients were status epilepticus free for the duration of follow-up

Table 15. Overview of several clinical studies on stiripentol (cont'd)

Study	Design	Treatments	Sample size and length of follow-up	Primary endpoints	Secondary endpoints	Main efficacy results
Inoue *et al*, 2009	Multicenter (6 centers in Japan), open-label	**Early period (4 weeks):** administration of STP at a dose of 50 mg/kg/day or 1,000 mg/day + AEDs at fixed dose. **Late period (4 weeks):** STP up to 100 mg/kg or 4,000 mg + AEDs at fixed dose. Mean STP dose: Late period: 59 mg/kg/day for patients 1 to 8 years of age	STP: 25 Follow up: 4 week baseline, STP added on at fixed dose (doses of concomitant AEDs adjusted), then 4 weeks treatment (early period); followed by adjustment of STP (higher dose) and other AEDs, then 4 weeks treatment (late period)	Number of responders defined as those with ≥ 50% reduction in the number of seizures during the treatment period compared to baseline	• Percent reduction in seizure frequency • Number of episodes of seizure clustering and status epilepticus • Duration of seizures	Early period: 61% responders Late period: 48% responders
De Liso *et al*, 2016	Single center (Necker Hospital in Paris, France); cross-sectional patient clinical characteristic retrospective review	• Polytherapy including different AEDs • Patients were mostly treated with triple therapy (STP combined with VPA and CLB in 91% of patients) • STP doses ranged from 35 to 50 mg/kg/day (mean 42 mg/kg/day)	54 patients of whom 92% (49) were prescribed STP Follow-up: up to 22 years (median 8 years)	Number of patients at the last follow-up classified as: • Having seizure daily • Having seizure weekly (defined as > 3/month) • Having seizure monthly (1–3/month) • Having seizure yearly (< 1/month) • In seizure remission	Number of patients at the last follow-up: • With seizures classified per seizures type (tonic-clonic, clonic focal, atypical absences, myoclonic) • With seizures classified per seizure duration (< 1 min, 1-5 min, > 5 min) • Classified according to intellectual disability (no disability, mild, moderate, severe)	Frequency of seizures at the last follow-up: • daily: 0% (0/54) • weekly: 37% (20/54) • monthly: 39% (21/54) • yearly: 20% (11/54) • seizure remission: 4% (2/54)
Myers *et al*, 2018	Multicenter (clinics in Australia and in the UK), open-label observational study	STP in dose up to 67 mg/kg/day or a maximum of 4 g per day + other AEDs (doses for clobazam and sodium valproate were kept below 0.5 mg/kg/day and 30 mg/kg/day respectively, when possible)	STP: 41 (41 patients with generalized tonic-clonic seizures 20 with focal seizures and 27 patients with status epilepticus)* Median duration of treatment was 37 months (interquartile range 13.5–66 mo, absolute range 2–141 mo) with 29 of 41 patients still on therapy at the time of most recent follow-up *patient may suffer from more than 1 condition	No. patients with ≥50% reduction in: • generalized tonic-clonic seizures • focal seizures • status epilepticus at the last follow-up visit (long-term)	No. patients with ≥50% reduction in: • generalized tonic-clonic seizures • focal seizures at 3 months after treatment initiation	At the last follow-up, patients with ≥50% reduction in: • generalized tonic-clonic seizures: 49% (20/41) • focal seizures: 55% (11/20) • status epilepticus: 41% (11/27) After 3 months, patients with ≥50% reduction in: • generalized tonic-clonic seizures: 56% (23/41) • focal seizures: 55% (11/20)
Yildiz *et al*, 2018	Single center (Istanbul, Turkey) retrospective study	STP mean maximum tolerated dose: 33.2 mg/kg/day (range: 31 to 40 mg/kg/day)	STP: 21 Mean duration of STP use: 41.2 mo (range: 24 to 64 mo)	• Number of responders defined as those with ≥ 50% reduction in the number of seizures • Frequency of status epilepticus	N/A	In 12 patients (57%), the seizure frequency decreased by more than 50%, and 2 of them were seizure-free. Status epilepticus was not recorded after STP treatment in 8 of 11 patients with status epilepticus

DIACOMIT®

(stiripentol) *250 mg, 500 mg*

capsules or powder for oral suspension

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