Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Stiripentol

Proprietary Product Name: Diacomit

Sponsor: Emerge Health Australia Pty Ltd

November 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AAT	Alpha-1 antitrypsin protein
ACM	Advisory Committee on Medicines
AE	Adverse event
AED	Anti-epileptic drug
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutical Classification System
CHMP	Committee for Medicinal Products for Human Use (EU)
CI	Confidence interval
CLB	Clobazam
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CMI	Consumer Medicines Information
C_{min}	Minimum plasma concentration
CNS	Central nervous system
CYP1A2	Cytochrome P450 1A2
CYP2B/3A	Cytochromes P450 2B/3A
EMA	European Medicines Agency (EU)
EU	European Union
EU-RMP	European Union–Risk Management Plan
FaSSIF	Fasted state simulated intestinal fluid
FeSSIF	Fed state simulated intestinal fluid

Abbreviation	Meaning
GABA	Gamma (γ)-aminobutyric acid
GGT	Gamma(γ)-glutamyl transferase
GIT	Gastrointestinal tract
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practice(s)
h	Hour(s)
ICH	International Conference on Harmonisation
ISE	Integrated Summary of Effectiveness
ITT	Intention to treat
LFT	Liver function test
MRT	Mean residence times
NCLB	Norclobazam
OATP1B1	(Solute carrier) organic anion transporter family member 1B1
OAT3	(Solute carrier) organic anion transporter family member 3
OR	Odds ratio
P-gp	P-glycoprotein
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per protocol
PSUR	Periodic safety update report
QSAR	Quantitative structure-activity relationship
RMP	Risk management plan
SAE	Serious adverse event
SCN1A	Sodium voltage-gated channel alpha subunit 1
SGF	Simulated gastric fluid
SMEI	Severe myoclonic epilepsy in infancy (also known as Dravet

Abbreviation	Meaning
	syndrome)
SS	Steady state
STP	Stiripentol
T_{max}	Time of maximum plasma concentration
$T_{1/2}$	Biological half-life
ULN	Upper limit of normal
US	United States
V/F	Apparent volume of distribution
VPA	Sodium valproate

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	11 September 2019
Date of entry onto ARTG:	13 September 2019
ARTG numbers:	281461, 281460, 281294 and 280985
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Active ingredient:	Stiripentol
Product name:	Diacomit
Sponsor's name and address:	Emerge Health Pty Ltd 22 Gillman St Hawthorn East VIC 3123
Dose forms:	Capsule and powder
Strengths:	250 mg and 500 mg
Containers:	Bottle and sachet
Pack size:	60
Approved therapeutic use:	*Diacomit is indicated for adjunctive treatment of generalised tonic-clonic and clonic seizures associated with severe myoclonic epilepsy in infancy (SMEI, also known as Dravet syndrome) in patients whose seizures are not adequately controlled with a benzodiazepine (usually clobazam) and valproate.*
Route of administration:	Oral
Dosage:	The dose of stiripentol is calculated on a mg/kg body weight basis. It is recommended to split the daily dose in two or three daily intakes (totalling the daily recommended dose per kg and per day). 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. Stiripentol dosage escalation should be gradual, starting with 20 mg/kg/day for 1 week, then 30 mg/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.

For further information refer to the Product Information (PI).

Product background

This AusPAR describes the application by Emerge Health Pty Ltd (the sponsor) to register Diacomit (stiripentol) for the following proposed indication:

> *Diacomit is intended for the treatment of severe myoclonic epilepsy in infancy (SMEI also known as Dravet syndrome).*

Epilepsy is a chronic neurological disorder characterised by intermittent, synchronised, abnormal electrical activity in part of the brain, resulting in localised or generalised activation of motor manifestations (for example, seizures), sensory manifestations (for example, sensory impressions), autonomic manifestations (for example, salivation) or complex manifestations (for example, cognitive or emotional). Seizures can be provoked or unprovoked. Primary generalised seizures involve the entire cortex from the seizure onset, whereas partial seizures are defined by their focal onset, regardless of their eventual extent or severity, that is, they can develop into a secondary generalised seizure by recruiting other parts of the brain. Partial seizures can be idiopathic, be caused by structural lesions (for example, tumour, scar, developmental abnormality) or be caused by regionally expressed genetic defects (for example, channelopathies).

Dravet syndrome (also known as severe myoclonic epilepsy of infancy (SMEI)) is a genetic epilepsy syndrome and an epileptic encephalopathy. It was first described by Charlotte Dravet, a French neuropsychiatrist, in 1978. Most patients with Dravet syndrome (70 to 80%) have mutations in the SCN1A gene;[1] which affects the associated voltage-gated sodium channel alpha-1 subunit protein.[2,3]Seizures associated with Dravet syndrome could be generalised, partial or myoclonic.

There is a variety of options to treat epileptic disorders. For Dravet syndrome specifically the main objectives are to reduce the length and number of seizures; to prevent status epilepticus and to improve quality of life overall. Both pharmacological and non-pharmacological measures should be used:

- Non-pharmacological management includes adherence to a ketogenic diet, neuromodulation techniques (for example, vagus nerve stimulation or deep brain stimulation), and avoidance of seizure triggers.
- Pharmacological management employs the use of certain antiepileptic drugs while avoiding others: valproate, clobazam, topiramate, levetiracetam, phenobarbital, ethosuximide, and bromides can be used, whereas carbamazepine and carbamazepine

[1] The sodium voltage gated channel alpha subunit 1 (SCN1A) gene codes for the SCN1A protein of the same name.
[2] Depienne, C. et al. (2009). Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients. J Med Genet, 2009; 46:183–191.
[3] Marini, C. et al (2009). SCN1A duplications and deletions detected in Dravet syndrome: implications for molecular diagnosis. Epilepsia, 2009; 50:1670–1678.

analogues; phenytoin, and lamotrigine should be avoided, as they can worsen the condition in most patients with Dravet syndrome.

Valproate with or without clobazam is typically used as first-line treatment. In some Dravet syndrome patients, the first-line therapies are not sufficient and additional therapy is needed. Stiripentol is a second generation anti-epileptic drug targeting generalised clonic and tonic-clonic seizures which may be associated with Dravet syndrome. While its exact mechanism of action is unknown, two main mechanisms of action are proposed by the sponsor:

- Positive modulation of the γ- GABAergic system;[4] (direct effect); and
- Hepatic clearance isozyme inhibition (indirect effect; reduction in clearance of concomitantly administered anticonvulsants which potentiates their effects).

Regulatory status

Diacomit (stiripentol) is a new chemical entity for Australian regulatory purposes.

On 23 June 2016, the TGA designated stiripentol (Diacomit) as an Orphan drug for:

> '*the treatment of severe myoclonic epilepsy in infancy (SMEI also known as Dravet syndrome)'.*

At the time the TGA considered this application, a similar application had been approved in the European Union (EU; via the centralised procedure), Canada and Japan, and had been submitted to the United States (US) and to Switzerland (see Table 1).

Table 1: International regulatory status of Diacomit (stiripentol) as of 15 July 2019

Region	Submission date	Status	Indication
EU (centralised procedure)	18 May 2005	Approved as conditional marketing authorisation on 4 January 2007. Switched to full marketing authorisation on 8 January 2014 (unlimited)	*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.*
Canada	8 October 2010	Approved 21 December 2012	*Diacomit (stiripentol) is indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate alone.*
Japan	6 January 2011	Approved 28 September 2012	*Diacomit is indicated for combination treatment with clobazam and sodium valproate for clonic seizure or tonic clonic seizure in patients with Dravet syndrome*

[4] Gabanergic pertains to the action of gamma (γ)-aminobutyric acid (GABA) or to the neural and/or metabolic pathways in which it functions.

Region	Submission date	Status	Indication
			for which clobazam and sodium valproate are not fully effective.
US	27 October 2015	Approved 20 August 2018	*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.*
Switzerland	9 November 2016	Approved 24 July 2018	*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.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2016-02336-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	31 October 2016
First round evaluation completed	26 April 2017
Sponsor provides responses on questions raised in first round evaluation	27 May 2017
Second round evaluation completed	21 August 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	2 July 2019
Sponsor's pre-Advisory Committee response	16 July 2019
Advisory Committee meeting	1-2 August 2019

Description	Date
Registration decision (Outcome)	11 September 2019
Completion of administrative activities and registration on ARTG	13 September 2019
Number of working days from submission dossier acceptance to registration decision*	242

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Approval is recommended for registration of the proposed product from a pharmaceutical chemistry perspective.

Bioequivalence study (capsule versus sachet)

This was a single centre, single dose, open label, randomised, 2 period, 2 sequence period crossover bioequivalence study between 2 x 500 mg stiripentol capsule versus 2 x 500 mg stiripentol powder for oral suspension sachet in 24 healthy male volunteers, under fed conditions.

Conclusion

Stiripentol powder for oral suspension sachet is not bioequivalent to stiripentol in capsule form with regards to the 90% confidence interval (CI) of the geometric mean ratio of maximum plasma concentration (C_{max}) being outside the acceptance criteria to conclude equivalence.

C_{max} of stiripentol in the powder in sachet is 23% higher than in the capsule dosage form. This information has been captured in the PI.

Biowaver of the 250 mg strength (for both capsule and powder for oral suspension sachet)

The bioequivalence study between capsule and powder in sachet were performed using only the 500 mg strength.

Nonclinical

The maximum recommended human dose is 50 mg/kg/day, which may be administered in 2 or 3 divided doses. Stiripentol is a pentenol derivative having no structural similarities in common with other known antiepileptic drugs (AEDs). Nonclinical studies were conducted over a period of 30 years, and some of the earlier studies (dating back to the mid 1970s) were undertaken before the introduction of Good Laboratory Practice (GLP) and International Council for Harmonisation (ICH) guidelines. However, the pivotal repeat dose toxicity studies were generally in accordance with the relevant ICH guideline for the

nonclinical assessment of pharmaceutical medicines and were GLP compliant. Studies conducted by the sponsor have been supplemented with published reports.

Summary of nonclinical evaluation report:

- There are some gaps and deficiencies in the nonclinical dataset which will need to be adequately addressed by clinical data, as detailed below.
- The primary pharmacology data is supportive of stiripentol activity for the proposed indication, although nonclinical data in support of the proposed combination (in particular, valproate) are limited.
- Adverse central nervous system (CNS) effects comparable to those seen with other anticonvulsant drugs are likely to be clinically relevant. Stiripentol is likely to interact with ethanol, benzodiazepines and barbiturates.
- The potential for adverse cardiovascular effects was not extensively investigated, with no human ether-à-go-go (hERG) potassium ion assay provided. There is limited evidence based on animal data for a lack of pro-arrhythmic potential for stiripentol alone. It is conceivable that stiripentol may enhance the pro-arrhythmic activity of co-administered drugs through pharmacokinetic interactions.
- The potential for interactions based on the induction of hepatic drug metabolising enzymes (most notably cytochrome P450 1A2 (CYP1A2), cytochromes P450 2B/3A (CYP2B/3A) and glucuronyl transferase) is uncertain.
- Stiripentol may also increase the systemic exposure of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), solute carrier organic anion transporter family member 1B1 (OATP1B1) and solute carrier organic anion transporter family member 3 (OAT3) substrates.
- In repeat dose toxicity studies, the identified target organs were the CNS, liver and kidney. Based on the modest exposure margins, these effects are of possible clinical relevance. The potential for increased toxicity due to co-administration with other drugs (including clobazam and valproate) was not investigated nonclinically. Although there was no evidence of human-relevant hepatotoxicity, stiripentol and clobazam each produce similar hepatotoxic effects in animals, and this together with stiripentol inhibition of clobazam metabolism may be a concern.
- Stiripentol is non-genotoxic, and the occurrence of hepatocellular adenomas and carcinomas in the mouse carcinogenicity assay is considered to be a species-specific effect resulting from hepatic enzyme induction, of unlikely clinical relevance.
- The proposed Pregnancy Category B1;[5] is not supported by the nonclinical evaluator, mainly based on the low estimated relative exposures achieved in the reproductive toxicity studies and adverse fetal effects. Category B3 is recommended.[6]
- The potential for phototoxicity was not adequately addressed in nonclinical studies.
- Two specified impurities were claimed to lack structural alerts for mutagenicity, when in fact they had not been subjected to quantitative structure-activity relationship (QSAR) analysis. This deficiency should be addressed by the sponsor.

[5] Pregnancy category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

[6] Pregnancy category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The nonclinical data provided for stiripentol and evaluated in this report have several limitations. Nonclinical support for the registration of Diacomit is conditional on the above deficiencies being adequately addressed by the relevant clinical investigations.

The Delegate subsequently commented that **t**he clinical aspects of the submitted dossier in respect of adverse effects and drug-drug interactions have been adequately assessed by the clinical evaluator, with appropriate recommendations in place.

Clinical

Pharmacokinetics

Studies providing pharmacokinetic (PK) information (general PK, bioequivalence and population PK) in the submission are shown in Table 3.

Table 3: Studies providing PK information

PK topic	Subtopic	Study ID	Primary aim
PK in healthy adults	General PK (single dose)	STIUNI (BC.337)	Pharmacokinetic parameters Pharmacokinetic linearity
	Enantiomer and racemate PK (single dose)	Greig (BC.287)	Pharmacokinetic profile of stiripentol R- and S-enantiomers Stiripentol racemate metabolism
	Bioequivalence † (single dose)	STIVAL (BC.481)	Relative bioavailability of stiripentol powder sachet for oral suspension, compared to stiripentol capsule
	Effect on CYP enzymes (multi-dose)	Pons (BC.345)	Effect of stiripentol on CYP1A2, CYP2D6 and CYP3A
	Food effect		No study conducted.
PK in special populations	Target population § (steady state), Single dose	STIPOP (STP167)	Steady state population pharmacokinetic parameters
	General PK data from efficacy studies in the target population § (steady state)	STICLO France (BC.299)	Pharmacokinetic parameters
		STICLO Italy (BC.385)	Pharmacokinetic parameters
		STP-1 (BC.609)	Pharmacokinetic parameters (including analysis of CYP2C19 genotypes)
	Hepatic/rena		No study conducted.

PK topic	Subtopic	Study ID	Primary aim
	l impairment		
	Elderly		No study conducted.
PK interactions			No study conducted.
Population PK analyses	Target population § (steady state)	STIPOP (STP167)	Steady state population pharmacokinetic parameters

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

- PK studies were conducted in healthy male volunteers aged from 19 to 38 years old.
- PK studies with stiripentol were not conducted in healthy children.
- Studies in the target population that provided PK data were mainly conducted in children with Dravet syndrome, but also in a small number of adults.
- Furthermore, the sponsor additionally relies on some literature sources (not evaluated for scientific rigour) to provide additional PK data, most notably: Levy *et al.* (1983);[7] Levy *et al.* (1984a);[8] Levy *et al.* (1984b);[9] May *et al.* (2012);[10] Ogungbenro *et al.* (2015);[11] Moreland *et al.* (1986).[12]

Summary of pharmacokinetics

After single oral, dose administration of 500, 1000, and 2000 mg of stiripentol, the mean C_{max} values were 2.63, 6.63 and 13.8 mg/L respectively (when a non-compartmental model was used). The corresponding time of maximum plasma concentration (T_{max}) values were 2.42, 2.42 and 2.96 h respectively (see Table 4). The mean residence times (MRT) for the 1000, and 2000 mg doses of stiripentol were 7.67 and 11.1 hours (h) respectively (STIUNI trial (Study BC.337); healthy male subjects).

Table 4: STIUNI trial (Study BC.337); Absorption data for stiripentol single doses (500, 1000, and 2000 mg) determined using a non-compartmental model

Parameter	STP 500 mg	STP 1,000 mg	STP 2,000 mg
Tmax (hr)	2.42 (0.76)	2.42 (1.00)	2.96 (1.01)
Cmax (mg/L)	2.63 (1.18)	6.63 (1.83)	13.8 (4.83)
AUC (mg/L·hr)	8.85 (3.77)	32.1 (10.17)	79.0 (24.2)

AUC = area under the concentration-time curve. AUC refers to $AUC_{0\text{-}t}$.

The mean ratios of dose-normalised area under the concentration time curve (AUC) for the 3 doses were: 4.03 for 1,000 mg/500 mg, 2.57 for 2,000 mg/1,000 mg and 9.63 for

[7] Levy, R.H. et al. (1983). Pharmacokinetics of stiripentol in normal man: evidence of nonlinearity. *J Clin Pharmacol*. 1983; 23: 523-533.
[8] Levy, R.H. et al. (1984). Michaelis-Menten Kinetics of Stiripentol in Normal Humans, *Epilepsia*, 1984; 25: 486-491.
[9] Levy, R.H. et al. (1984). Stiripentol kinetics in epilepsy: Nonlinearity and interactions, *Clin. Pharmacol. Ther*. 1984; 36: 661-669.
[10] May, T.W. et al. (2012). Concentrations of stiripentol in children and adults with epilepsy: the influence of dose, age, and comedication. *Ther Drug Monit*. 2012; 34:390-397.
[11] Ogungbenro K, and Aarons L; (2015). CRESim & Epi-CRESim Project Groups. A physiologically based pharmacokinetic model for clobazam and stiripentol in adults and children. *Pharm Res*. 2015; 32:144-57.
[12] Moreland, T.A. et al. (1986). The metabolic fate of stiripentol in man, Drug Metab Dispos, 1986; 14: 654-662.

2,000 mg/500 mg. The PK data supported a small degree non-linearity, that is, statistically significant more than proportional increases in C_{max} and the area under the concentration-time curve from dosing (time zero) to last measurable concentration (AUC_{0-t}). The absorption phase appears to be non-linear, but elimination appears to be linear.

A comparative bioavailability study (STIVAL trial; Study BC.481) in healthy male subjects also provided PK data after single oral dose administration of 1000 mg of stiripentol in either powder or capsule form.

Table 5: STIVAL trial (Study BC.481); Absorption data for stiripentol single doses (1000 mg only; powder versus capsule) determined using a non-compartmental model

	Test Sachet	Reference Capsule
T_{lag} (hr)	0.03 (0.12)	0.37 (0.33)
Tmax (hr)	2.96 (0.94)	2.94 (0.96)
Cmax (mg/L)	7.32 (2.10)	5.99 (1.75)
$AUC_{0-\infty}$ (mg/L·hr)	35.93 (11.94)	33.87 (11.84)
AUC_{0-t} (mg/L·hr)	32.97 (11.05)	30.23 (10.81)

- When the compartmental model was used, it was shown that a two-compartment model with zero order absorption provided the best fit to the data.
  - The lag time was 0.48 to 0.87 h;
  - Biological half-life ($T_{1/2}$) beta values were 4.4, 10.1 and 13.7 h from the lowest to the highest dose, but the beta half-live values for the two highest doses were not statistically significant (STIUNI trial; Study BC.337);
  - MRT, $T_{1/2}$ and area under the concentration-time curve from dosing (time zero) to infinity ($AUC_{0-\infty}$) were only determined for the 1000 and 2000 mg doses: MRT; 7.67 and 11.1 h, respectively; $T_{1/2}$; 7.8 (1.9) h and 11.0 (4.2) h, respectively; $AUC_{0-\infty}$; 40.6 (16) mg/L x h and 107 (35.7) mg/L x h, respectively (STIUNI trial/StudyBC.337);
  - The data (STIUNI trial/StudyBC.337) supported non-linearity (that is, more than proportional increases in AUC; the nonlinearity followed Michaelis-Menten kinetics in healthy volunteers, and also in the target population.[8] The ratio increased significantly with dose (Friedman's test, $p < 0.05$). The study authors concluded that the absorption of stiripentol was non-linear, but elimination was linear (compared with non-compartmental model above).
- Data after multiple dosing suggest that steady state can be achieved after a range of approximately 2 to 5 days of dosing. Half-live duration, apparent clearance and apparent volume of distribution increased with body mass and the associated dose (STIPOP trial). Therefore, smaller children with smaller doses will achieve steady state (SS) in the earlier part of the 2 to 5 day range.

Table 6: STIPOP trial (Study STP167); PK parameters in relation to body mass

Body weight (kg)	CL/F (L/hr)	V/F (L)	T1/2 (hr)
10	2.60 ± 0.18	32.0 ± 3.8	8.5 ± 1.3
20	3.51 ± 0.24	63.9 ± 7.7	12.6 ± 1.9
30	4.19 ± 0.29	95.9 ± 11.5	15.9 ± 2.4
40	4.74 ± 0.33	127.8 ± 15.3	18.7 ± 2.8
50	5.22 ± 0.36	159.8 ± 19.2	21.2 ± 3.2
60	5.65 ± 0.40	191.8 ± 23.0	23.5 ± 3.5

Source: [5.3.3.5: STP167, Appendix 16.1.10, Table 8.1.7-1]

SEs are based on bootstrap results (SD)

CL/F = apparent clearance, V/F = apparent volume of distribution, $t_{1/2}$ = biological half-life.

The Delegate commented that children will probably achieve SS in the later as opposed to the earlier part of the 2 to 5 day range.

- The above data revealed values for apparent volume of distribution in 35 children (1 to 17.6 years) with Dravet syndrome (receiving sodium valproate and clobazam additional to stiripentol):
  - The apparent volume of distribution was body mass-dependent and ranged from 32.0 to 191.8 L, as body weight increased from 10 to 60 kg;
  - For apparent clearance (CL/F), the coefficients of variation were 16% (inter-individual) and 32% (inter-occasion); and
  - Coefficient of variation was 23%.
- It appears that the non-linearity of stiripentol continues with multiple dosing. Clearance decreases with multiple dosing leading to increased plasma concentrations in line with Michaelis-Menten kinetics and therefore, steady state might be reached later than predicted from single dose half-life. Regarding accumulation, the sponsor states:

  > 'When one examines all the available information on level-dose relationship in children, no concern has emerged with that aspect of stiripentol dosing since the drug is generally introduced gradually, over a few weeks. A dose of 50 mg/kg/day yields a steady state concentration of approximately 10 mg/L as long as stiripentol is administered with non-inducing drugs such as sodium valproate and clobazam (a table in the clinical submission dossier).' '[…] the actual significance of 'unexpected' or 'more than proportional accumulation' appears to be limited, particularly in children.'

Delegate's comments on pharmacokinetics

- Reduction in dosing interval or dosage might be required in those with large body frame in order to avoid accumulation in multiple dosing. In regards to this the Delegate commented that:
  - There is extensive post-market experience, in which there was no overt evidence of accumulation issues with stiripentol.
  - There appears to be no known active metabolites of stiripentol.
  - Some of the provided PK data was derived from the target population (that is, children with Dravet syndrome) at steady state.
  - There is some available evidence, that there is no further accumulation after the steady state has been reached, for example, the physiologically based PK model for clobazam and stiripentol in adults and children conducted by Ogungbenro *et al*. (2015);[11] fitted to plasma concentration data obtained from the literature (Levy *et al*. (1983));[7] for single dosing, and Levy *et al*. (1984a);[8] for multiple dosing.
- The sponsor states that there is no evidence of a circadian rhythm on the PK of stiripentol.
- The sponsor reports that stiripentol is in Biopharmaceutical Classification System (BCS) Class II (high permeability, low solubility). Based on metabolic studies, the sponsor reports that it is likely that a very high percentage (approximately 90%) of an oral dose of stiripentol is absorbed. The following solubility values were reported:
  - Water (pH 1 to 7.5): 0.045 mg/L (between 0.04 and 0.05);
  - SGF (simulated gastric fluid) (pH = 1.1) = 0.0432 mg/mL;
  - FeSSIF (fed state simulated intestinal fluid) (pH = 5.0) = 0.0811 mg/mL;

  - FaSSIF (fasted state simulated intestinal fluid) (pH = 6.5) = 0.2009 mg/mL.

- The study by Levy *et al.* (1983);[7] determined the extent of plasma protein binding and blood-to-plasma ratio in human samples. Mean values of unbound fraction determined in spiked samples were 0.8 ± 0.04% at 30 mg/L and 1.04 ± 0.05% percent at 60 mg/L. The mean value of unbound fraction determined in samples from dosed subjects was 1.01 ± 0.24%, while the stiripentol concentration range was 1.69 to 3.83 mg/L. The blood to plasma ratio was determined for each subject using samples drawn at 1 and 2 hours after dosing with the 1200 mg dose. The mean value was 0.58 ± 0.08 (that is, close to the haematocrit value). Based on the above results, it can be concluded that stiripentol is highly plasma bound (approximately 99%).
- Absolute bioavailability of stiripentol was not determined, as no intravenous formulation was available for testing.
- The pivotal clinical trials used the same formulations as proposed in this application, namely the capsule and sachet (powder) form.
- After a single dose administration, mean C_{max} of stiripentol was 23% higher after the sachet formulation (7.32 µg/mL) compared to the capsule formulation (5.99 µg/mL), but the mean AUC_{0-t}, $AUC_{0-\infty}$, and T_{max} were not statistically different (STIVAL trial; Study BC.481).
- A prediction of C_{max} values at steady state (STIVAL trial; StudyBC.481), showed that the single dose difference in C_{max} between sachet and capsule decreased when dosed more than once daily (16.3% difference with once daily dosing, 13.5% difference with twice daily dosing, and 12.3% difference with three times daily dosing).
- The sponsor states that the effect of food on the bioavailability/main absorption parameters of stiripentol has not been studied. However, the proposed PI contains the following wording: 'The powder should be mixed in a glass of water and should be taken immediately after mixing during a meal. Stiripentol must always be taken with food due to rapid degradation following exposure to gastric acid in an empty stomach.'

Drug interactions

All studies relevant to this application have included clobazam and valproate, and subsequently the measured PK data of stiripentol in the target population (patients with Dravet syndrome) were always in relation to co-administration to these medicines.

- Levetiracetam (no CYP metabolism): no significant interaction based on the CYP system is expected. There is no actual study data, but a significant interaction is unlikely.
- Phenobarbital (CYP2C9, 2C19, 2E1 substrate; CYP1A2, 2A6, 2B6, 2C8, 2C9, 3A4 inducer; CYP2A6 inhibitor; P-glycoprotein inducer/substrate): may decrease the serum concentration of stiripentol. Stiripentol may increase the serum concentration of phenobarbital. Study data (literature) showed that phenobarbital clearance decreased in the presence of stiripentol 2400 mg/day.
- Ethosuximide (CYP3A substrate): may increase the serum concentration of CYP3A4 substrates (such as stiripentol). There is no actual study data.
- Bromide: no significant interaction was observed in Study STP-1.

In Dravet syndrome, the following interactions may exist for these drugs which are much less commonly used:

- Carbamazepine (CYP3A substrate; CYP3A5 inhibitor; CYP3A4, 3A5 inducer; P-glycoprotein inducer): stiripentol may increase the serum concentration of carbamazepine. Study data (literature) showed that stiripentol reduced carbamazepine clearance by approximately 50%.

- Phenytoin (CYP2C9, 2C19 substrate; CYP1A2, 3A4, 3A5 inducer; P-glycoprotein inducer): may decrease serum concentration of stiripentol. Stiripentol may increase the serum concentration of phenytoin. Study data (literature) showed that stiripentol reduced phenytoin clearance.

The clinical evaluator states that there appears to be no data on the potential interactions with the contraceptive pill contrary to the relevant EU guideline.[13] However, given the knowledge about CYP interactions, the following can be reasonably expected: CYP3A4 inhibitors, such a stiripentol, may increase the exposure of oestrogen or progestin containing contraceptives when used concomitantly. Oestrogen or progestin containing contraceptives may increase the exposure of CYP1A2 or CYP3A substrates, such a stiripentol. The clinical significance of these potential interactions is not known.

Pharmacodynamics

- No clinical studies providing pharmacodynamic information were submitted with this application.
- No definite data on the relationship between plasma concentration and effect is available.
- Absence of clinical pharmacodynamic studies is acceptable given the provision of extensive efficacy and safety data.

Dose finding studies

- No formal dose-finding study has been conducted with stiripentol in Dravet syndrome patients.
- No pivotal study investigated more than one dose regimen.

Efficacy

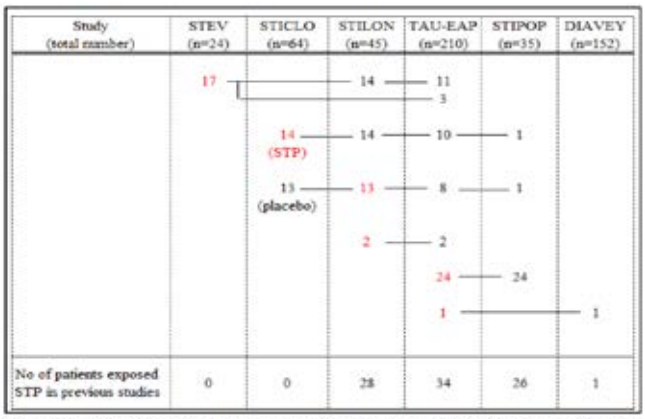
Studies identified as providing evaluable efficacy data in the submission:

- Two pivotal or main efficacy studies conducted in children with Dravet syndrome using stiripentol as add on therapy to valproate and clobazam treatment;
- Five supportive efficacy studies involving children.

A number of patients in the clinical studies took part in more than one study. The patient disposition across those studies is shown in Table 7.

[13] European Medicines Agency (EMA), Committee for medicinal products for human use (CHMP), Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders, CHMP/EWP/566/98 Rev.3, 26 July 2018.

Table 7: Patient disposition across stiripentol clinical studies



Red represents First Exposure to STP in the 71 patients who were enrolled in more than 1 clinical trial

Pivotal or main studies (STICLO trials: STICLO France and STICLO Italy)

Phase III, multicentre, randomised, double blind, parallel group, placebo controlled, comparative superiority clinical trials in children with Dravet syndrome (SMEI) evaluating the efficacy of stiripentol as add-on therapy to (already) optimised valproate and clobazam treatment.

The design of both studies is very similar with the protocol being essentially identical. Consequently, the two studies have been grouped together in this report.

The sponsor has provided a justification for pooling some results of the STICLO trials:

- Similar subject population;
- Same design (including endpoint and dosage regimen);
- Favourable statistical assessment of data pooling ability (based on demographic data and the primary endpoint).

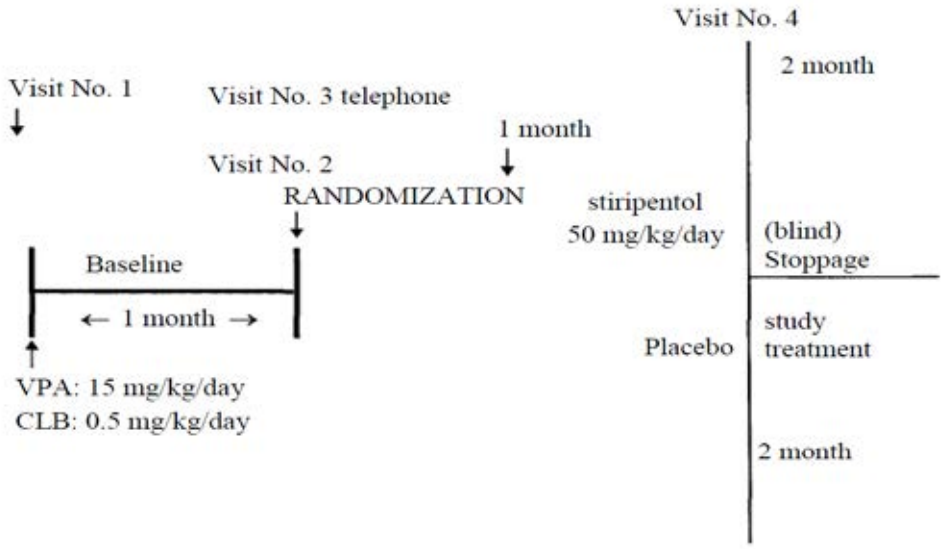
The clinical evaluator considered the justification for pooling results was acceptable.

The primary efficacy objective was to demonstrate the efficacy of stiripentol as add-on therapy in combination with clobazam and valproate in children with SMEI and whose seizures were severe and refractory (the STICLO Italy trial protocol specified clonic seizures).

The secondary outcome objectives were to:

- Study the safety profile of this treatment; and
- Document steady state plasma concentrations of stiripentol as well as those of concomitant medications before and after treatment with stiripentol.

Figure 1: Outline of the study design schema for both STICLO trials (France and Italy)



VPA = sodium valproate; CLB = clobazam

Primary efficacy outcome

STICLO France

Responders are shown in Table 8(intention-to-treat analysis set) and Table 9 (per-protocol analysis set).

Table 8: STICLO trial France; Responders, intention-to-treat analysis set (n = 41)

	responders	frequency	95% CI of responder percentage
Stirpentol, N=21	15	71.4 %	52.1 – 90.7
Placebo, N=20	1	5.0 %	0 – 14.6

The risk (treatment success) difference between treatment groups was 66.4% (95% CI: 44.8%, 88.4%) (Odds ratio (OR) = 47.5) (P < 0.00002).

Table 9: STICLO trial France; Responders, per-protocol analysis set (n = 16)

PP	Responders	Frequency	95% CI of responder percentage
Stiripentol	15/20	75%	56.0 - 94.0
Placebo	1/16	6.25%	0.0 - 18.1

The risk (treatment success) difference between treatment groups was 68.7% (OR = 45.0).

The above does not contain an analysis of the difference between the two groups.

STICLO Italy

Responders are shown in (intention-to-treat analysis set) and (per-protocol analysis set).

Table 10: STICLO trial Italy; Responders, intention-to-treat analysis set (n = 23)

	Responders	Frequency	95% CI for responders percentage
Stiripentol	8/12	66.7%	34.9%-90.2%
Placebo	1/11	9.1%	0.0%-41.3%

The risk (treatment success) difference between treatment groups was 57.6%; OR = 20.00 (P = 0.009).

Table 11: STICLO trial Italy; Responders, per-protocol analysis set (n = 20)

	Responders	Frequency	95% CI for responders percentage
Stiripentol	8/11	72.7%	39%-94%
Placebo	1/9	11.1%	0.281%-48.2 %

The risk (treatment success) difference between treatment groups was 61.6%; OR = 21.33 (p ≅ 0.01).

Pooled STICLO trial France/STICLO trial Italy

Responders are shown in Table 12, odds ratios are shown in Table 13.

Table 12: Pooled STICLO trial France/STICLO trial Italy; Responders, intention-to-treat analysis set (n = 64)

	STICLO France N=41		STICLO Italy N=23		STICLO Total N=64	
	STP N=21	Placebo N=20	STP N=12	Placebo N=11	STP N=33	Placebo N=31
Percentage change from baseline in seizure frequency*						
n	21	20	11	9	32	29
Mean ± SD	-62.0 ± 51.2	12.1 ± 44.4	-74 ± 26.7	-13 ± 62.0	-66 ± 44.2	4.3 ± 50.7
Median	-87.5	12.1	-81.2	-27.4	-84.4	-5.8
Min – Max	-100 – 72.6	-75 – 119	-100 – -33	-87 – 140	-100 – 72.6	-87 – 140
p value [1]	0.0003		0.0056		<0.0001	
Responder analysis†						
No of responders/total (Responder Rate) [95% CI]	15/21 (71.4%) [52.1 – 90.8]	1/20 (5.0%) [0.0 – 14.6]	8/12 (66.7%) [40.0 – 93.3]	1/11 (9.1%) [0.0 – 26.1]	23/33 (69.7%) [54.0 – 85.4]	2/31 (6.5%) [0.0 – 15.1]
p value [2]	<0.0001		0.0098		<0.0001	

Source: [5.3.5.3; ISE, Table 3-8]
*: Frequency of generalized tonic-clonic or clonic seizures.
†: Responder is defined as a patient with a ≥ 50% decrease in frequency of generalized tonic-clonic or clonic seizures.
[1] Wilcoxon Test; [2] Fisher's Exact Test.
CI=confidence interval; SD=standard deviation.

The risk (treatment success) difference between pooled treatment groups was 63.2% (P < 0.0001). 69.7% of subjects in the stiripentol group qualified as responders versus 6.5% in the placebo group.

Table 13: Odds ratios, (not adjusted for covariates) for pooled treatment response

	Odds ratio (reported by sponsor)	Odds ratio (ITT population)	Odds ratio (PP population)	Clinical evaluators comment
Pooled STICLO trials	34.50	33.35	33.06	

	Odds ratio (reported by sponsor)	Odds ratio (ITT population)	Odds ratio (PP population)	Clinical evaluators comment
STICLO trial France	47.50	47.50*	45.00	The sponsor appeared to have used the intention to treat (ITT) population for the pooled odds ratio calculation.
STICLO trial Italy	21.33	20.00	21.33*	The sponsor appeared to have used the per protocol (PP) population for the pooled odds ratio calculation.
*odds ratio matches the odds ratio reported by the sponsor				

Additional *post hoc* covariate adjusted analysis:

- Assessed a possible efficacy effect of increased plasma concentrations of clobazam, or its active metabolite, norclobazam, due to the presence of stiripentol.
- Used a logistic model with treatment response as the dependent variable and, treatment group (stiripentol or placebo) as the independent variable.
- The following scenarios were considered:
  - Stiripentol and no adjustment for clobazam or norclobazam;
  - Stiripentol and a single covariate (change in clobazam (or norclobazam) plasma concentrations from Baseline;
  - Stiripentol and two covariates (change in clobazam and norclobazam plasma concentrations from Baseline).
- Only clobazam and its active metabolite, norclobazam, were considered in the logistic analysis. An analysis to adjust for valproate was not conducted, as valproate levels only increased marginally due to stiripentol administration, at least relative to norclobazam levels.
- Odds ratios of the treatment effect (adjusted for clobazam, norclobazam, and clobazam + norclobazam) (with corresponding 95% confidence interval (CI)) were the outputs. Summary of odds ratios adjusted and unadjusted for the impact of clobazam and norclobazam on the response to stiripentol is shown in Table 14.

Table 14: Odds ratios adjusted and unadjusted for the impact of clobazam and norclobazam on the response to stiripentol

	STICLO (France and Italy) Odds (95% CI)	STICLO France Odds (95% CI)	STICLO Italy Odds (95% CI)
No Adjustment	34.5 (6.76 – 176.08)	47.5 (5.15 – 438.49)	21.3 (1.81 – 251.26)
Adjusted for CLB	23.8 (4.53 – 125.42)	40.0 (3.56 - 448.45)	16.9 (1.49 – 191.46)
Adjusted for NCLB	19.8 (2.59 – 151.54)	17.6 (1.23 – 251.77)	28.6 (0.90 – 909.40)
Adjusted for CLB & NCLB	18.2 (2.34 – 141.04)	20.0 (1.32 – 303.33)	28 (0.89 – 883.02)

CLB = clobazam, NCLB = norclobazam.

The clinical evaluator stated that the odds ratio provided for STICLO trial France were derived from the ITT population; the odds ratios for STICLO trial Italy were derived the PP population. If pooled ITT data (STICLO trials France + Italy) had been used, all the pooled

odds ratio values would have been slightly lower (with 33.35 as the unadjusted pooled odds ratio). Out of all three sets of odds ratios, only the STICLO France column reflects an accurate result for the ITT population.

Despite the population choice inaccuracies, the results essentially could be interpreted such that even though the stiripentol may have an effect on clobazam and/or norclobazam levels, stiripentol appears to have an effect on seizure activity itself. This is further supported by further *post hoc* analyses showing:

- No statistically significant difference of clobazam or norclobazam minimum plasma concentration (C_{min}) and AUC_{inf} values in responders compared to non-responders (STICLO trials France/Italy and Study STP-1).
- No statistically significant difference in responder proportion when comparing patients with or without concomitant clobazam treatment (DIAVEY and Laux chart review).

Other efficacy outcomes

Decrease in seizures by at least 50%

- STICLO trial France
  - Intention-to-treat analysis set (n = 41): occurred in 71.4% (15 out of 21) and 5.0% (1 out of 20) of the stiripentol and placebo groups respectively. Reported that 9 (42.6%, 9 out of 21) patients in the stiripentol group were completely seizure free compared with 0 (0%) in the placebo group.
  - Per-protocol analysis set (n = 36): results are shown in Table 15.

Table 15: STICLO trial France; Variation in the number of seizures, per protocol analysis set

	stiripentol N = 20	placebo N = 16	significance level chi 2
decrease = 100 %	9 (45%)	0	
decrease >50% < 100%	6 (30%)	1 (6%)	
decrease <50%	3 (15%)	5 (31%)	p < 0.01
increase <50%	2 (10%)	8 (50%)	
increase >50%	0	2 (13%)	

- STICLO trial Italy
  - Per protocol analysis set (n = 20): occurred in 73% (8 out of 11) and 11% (1 out of 20) of the stiripentol and placebo groups respectively (as per Table 16). Reported that 3 (27%, 3 out of 11) patients in the stiripentol group were completely seizure free compared with 0 (0%) in the placebo group. The sponsor reported p ≅ 0.05 for overall-strata comparisons, and p = 0.01 when only the actual criterion of decrease by at least 50% is used.

Table 16: STICLO trial Italy; Variation in the number of seizures, per protocol analysis set

	Stiripentol n = 11	Placebo n = 9	Significance (Chi2)
Decrease = 100%	3 (27%)	0	
Decrease > 50% < 100%	5 (45%)	1 (11%)	
Decrease < 50%	3 (27%)	7 (78%)	p ≅ 0.05
Increase < 50%	0	0	
Increase > 50%	0	1 (11 %)	

- Pooled STICLO trials France and Italy
  - In a *post hoc* analysis, the sponsor reported on the same endpoint type (seizure reduction compared to baseline) using different strata which is different to the trial protocol (decrements of 20% instead of 50%).
  - Furthermore, the pooled intention to treat analysis set was used (n = 64). The results, together with that for each individual study, are shown in Table 17.

Table 17: Pooled STICLO trials France and Italy; Variation in the number of seizures, per protocol analysis set

Percent Reduction in Seizure Frequency	STICLO France N=41		STICLO Italy N=23		STICLO Total N=64	
	Stiripentol N=21	Placebo N=20	Stiripentol N=12	Placebo N=11	Stiripentol N=33	Placebo N=31
100% *(Seizure free)*	9 (42.9%)	0 (0.0%)	3 (25.0%)	0 (0.0%)	12 (36.4%)	0 (0.0%)
>80%-<100%	2 (9.5%)	0 (0.0%)	3 (25.0%)	1 (9.1%)	5 (15.2%)	1 (3.2%)
>60%-80%	3 (14.3%)	1 (5.0%)	1 (8.3%)	0 (0.0%)	4 (12.1%)	1 (3.2%)
>40%-60%	1 (4.8%)	1 (5.0%)	2 (16.7%)	1 (9.1%)	3 (9.1%)	2 (6.5%)
>20%-40%	2 (9.5%)	3 (15.0%)	2 (16.7%)	3 (27.3%)	4 (12.1%)	6 (19.4%)
0-20%	1 (4.8%)	2 (10.0%)	0 (0.0%)	3 (27.3%)	1 (3.0%)	5 (16.1%)
< 0% Increased in frequency (worsened)	3 (14.3%)	13 (65.0%)	0 (0.0%)	1 (9.1%)	3 (9.1%)	14 (45.2%)
Missing	0 (0.0%)	0 (0.0%)	1 (8.3%)	2 (18.2%)	1 (3.0%)	2 (6.5%)
p-value [1]	0.0003		0.2289		<0.0001	

Source: [Appendix: SAS output, Table 3.07A, Table 3.07B, Table 3.07C]
[1] Fisher's Exact Test.

Withdrawals, that is, the percentage of children withdrawn from the study in each treatment group

- STICLO trial France
  - Intention to treat analysis set (n = 41): In the treatment group, 1 subject (5%, 1 out of 21) was withdrawn from the study compared to 4 subjects (20%, 4 out of 20) in the placebo group. There was no significant difference between the percentage of subjects withdrawn from the study in the two groups (p = 0.184).
  - The patient in the treatment group was withdrawn from the study due to status epilepticus. In the placebo group, patients were withdrawn from the study for status epilepticus (1 subject), lack of improvement (2 subjects), and drowsiness with motor deficiency (1 subject).
- STICLO trial Italy
  - Per protocol analysis set (n = 20): In the treatment group, 1 subject (9%, 1 out of 11) was withdrawn from the study compared to 2 subjects (22%,2 out of 9) in the placebo group. All subjects withdrew at Visit Number 3. The patient of the stiripentol group was withdrawn for adverse events (drowsiness, balance symptoms). In the placebo group, the patients were withdrawn for worsening and lack of improvement.

Comparison of seizure frequency between comparison period (Months 1 and 2 considered separately) and baseline period

- STICLO France
  - Intention to treat analysis set (n = 41), first month versus baseline; per protocol analysis set (n = 36), second month versus baseline (as not all subjects completed the study). Although, there was no statistical difference between the two treatment groups with regard to the number of tonic-clonic seizures in the baseline period (that is, before stiripentol treatment), there were statistically significant differences between the two treatment groups with regard to:

§ Differences in the number of tonic-clonic seizures in Month 1 and Month 2.

§ Differences in the relative change in Month 1 and Month 2 compared to baseline.

Table 18: STICLO trial France; Seizure frequency between comparison period (Months 1 and 2 considered separately) and baseline period

	stiripentol	placebo	significance level Mann-Whitney
Number of tonic-clonic seizures during baseline period *min – max* *n*	17.9 ± 17.3 3.9 - 72.9 *21*	18.5 ± 17.0 4.1 - 76.2 *20*	NS
Number of tonic-clonic seizures during month 1 of the comparison period *min-max* *n*	2.72 ± 4.06 0.00 - 13.30 *21*	23.82 ± 36.55 3.87 - 166.67 *20*	p < 0.001
Rate of change between month 1 and baseline	decrease of 83.2 % ± 28.0	increase of 11.3 % ± 54.7	p < 0.001
Number of tonic-clonic seizures during month 2 of comparison period *min-max* *n*	5.15 ± 7.73* 0.00 - 26.8 *20*	13.80 ± 7.33µ 2.61 - 23.00 *16*	p < 0.002
Rate of change between month 2 and baseline	decrease of 68.6 % ± 41.9	increase of 7.37 % ± 37.64	p <0.002

*The average number of seizures and the relative change in this number during month 2 of the comparison period compared to baseline was calculated only in patients who completed the study. Patients who were withdrawn from the study (No. 1, 7, 37 and 56 for the placebo group and No. 5 for the stiripentol group) were not taken into account.

- STICLO trial Italy
  - Intention-to-treat analysis set (n = 23), first month versus Baseline; per-protocol analysis set (n = 20), second month versus Baseline (as not all subjects completed the study): Although, there was no statistical difference between the two treatment groups with regard to the number of tonic-clonic seizures in the baseline period (that is, before stiripentol treatment), there were statistically significant differences between the two treatment groups with regard to:
    § Differences in the number of tonic-clonic seizures only in Month 1;
    § Differences in the relative change in compared to baseline only in Month 1.
  - The differences in Month 2 in the above were not statistically significant as per Table 19.

Table 19: STICLO trial Italy; Seizure frequency between comparison period (Months 1 and 2 considered separately) and baseline period

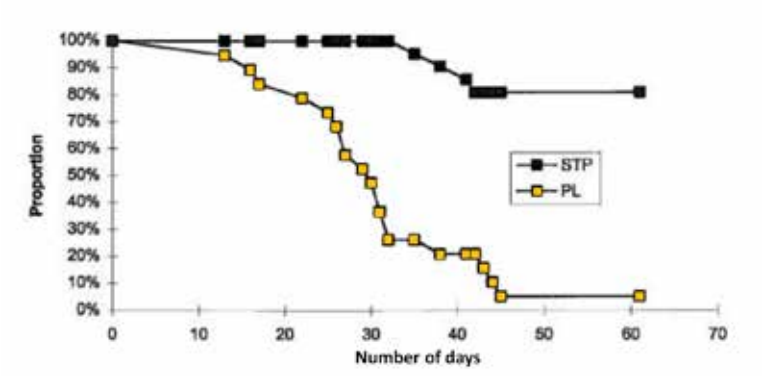
	Stiripentol	Placebo	Significance
Number of tc seizures during baseline *min-max* *n*	33.6 ± 28.2 *2.14 – 86.1* ***12***	27.4 ± 28.6 *3.75 – 101* ***11***	p = 0.818
Number of tc seizures during the 1st month of the comparison period *min-max* *n* Variation rate between baseline and the 1st month	4.7 ± 7.3 *0.00 – 24.2* ***12*** -89.5 ± 15.7 %	29.0 ± 35.6 *0.94 – 126* ***11*** +5.5 ± 55.4 %	p = 0.0003 p < 0.05
Number of tc seizures during the 2nd month of the comparison period *min-max* *n* Variation rate between baseline and the 2nd month	9.8 ± 10.0 *0.00 – 38.7* ***11*** -74.3 ± 26.3 %	16.7 ± 11.3 *0.49-31.8* ***9*** -12.7 ± 61.9 %	NS NS

*The mean number of seizures and the relative variation of this number during the 2nd month of the comparison period compared to baseline were calculated only in patients having completed the study

Time elapsed until the number of seizures as that of the 1 month baseline period are reached

- STICLO trial France
  - The sponsor claims that the comparison did not show any significant differences between the two treatment groups, even though the proportion of patients that continue to have fewer seizures than in the baseline period remain relatively high in the stiripentol group.
  - The report authors postulated that this was due to the small sample size and that an additional analysis showed that frequency of rises was significantly higher ($p < 0.000002$) in the placebo group (94.7%) than in the treatment group (19.0%).
  - The figure below shows a Kaplan-Meier plot of the results. The yellow squares denote the placebo data points and the black squares denote the stiripentol data points. Proportion refers to the proportion of patients (in %) who have not reached the same number of seizures in the comparison period compared to the baseline period. Day 0 was the first day of the comparison period and Day 60 is the last day. The plot does not extend into the open label period.

Figure 2: STICLO trial France; Time elapsed until the number of seizures as that of the 1 month baseline period are reached



STP = stiripentol, PL = placebo.

- STICLO trial Italy

- No results were provided and the following justification given: 'The latent time to obtaining the same number of seizures as that during the baseline month should have been analysed as an actuarial curve, using the Kaplan-Meier technique. This was impossible given the small number of patients included in this study.'

Other efficacy studies:

- STEV trial (Study BC.288): The STEV trial was a Phase II, bicentre, prospective, non-randomised, single group, single blind trial, to investigate stiripentol in 233 children with severe refractory epilepsy (24 children with Dravet syndrome, 20 with an evaluable efficacy result).
- STILON trial (STP 139-STILON) (Study BC.387): The STILON trial was a Phase III, multicentre (39 centres), prospective, non-randomised, single group, open label trial, to investigate stiripentol in 155 children with refractory epilepsy (45 children with Dravet syndrome). The STILON trial was mainly a safety study. It had efficacy data, even though this was not the primary objective.
- TAU-EAP trial (Study BC.458): The TAU-EAP trial was a multicentre (77 sites) prospective, non-randomised, single group, open label trial to investigate stiripentol in 272 children with Dravet syndrome. The TAU-EAP trial (Study BC.458) was mainly a safety/pharmacovigilance study with limited efficacy data.
- STP-1 trial (Study BC.609): The STP-1 trial was a Phase III, multicentre (11 centres), prospective, non-randomised, open label trial, to investigate stiripentol in 30 Japanese subjects with Dravet syndrome.
- DIAVEY trial (Study BC.627): The DIAVEY trial was a dedicated safety study with limited efficacy data.

A summary of retrospective chart reviews from the literature is shown in Table 20.

Table 20: Summary of retrospective chart reviews from the literature

Type of Trial	Trial Number/ Location of Study Report	Objectives of the Trial	Trial Design/ Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Concomitant Antiepileptic Drugs	Trial Population	Duration of STP Treatment	Efficacy Results
Retrospective Chart Review of Dravet syndrome Patients Treated with STP								
Efficacy	Thanh et al., 2002 [5.4]	Efficacy and safety in patients receiving long term STP treatment	Single center, Open-label	STP 250 mg and/or 500 mg capsules or sachets 50 mg/kg/day the first 6 months then flexible; up to 100 mg/kg/day if judged necessary by the Investigator 2 or 3 divided doses, Oral route	CLB and VPA	46 Dravet syndrome patients: 25 males/ 21 females Median age 23 mos.	Median: 2.9 years	• Seizure frequency decreased from 9 seizures/month (prior to STP treatment) to 3 seizures/month (after STP treatment); p<0.001 • Seizure duration decreased from 7.5 mins (prior to STP treatment) to 1.5 mins (after STP treatment); p<0.001 • 10/46 (22%) patients became free of status epilepticus during STP treatment
Efficacy	Laux [5.3.5.2; Laux]	Assess whether efficacy of STP can be explained only by increased plasma concentrations of CLB and NCLB associated with STP treatment or whether STP has intrinsic antiseizure efficacy	Single center Retrospective chart review	STP 250 and 500 mg capsules and 250 and 500 mg sachets STP doses -10 to 30 mg/kg/day: 31% patients 30 to <50 mg/kg/day: 38% patients 50 to 100 mg/kg/day 31% patients Oral route	CLB: 76% of patients VPA: 48% of patients Topiramate: 24% of patients Plus various other AEDs	29 Dravet syndrome patients 15 males/14 females Age range: 2 to 22 yrs	Chart review of 1st 12 weeks of STP treatment	Similar response rate among the 3 groups were observed: Group 1 (patients on STP+CLB titrated up to maximum CLB dose): 12 of 16 (75%) responders, Group 2 (patients on STP+CLB not titrated up to maximum CLB dose): 4 of 6 (67%) responders, Group 3 (patients not treated with CLB): 5 of 7 (71%) responders
Efficacy	Inoue et al., 2009 [5.4]	Efficacy and safety of STP added on to various AEDs in Dravet syndrome patients treated in Japan	Multicenter (6 centers) Open-label	Early period: STP dose : 50 mg/kg/day Late period STP dose range: 30 to 100 mg/kg/day Mean 59 mg/kg/day)	Various AEDs, Mainly VPA (22 patients) CLB (11 patients)	25 Dravet syndrome patients 7 males/18 females Age range 1 to 22 yrs	14 months	Number (%) of responders : Early period: 14/23 (61%) Late period : 11/23 (48%)
Efficacy	Wirrell et al., 2013 [5.4]	Retrospective Chart analysis of the efficacy and safety of STP in Dravet syndrome patients treated in the US	Multicenter (13 centers) Retrospective chart review	STP 250 and 500 mg capsules and 250 and 500 mg sachets Maximum median dose: 42 mg/kg/day Oral route	Mainly CLB + VPA No CLB in 6 patients	82 Dravet syndrome patients: 38 males/ 44 females Median age: 6.9 yrs	Mean treatment duration: 28.5 ± 20.3 months	Overall Reduction in Mean Seizure Frequency Marked reduction: 31% Mild reduction: 35% No change: 31% Worsening: 3%

STP = stiripentol; VPA=valproate; CLB=clobazam

Clinical evaluator's conclusions on clinical efficacy

- In the STICLO trial France, the risk (treatment success) difference between treatment groups (stiripentol versus placebo) was 66.4% (95% CI: 44.8%, 88.4%); odds ratio (OR) = 47.5 ($p < 0.00002$).
- In STICLO trial Italy, the risk (treatment success) difference between treatment groups (stiripentol versus placebo) was 57.6% (95% CI: 34.9%, 90.2%); OR = 20.00 ($p = 0.009$).
- In both pivotal trials, separately and pooled results showed a significant treatment effect favouring stiripentol over placebo. The effect was large enough to be clinically significant. Even when the lower limit of the confidence interval of the risk difference is used, the results show a clinically significant difference between the treatment groups, both in relative and absolute terms. The secondary endpoint results were generally supportive. No patients in the placebo groups reached seizure-free status.
- The *post hoc* covariate adjusted analysis was suggestive of an independent stiripentol effect on seizure activity but, the latter does not influence the support for the proposed indication of stiripentol as an adjuvant.
- In the pooled STICLO France/Italy trials, the secondary efficacy outcome as in the decrease in seizure distribution was supportive of efficacy response in the stiripentol group but not in the placebo group (non-response).

- The non-pivotal studies were generally supportive of efficacy in the target population for the proposed indication, but only in conjunction with the pivotal study data.
- The pivotal trials (STICLO France/Italy) enrolled only children over the age of 3 years. Some of the studies included children that were younger, for example, the STEV trial (2 months to 15 years) (> 5 kg), DIAVEY trial (6 months to 25 years), but the exposure was low .The Integrated Summary of Effectiveness (ISE) did not stratify children under 3 years further; they were grouped together. It would have been advantageous to stratify the population further to obtain data separately for children between 1 and 2 years of age, and children under 1 year.
- No adults were involved in the pivotal trials. A limited number of adults were included in the STP-1 (n = 4), STILON (n = 3), and DIAVEY trials. Limited data from the literature supports ongoing efficacy in adults.
- There is no information on efficacy and safety of stiripentol in patients with hepatic or renal impairment, and use in those populations is not recommended.
- Neither sex nor age seemed to have significantly influenced the stiripentol response. No definite statement with regard to presence of SCN1A mutation on efficacy could be made, as SCN1A negative patient numbers were too small.
- It can be assumed that the study population is sufficiently similar to a real world Dravet syndrome paediatric population to support external validity.
- Ideally, the lowest possible dose that adequately controls seizures should be used. Doses could potentially be adjusted to the lower end of the recommended 40 to 60 mg/kg/day range for older children, and adolescents. Drug monitoring may have a role and should be considered, especially when doses are changed due to increases in weight or lack of response.
- Stiripentol has the potential for significant interaction effects. Efficacy would be affected, if the interactions were to lead to a significant decrease of stiripentol concentrations.
- The pivotal trials did not provide longer term data. The pivotal trials only had maintenance data for 12 weeks (if the 4 week open label period is also taken into account).
- The STILON and STP-1 trials provided longer-term efficacy data. In the STILON trial, the mean duration of stiripentol treatment was 2.92 years (range: 0 to 4.2 years). The seizure frequency remained similar throughout the study). In the STP-1 trial (Study BC.609), longer term data indicated no loss of efficacy either.

Clinical evaluator's summary comment on efficacy

- Overall, the efficacy for the proposed indication in the pivotal trial population has been established (patients aged 3 to 18). Younger children or adults were not included in the pivotal trials. Even though the trials were relatively small and designed prior to the implementation of the relevant guidelines, the treatment effect in the pivotal trials was large enough to be shown in that relatively small population, and is also clinically significant. Only clonic and tonic-clonic seizures were considered in the pivotal trials and this is reflected in the (updated) proposed indication. The *post hoc* clobazam/norclobazam covariate adjusted analysis was generally supportive of efficacy of stiripentol, and potentially also supportive of an intrinsic effect of stiripentol.
- The study population is considered to be sufficiently similar to a real world Dravet syndrome paediatric population to support external validity. Uncertainties remain regarding limited data for children under the age of 3 years of age, and adults. The data

for those age groups and long term data for all ages did not originate from the pivotal trials, but from the non-pivotal studies that had methodological limitations.

Safety

- There were a total of 529 patient exposures (equating to 438 unique/actual patients) to stiripentol in the efficacy, safety and pharmacology studies in the target population. The mean dose was 49.2 ± 21.2 mg/kg/day (median: 48.4 mg/kg/day) in n = 524. The mean treatment duration (unique/actual patients) was 2.21 ± 1.84 years (median: 1.75 years; range: 0 to 8.50 years) in n = 437. The sponsor estimated a patient exposure of approximately 2,500 (post-market studies and the literature). No indication of exposure in patient years (or a similar unit) was given.
- The most common safety issues were deranged liver function tests, weight loss/decreased appetite/anorexia, ataxia, and fatigue/somnolence. Haematological derangements, such as neutropaenia or thrombocytopaenia, were seen more prominently in longer term studies.
- Table 21 compares the adverse events (AEs; ≥ 5%) across all clinical studies (stiripentol compared to placebo).

Table 21: Adverse events (≥ 5%) across all clinical studies

AE PREFERRED TERM	STP N=529 n	(%)	PLACEBO N=31 n	(%)	P-VALUE*
Anorexia	54	(10.2)	3	(9.7)	0.9244
Aspartate aminotransferase increased	34	(6.4)	0	(0.0)	0.1453
Ataxia	39	(7.4)	7	(22.6)	0.0027
Decreased appetite	45	(8.5)	0	(0.0)	0.0904
γ-GT increased	42	(7.9)	0	(0.0)	0.1028
Somnolence	77	(14.6)	7	(22.6)	0.2239
Weight decreased	27	(5.1)	2	(6.5)	0.7421

*: Chi-square test
Source: [Appendix 4: SAS output, Table 3-23.8.0]

- Table 22 shows all AEs ≥ 5% in the non-pivotal studies.

Table 22: Adverse events ≥ 5% in the non-pivotal studies

AE preferred term	STEV N=24 n	(%)	STILON N=45 n	(%)	STIPOP N=35 n	(%)	STP-1 (Short term) N=24 n	(%)	STP-1 (long term) N=27 n	(%)	TAU-EAP N=210 n	(%)	DIAVEY N=152 n	(%)
anorexia/decreased appetite	16	(66.7)	6	(13.3)	0	(0.0)	14	(58.3)	9	(33.3)	19	(9.0)	26	(17.1)
ataxia	5	(20.8)	1	(2.2)	0	(0.0)	13	(54.2)	2	(7.4)	2	(1.0)	8	(5.3)
somnolence	8	(33.3)	1	(2.2)	0	(0.0)	19	(79.2)	5	(18.5)	11	(5.2)	14	(9.2)
weight decreased	2	(8.3)	4	(8.9)	0	(0.0)	2	(8.3)	2	(7.4)	5	(2.4)	4	(2.6)
AST increased	0	(0.0)	0	(0.0)	0	(0.0)	3	(12.5)	1	(3.7)	0	(0.0)	29	(19.1)
γ-GT increased	0	(0.0)	0	(0.0)	0	(0.0)	8	(33.3)	1	(3.7)	2	(1.0)	31	(20.4)

Source: [Appendix 4: SAS output, Table 3-23.1.0, Table 3-23.3.0, Table 3-23.4.0, Table 3-23.5.0, Table 3-23.6.0, Table 3-23.7.0]

- In the PK studies in healthy volunteers, all AEs were reported as mild to moderate and, considered to be unlikely related to stiripentol (with exception of the 2 AEs in the Greig study which was judged to be possibly related).
- No deaths occurred in the pivotal trials or the PK studies conducted in healthy volunteers. 11 of 438 (2.5%), unique/actual Dravet syndrome patients died while being treated with stiripentol. The sponsor stated none of the deaths were considered to be related to stiripentol. None of the deaths were preceded by a serious adverse event (SAE). The 9 deaths that occurred in non-Dravet syndrome patients on stiripentol were considered to be unlikely or improbably related to the study drug.

- No serious adverse events occurred in the PK studies conducted in healthy volunteers. Across all clinical trials in Dravet syndrome patients, 157 SAEs were reported in 68 patients. None of those events were fatal. 41 (26.1%) SAEs in 19 patients were considered possibly or potentially related to stiripentol. None of those occurred in the pivotal trials. Other than neurological SAEs ascribed to lack of efficacy, the other SAE domains were mainly gastrointestinal and haematological, in keeping with the overall AE profile, but with increased severity.
- Across all clinical trials in Dravet syndrome patients, 20 patients discontinued treatment with stiripentol prematurely due to AEs (28.9% out of 69 patients who discontinued). The proportion of withdrawals due to AEs in the double-blind pivotal trials (3.0%) and in the non-pivotal trials (4.1%) was comparable.
- Regarding adverse events by systems:
  - CNS: somnolence and ataxia (including hypotonia, balance disorder, gait disturbance, hyperkinesia, fall and abnormal coordination) were the most common events (stiripentol versus placebo: 66.7% versus 22.6% for somnolence and 48.5% versus 38.7% for ataxia). The STP-1 trial appeared to have a much higher proportion of somnolence/sedation (79.2%) and ataxia (54.2%) than the European studies (at least in the early stages), which decreased as treatment progressed. The DIAVEY and TAU-EAP trials were long term studies with lower proportions of somnolence/sedation and ataxia and no occurrences of falls.
  - Behaviour: Aggression and agitation were more frequent in the stiripentol group (pooled data (stiripentol versus placebo): aggression 9.1% versus 0%, and agitation 27.3% versus 16.1%). They occurred less frequently in the longer term non-pivotal studies.
  - Gastrointestinal tract (GIT): Anorexia was the most common AE. The occurrence of nausea or vomiting was relatively low. The proportion of subjects experiencing anorexia/loss of appetite across all the pivotal clinical trials was relatively high (pivotal trials: 45.5% (stiripentol) versus 9.7% (placebo). The proportions appeared to decrease in the non-pivotal long-term data. The incidence of weight loss ranged from 2.4% (TAU-EAP trial) to 28.6% (STICLO trial France) and seemed to be higher during the short-term than the long-term clinical trials, and, in the pivotal trials, more likely to be associated with anorexia.
  - Liver function tests (LFT): No ≥ Grade 3 elevated transaminases occurred in the pivotal trials, but 4 cases in the non-pivotal trials, 3 of which were possibly or probably related to stiripentol. There appear to be no cases fulfilling Hy's Law;[14] criteria (no bilirubin increases, no jaundice).
  - Haematology: Neutropaenia was common in most patients and did not lead to discontinuation. It improved or normalised despite continued stiripentol treatment. Thrombocytopaenia was mild to moderate in most cases, but 3 patients in the STP-1 trial had Grade 3 thrombocytopaenias. Thrombocytopenia could be potentially related to concomitant valproate use. In one patient in the STILON trial, one patient in the TAU-EAP trial and 2 patients in the DIAVEY trial, thrombocytopenia was considered a SAE.
  - Serious skin reactions: Minor skin reactions occurred in a small amount of patients (including angioedema, rash, erythema, photosensitivity, alopecia, dermatitis, eczema). Post-marketing data revealed two cases of Stevens-Johnson syndrome and one case of palmar-plantar erythrodysaesthesia syndrome. Out of the two reported cases of Stevens-Johnson syndrome, one appears to be unrelated to

[14] Hy's Law: alanine aminotransferase (ALT) >3 x upper limit of normal (ULN) and total bilirubin > 2 x ULN

stiripentol; the other case could potentially be related, but an association with valproate appears more likely. The case of perceived 'palmar-plantar erythrodysaesthesia syndrome' appeared to have been an infection instead.

  - Developmental effects: There was no clear evidence on the effects of stiripentol on failure to thrive, growth retardation, psychomotor and mental development/behaviour, separate from the sequelae of Dravet syndrome itself.

- Regarding special groups:
  - Gender: With the exception of somnolence, AEs in the pivotal trials appeared to occur slightly more often in males than females (males: 57.1%; females: 73.7%). In the non-pivotal trials, the AEs were not significantly different.
  - Age: Although, ataxia appeared to occur more often in the age group 1 to ≤ 6 years, the AE incidence was comparable across age groups below 17years (when analysing common AEs (> 5%)). Data were limited for patients over 17 years of age.
- From the limited data available on doses greater than 60 mg/kg/day, there appears to be no significant difference in AEs at higher doses. Given the small exposure, this may not be true for more rare events.
- Post-marketing experience reflected the events found in the pre-marketing studies for example, abnormal LFTs, neutropaenia/thrombocytopaenia, ataxia, aggression.

Clinical evaluator's comment on safety

- Overall, the safety profile of stiripentol has been adequately characterised and is acceptable. The exposure (including longer term exposure) was adequate and, there was sufficient post-marketing experience. Generally, the post-marketing data reflected the safety data found in the clinical studies. Drug monitoring should be considered at regular intervals when clinically appropriate (for example, when the dose is changed, when the efficacy is decreasing, or when there is an increase in adverse event severity or frequency) for risk mitigation purposes.
- The limitations/potential issues in the profile include the following:
  - Limited data for children under 3 years and adults.
  - No data for patients with hepatic or renal impairment.
  - Non-conclusive evidence regarding dose related increase in adverse events, in particular in the context of a potential increased concentration dose ratio with daily dose and age increases.
  - Inability to compare the profile to a drug in the same class.
  - Drug monitoring issues, as stiripentol is highly protein bound, and measuring the free fraction may not be possible.
  - Interactions with AEDs that may increase the stiripentol concentration and potentially AEs.

Risk management plan (RMP)

- Significant pharmacokinetic drug interactions occur with Diacomit. This requires dose adjustment of anti-epileptic drugs used in combination with stiripentol and precaution with certain other drugs.
- The sponsor has submitted European Union–Risk Management Plan (EU-RMP) version 3.0 (9 June 2017; data lock point 18 August 2016), which supersedes EU-RMP version

2.0, 04 October 2016 (same data lock point) and Australian Specific Annex (ASA) version 0.1 (5 October 2016), in support of this application. The ASA was not updated.

- The sponsor has revised the summary of safety concerns in the EU-RMP version 3.0 provided in the response to TGA questions; see Table 23 below.

Table 23: Summary of safety concerns

Summary of safety concerns (adapted from EU-RMP v3.0-Part II: Module SVIII)	
Important identified risks	Hepatic disorders • Liver function test abnormal; • Hepatic enzyme increased (ALT ↑ , alpha-1 antitrypsin protein (AAT) ↑, gamma-glutamyl transferase (GGT) ↑)
	Interactions with clobazam, valproate and/or carbamazepine including: • Haematological changes (associated with valproate and clobazam) • Neurological disorders • Gastrointestinal adverse reactions, including weight loss
Important potential risks	Convulsion/lack of efficacy
	Death/sudden unexpected death in epilepsy
	Interactions with other AED/food
	Serious skin reactions
Missing information	Renal disease
	Pregnancy and Lactation

- Only routine pharmacovigilance and routine risk minimisation activities are proposed to monitor and mitigate the risks associated with Diacomit.[15] This approach is considered acceptable.

Conclusions

The proposed risk management activities are acceptable. The recommendations made in the first round evaluation (recommendations 1 to 7) have been addressed satisfactorily, as outlined in the RMP evaluation report. There is one new recommendation at the second round of evaluation:

[15] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- Recommendation 8: The sponsor should provide either an updated ASA to the EU-RMP version 3.0, or an assurance that the EU-RMP will be implemented, in its entirety, unadapted in Australia.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording will be provided after the sponsor has clarified their intention to revise the ASA, or implement the EU RMP in its entirety.

Risk-benefit analysis

Delegate's considerations

As mentioned in the background information, Dravet syndrome (also known as SMEI) is a genetic epilepsy syndrome and an epileptic encephalopathy (first described by Charlotte Dravet, a French neuropsychiatrist, in 1978). The syndrome is associated with high mortality and not many patients live beyond the age of 30. Most patients with Dravet syndrome (70 to 80%) have mutations in the SCN1A gene which affect the associated voltage-gated sodium channel alpha-1 subunit.

The sponsor stated that valproate with or without clobazam is typically used as first-line treatment. In some Dravet syndrome patients, the first-line therapies are not sufficient and additional therapy is needed, for example, in the form of stiripentol targeting generalised clonic and tonic-clonic seizures which may be associated with Dravet syndrome.

While its exact mechanism of action is unknown, two main mechanisms of stiripentol action are proposed by the sponsor:

- Positive modulation of the GABAergic system (direct effect);
- Hepatic clearance isozyme inhibition (indirect effect; reduction in clearance of concomitantly administered anticonvulsants which potentiates their effects).

Stiripentol is a second line generation anti-epileptic drug, unrelated to any other currently registered anticonvulsant drug.

All modules' evaluators support approvability of the submission for use in Dravet syndrome. The sponsor's amended proposed indication was:

> *Diacomit is indicated for adjunctive treatment of generalised tonic-clonic and clonic seizures associated with severe myoclonic epilepsy in infancy (SMEI, also known as Dravet syndrome).*

This was amended by the clinical evaluator in line with the evaluated data and, close to the EU/Canada approved indication to:

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

The Delegate further wishes slight modification to the proposed indication for simplicity to:

> *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.*

The Delegate is agreeing in principle, to the PI modifications suggested by all modules' evaluators as they relate particularly to safety issues including, any changes to which the sponsor has agreed to include in a revised RMP and ASA.

Proposed action

The evaluated evidence, based on submitted data, gave the Delegate the impression at this stage that the application is approvable subject to resolving issues, arising from the Advisory Committee on Medicines (ACM) deliberations, finalising matters relating to the suggested PI modifications as per the modules' evaluators to the satisfaction of the TGA.

Request for ACM advice

1. Consideration of the modifications (clinical evaluator and Delegate) to the sponsor's proposed indication.

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory Committee Considerations[16]

The ACM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Diacomit film coated tablets, containing 250 mg and 500 mg of stiripentol.

The ACM considered this product to have an overall positive benefit-risk profile for the proposed indication:

> *Diacomit is indicated for adjunctive treatment of generalised tonic-clonic and clonic seizures associated with severe myoclonic epilepsy in infancy (SMEI, also known as Dravet syndrome) in patients whose seizures are not adequately controlled with a benzodiazepine (usually clobazam) and valproate.*

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice:

1. Consideration of the modifications (as per the clinical evaluator and Delegate) to the sponsor's proposed indication.

[16] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

The ACM expressed concern about narrowing the indication to specify use of stiripentol only when co-administered with clobazam and sodium valproate. While such a restriction would match the evidence from trials, the ACM advised that some patients are not able to tolerate clobazam in particular, and that a more restricted indication might have the consequence that these patients would be unable to access this medication.

2. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM was of the view that the plan to limit prescribing to paediatric neurologists, as outlined in the RMP/PI/Consumer Medicines Information (CMI), was inappropriate. The ACM advised that patients with Dravet syndrome do survive into adulthood and that restricting prescribing to paediatric specialists could create access difficulties. The ACM also advised that general paediatricians would not be well placed to manage this condition, and that prescription by general practitioners is also unlikely to occur in practice as these patients are generally managed through specialist clinics in public hospitals. The ACM was of the view that initiation of prescription by neurologists would be appropriate, as this accommodates both paediatric and adult patients as well as facilitate continuation of management by general paediatricians and practitioners, when the initiating neurologist is unavailable.

General advice

The ACM observed that the references in the PI to breastfeeding are confusing and inconsistent and suggested the wording be reviewed to clarify the intent such as:

> 'It is not expected that Dravet syndrome affected females will conceive and have children. However, as there are no human studies on the excretion of stiripentol in breast milk, and given that stiripentol passes freely from plasma into milk in the goat, breast feeding is not recommended while on treatment with stiripentol. In the unlikely event that stiripentol therapy is maintained while breast feeding, the breast fed infant should be carefully monitored for potential adverse effects'.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Diacomit (stiripentol) capsule and powder, indicated for:

> *Diacomit is indicated for adjunctive treatment of generalised tonic-clonic and clonic seizures associated with severe myoclonic epilepsy in infancy (SMEI, also known as Dravet syndrome) in patients whose seizures are not adequately controlled with a benzodiazepine (usually clobazam) and valproate.*

Specific conditions of registration applying to these goods

- The Diacomit EU-Risk Management Plan (RMP) (version 3.0, dated 9 June 2017, data lock point 18 August 2016), with Australian Specific Annex (version 0.1, dated October 2016), included with submission PM-2016-02336-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.

  Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-

periodic safety update report (Rev1) Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- Diacomit is to be included in the Black Triangle Scheme. The PI and CMI for Diacomit must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Attachment 1. Product Information

The PI for Diacomit approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au