CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206709Orig1s000
207223Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	206709
PDUFA Goal Date	August 20, 2018
OSE RCM #	2016-2640
Reviewer Name(s)	Charlotte Jones, MD, PhD, MSPH
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins Parker, PharmD
Review Completion Date	July 5, 2018
Subject	Evaluation of Need for a REMS
Established Name	Stiripentol
Trade Name	Diacomit
Name of Applicant	Biocodex, SA C/O KM Pharmaceutical Consulting LLC
Therapeutic Class	Anticonvulsant
Formulation(s)	206709 Oral capsule, 250 mg and 500 mg
Dosing Regimen	50 mg/kg administered in 2 or 3 doses.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Diacomit (stiripentol) is necessary to ensure the benefits outweigh its risks. KM Pharmaceutical Consulting LLC submitted for Biocodex SA a New Drug Applications (NDA) 206709 stiripentol 250 mg and 500 mg capsules with the proposed indication (at the time of this review) for treatment of seizures associated with Dravet syndrome in patients (b) (4) years of age and older taking clobazam.[1] Dravet Syndrome (DS) a pharmacoresistant epilepsy of childhood. The primary risks associated with Diacomit include somnolence, anorexia, and neutropenia. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and DNP agree that a REMS is not necessary to ensure the benefits of stiripentol outweigh its risks. The serious nature of DS coupled with the similarity of stiripentol's risks to other approved anticonvulsants, which the likely prescribing population should be familiar with, mean that further risk mitigation beyond labeling is not necessary.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Diacomit (stiripentol) is necessary to ensure the benefits outweigh its risks. KM Pharmaceutical Consulting LLC submitted for Biocodex New Drug Applications (NDA) 206709 with the proposed indication (at the time of this review) for treatment of seizures associated with Dravet syndrome in patients (b) (4) years of age and older taking clobazam.[1] This application is under review in the Division of Neurology Products (DNP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Diacomit (stiripentol), a new molecular entity, is a pentenol derivative that is structurally different from other known antiepileptic drugs (AEDs).[a] Stiripentol (STP) was proposed for the (b) (6) treatment of (b) (4) seizures associated with DS. The proposed indication, at the time of this review, is for treatment of seizures associated with Dravet syndrome in patients (b) (4) years of age and older taking clobazam.[1] The mechanism of action is thought to involve potentiation of the GABAergic and glutamatergic transmissions in the central nervous system. STP is a positive allosteric modulator of the $GABA_A$ receptor and acts at a neuronal site different from those of the other allosteric modulators, such as barbiturates and benzodiazepines. The proposed dosage form is 250 mg and 500 mg capsules. The agency recommended dosage is 50 mg/kg daily divided in two or three divided doses. Patients

[a] Section 505-1 (a) of the FD&C Act: FDAAA factor (F): *Whether the drug is a new molecular entity*.

should be dosed according to body weight. [redacted] (b) (4)[1]

STP was approved as adjunct therapy with valproate (VPA) and clobazam (CLB) in the treatment of Dravet Syndrome by the European Medicines Agency on January 8, 2014 (full marketing authorization) where it was also designated as an orphan medicinal product.[2] STP was approved by the Japanese Health Authority on September 28, 2012, Health Canada on December 21, 2012 and Australian Government Department of Health, Therapeutic Goods Administration with an implementation date of February 1, 2018 as a New Chemical Entity. No adverse actions have been taken against stiripentol in any country since approval in the EU, Canada, and Japan.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 206709 relevant to this review:

- 10/30/2008: Orphan designation (08-2661) granted to stiripentol oral capsules, IND 107979, for the treatment of Dravet syndrome.
- 12/16/2013: Applicant informed at pre-NDA meeting that the need for a REMS for stiripentol would be evaluated during the review.
- 12/20/2017: Submission of full application for NDA 206709 for filing. PDUFA Time clock initiated.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Severe myoclonic epilepsy in infancy (SMEI) or Dravet syndrome (DS) is a pharmaco-resistant epilepsy of infancy. Estimates of DS in the US range between 1/20000 to 1/40000.[3,4,b] Dravet syndrome typically presents with prolonged febrile or temperature sensitive seizures before a child's first birthday and both febrile and afebrile generalized tonic clonic seizures and status epilepticus are common. Over time other seizure types including myoclonic, absence, and partial seizures may occur. Frequent hospitalization for status epilepticus is common in the early years of the disorder when seizures may be a daily occurrence. Children with DS are developmentally normal prior to seizure occurrence however after the first year developmental delays become evident along with autistic behaviors, ataxia and other motor symptoms.[5,6] Independent living during adulthood is the exception for patients with Dravet Syndrome.[7] In individuals with DS, up to 21% experience premature mortality.[8] Sudden unexpected death in epilepsy (SUDEP) and status epilepticus are the most common causes of death accounting for 81% of

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

deaths in patients with DS.[9c] Genetic mutations in the SCN1A gene occur in 40% to 80% of children with a clinical diagnosis of DS, not all pathologic mutations in the SCN1A gene are associated with DS.[4,10]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Dravet syndrome is a pharmacoresistant epilepsy with most patients continuing to have seizures even on polypharmacy. Valproic Acid (VPA) and Clobazam (CLB) are identified as first line therapy by experts in the field and clinical practice, although neither has a specific indication for DS.[11,12] Topiramate and the Ketogenic Diet as well as foreign-sourced stiripentol are identified as recommended second line therapies for patients who do not respond to Valproic Acid or Clobazam. [11,12] Stiripentol continues to be requested under the Agency's expanded access program for individual patients, with requests as recently as December 13, 2017. Ninety six percent of patients will continue to have seizures even when treated with VPA, Clobazam, and Stiripentol, as well as other therapies, reinforcing the intractable nature of this patient population and the high unmet medical need.[7] The combination of VPA, CLB and STP was ongoing with a mean of 10 years of exposure in one institution's DS population, reinforcing the chronic nature and long term treatment need for this population.[7d] The drug cannabadiol, was approved by the FDA for the treatment of dravet syndrome on June 25, 2018 with warnings related to hepatocellular injury when used with VPA.[13] Status epilepticus, which leads to a third of deaths in this patient population, demonstrates the need for improved seizure control.[9,12] Commonly used anticonvulsants carbamazepine, oxcarbazepine, phenytoin, and lamotrigine may exacerbate seizures in patients with DS and should be avoided.[12]

A commonly used non- FDA approved treatment options for patients with DS is the Ketogenic Diet. This isa low carbohydrate, high fat diet. Side effects include weight loss, bone loss, nephrolithiasis, hyperlipidemia. The diet is very restrictive and may be difficult to maintain for patient and family. [14]

4 Benefit Assessment

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be with treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (D): *The expected or actual duration of treatment with the drug.*

The efficacy and safety of STP for the adjunctive treatment of DS was demonstrated in one pivotal phase three trial (STICLO France 299) and a supportive trial, STICLO Italy 385, that was too small to qualify as a pivotal trial. The two studies were similar in design and used similar protocols: multicenter, randomized, double-blind, and placebo-controlled. Patients were included in these studies if they had DS based on clinical criteria as described by Dravet,[15] and were between 3-18 years old. Each of these studies had the same primary efficacy endpoint: a reduction in generalized tonic or tonic clonic seizures >50% compared to the patient's 1-month baseline frequency while they received optimized antiepileptic treatment with VPA and CLB. This was followed by 2 months of double blinded STP or placebo. STP was given at a dose of 50 mg/kg divided 2-3 times a day. Seizure frequency was recorded by parents and/or caregivers in a diary. The clinical reviewer provided Table 1 which shows the number of patients who had a ≥50% decrease in the frequency of seizures during Month 2 of the 8-week double blind treatment period compared to baseline.[16] The clinical reviewer concludes "Stiripentol under the conditions of treatment in the STICLO Studies where sodium valproate and clobazam were obligatory concomitant medications is an effective treatment for the seizures of Dravet syndrome."[16] In addition to the pivotal and supportive trials there were 19 previously completed trials submitted by the sponsor which were not done as a part of an IND and occurred between 1998-2012, these studies are identified in Appendix 1 . Of the 19 trials Six non-pivotal trials included DS patients and are highlighted in green in Appendix 1.

Table 1 Efficacy Results at End of Treatment in the Intent-to Treat Population across the Pivotal STILCO France and supportive STILCO Italy trials

	STICLO France- Pivotal N=41		**STICLO Italy - Supportive N=23**	
	Stiripentol N=21	**Placebo N=20**	**Stiripentol N=12**	**Placebo N=11**
No of responders/total	15/21	1/20	8/12	1/11
(Responder Rate)	(71.4%)	(5.0%)	(66.7%)	(9.1%)
[95% CI]	[52.1 – 90.8]	[0.0 – 14.6]	[40.0 – 93.3]	[0.0 – 26.1]
p-value [2]	<0.0001		0.0098	

5 Risk Assessment & Safe-Use Conditions

The overall safety population included 1090 subjects; healthy volunteers, Dravet syndrome patients, and non-DS patients. The pivotal phase three studies Stilco France and Italy, which were used to demonstrate efficacy, included 2 months of treatment for STP exposed patients. Six non- pivotal trials included DS patients and are highlighted in green in Appended Table 1. 438 unique (not counted twice due to presence in multiple trials) DS patients were exposed to STP in pivotal and non-pivotal clinical trials. Nine hundred and eleven non- DS patients participated in STP trials and this group includes patients who may have been enrolled in more than one trial.

5.1 DEATHS

There were no deaths in the pivotal studies STILCO 299 & 385. In TAU-EAP trial, a long term open label extension safety study of STP in DS patients, there were 5 deaths and all were attributed to probable or possible SUDEP (Sudden Unexpected Death in Epilepsy Patients). Of note, three of the five deaths occurred in patients who started STP while younger than the age allowed for the pivotal trials. Death occurred between 54 to 1040 days after starting treatment with STP. The SUDEP rate for this population was 9.6/1000 patient years.

In DIAVEY 627 a long term open labeled safety study of mixed DS and non-DS patients, there were 6 deaths in DS patients. Three were probable or possible SUDEP, 1 was related to infection and 2 had inadequate data to determine cause of death. The identified SUDEP rate for DS patients in this trial was 13.1 per 1000 patient years.

The clinical reviewer assessed the rate of SUDEP in the STP DS treated population as high, but in accordance with the rate seen in patients with intractable epilepsy awaiting surgery, and did not feel that the rate was excessive.[17]

5.2 SERIOUS ADVERSE EVENTS

The definition of a serious adverse event varied among the 19 trials submitted by the sponsor which were not done as a part of an IND and occurred between 1998-2012. Many of the definitions of serious adverse events used in these trials did not include less serious events with the potential for serious outcomes. The clinical reviewer assessed that the definitions used are adequate to allow analysis of serious adverse events.[17] The pivotal studies STILCO Italy and France lasted 2 months and included 64 patients there were 3 SAEs in patients on STP. The three SAE's included two patients with seizure and 1 patient with a rash. The patient with rash on STP resolved with dechallenge and did not recur with re-challenge. There were 5 SAEs in the placebo treated patients; 3 seizure related, 1 somnolence and 1 motor dysfunction.

In the nonpivotal studies in 496 DS patients treated with STP 71 (14.3% of patients) experienced a total of 160 SAEs. Serious adverse events with the highest frequency were Seizure 3.43%, Decreased appetite 2.22%, Status epilepticus 1.61%, Death 1.41% Pneumonia 1.01% Pyrexia 1.01%, Somnolence 1.01% and Thrombocytopenia 0.81%. In Non-DS patients in the analyzed nonpivotal studies there were 187 patients with an SAE. Serious adverse events with the highest frequency in this group were seizure 5.3%, status epilepticus 2.7% arthropathy .53%, death 1.1% dizziness 0.53% and fall 1.1%.[18]

5.2.1 Anorexia/Weight loss

Among patients in the non-pivotal phase 2 or 3 studies, SAE's of anorexia or decreased appetite occurred in 11 of 716 patients for an incidence of 1.54% with 3 patients discontinuing the medication due to this adverse reaction. The clinical reviewer identified 5 of the 11 patients likely had a causal relationship to STP based on association with STP treatment, temporal relationship, partial dechallenge response, or discontinuation of STP.

5.2.2 Somnolence

Somnolence was noted to occur in 44% more patients treated with stiripentol than control in the pivotal and supportive trials. In the other nonpivotal trials used to assess safety, somnolence and drowsiness was the most common AE occurring in 203/716 unique patients. There were 5 SAEs categorized in the combined safety cohort as somnolence or ataxia. As the clinical reviewer pointed out, in a neuroactive drug to treat seizures these effects are not unexpected.

5.2.3 Neutropenia

Neutropenia was not noted in the pivotal trial. In controlled studies at the end of study there were 6(18%) of patients in the STP arm and 1 (3%) of patients in the placebo arm with neutrophil counts less than 1500. A single patient had SAE and discontinued STP due to a decline to < 1000 neutrophils/ mm^3 at 40 days of STP treatment. There was a consistent decline in neutrophil counts across studies. In a nonpivotal open label study there were frequent adverse events of infection but it is uncertain if this is related to a a decline in the absolute neutrophil count < 1000 in 38% of the patients with baseline data.

6 Expected Postmarket Use

The proposed indication for stiripentol is (b) (4) treatment for patients with Dravet Syndrome. This combination of pharmacoresistant epilepsy and the need for adjunctive treatment should result in the majority of these patients being diagnosed, receiving care and being prescribed stiripentol in comprehensive epilepsy centers.[19] These centers with neurologists, pediatric neurologists and epileptologists will have the experience with anticonvulsants and the risks associated with them, both generally and specifically for stiripentol, and the adjunctive therapies that are required when using stiripentol. The risks associated with STP are also risks associated with other anticonvulsants used for the treatment of Dravet. The dispensing of stiripentol will occur in outpatient and inpatient pharmacies. The agency plans to request a formal QT study as a post marketing requirement, as prolongation of QT is common to anticonvulsants.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for stiripentol beyond routine pharmacovigilance and labeling. The label will include information regarding the North American Antiepileptic Drug Pregnancy Registry which is included in all anticonvulsant labels.

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of stiripentol based on the demonstrated efficacy, the seriousness of Dravet syndrome and an adequate benefit/risk profile.

Dravet syndrome is a pharmacoresistant epilepsy with most patients continuing to have seizures even on polypharmacy. The recurrent prolonged seizures and cognitive impairment, as well as the increased risk of sudden unexpected death in epilepsy patients, impacts every aspect of life for the patients and their families.

One pivotal trial and one supportive trial demonstrated the effectiveness of stiripentol in the current application and demonstrated the superiority of stiripentol used with VPA and Clobazam to placebo. The long-term safety was demonstrated with an additional 19 studies that were completed outside of the development plan used to support efficacy for this NDA.

The serious risks associated with stiripentol, that are not risks of Dravet syndrome itself, include anorexia, weight loss, somnolence, and neutropenia. The proposed labeling at the time of this review includes warnings for these risks in Warnings and Precautions. These effects are common to many anticonvulsants due to their impact on the nervous system and are similar to other anticonvulsants used in this population, specifically clobazam. Neutropenia is also seen in other anticonvulsants and can be monitored, the label will recommend obtaining at baseline and every 6 months to monitor for a decline in neutrophil counts.

Therefore, based on the data available, the prescribing population's likely familiarity with stiripentol and the risks associated with use, which are not unique compared with the risks associated with other anticonvulsants used in the pharmacoresistant epilepsy population, DRISK is not recommending a REMS for the management of the risks of stiripentol at this time.

9 Conclusion & Recommendations

Based on the data, the benefit-risk profile of stiripentol is favorable therefore, a REMS is not necessary to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

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10.2 APPENDIX 1

Clinical Trials of Stiripentol[16]

Study name	study number	Date*	category	type	objective	design	Test Product(s); Dosage Regimen; Route of Administration	population	n	duration	seizure type	Data presentation	comment
STIVAL	BC.481	2007	5	BA-PK	BA	OL-Crossover	STP 500 mg capsules and STP 500 mg powder for oral suspension in (b) (4) 1,000 mg, Oral route	Healthy	24	single dose	none	PDF- Written	
Greig	BC.287	1993	5	BA-PK	PK	OL-Crossover	STP 300 mg capsules 1,200 mg R-STP, 1,200 mg S-STP, 1,200 and 2,400 mg racemic STP Oral route	Healthy	6	single dose	none	PDF- Written	
STIUNI	BC.337	2002	5	BA-PK	PK	OL-Crossover	STP 500 mg capsules 500, 1000, 2,000 mg Oral route	Healthy	12	single dose	none	PDF- Written	
Pons	BC.345	1995	5	BA-PK	CYP	OL	STP 500 mg capsules Day 1: 1,000 mg (500 mg twice a day) Day 2: 2,000 mg (1,000 mg twice a day) Day 3-13: 3,000mg (1,500 mg twice a day) Day 14: 1,500 mg in the morning, Oral route	Healthy	13	single dose	none	PDF- Written	
STIPOP	STP167	2008	2	BA-PK	PK	OL	STP 250 and 500 mg capsules and STP 250 and 500 mg powder for oral suspension ir (b) (4) 50 mg/kg/day, Oral route	DS	35	from other studies	DS	xpt	
STICLO France	BC.299	1998	1	STP efficacy, add on to VPA, CLB	DS efficacy	DB	STP 250 and 500 mg capsules 50 mg/kg/day, Oral route	DS	42	8 weeks	DS	xpt	

Study name	study number	Date*	category	type	objective	design	Test Product(s); Dosage Regimen; Route of Administration	population	n	duration	seizure type	Data presentation	comment
STICLO Italy	BC.385	2000	1	STP efficacy, add on to VPA, CLB	DS efficacy	DB	STP 250 and 500 mg capsules 50 mg/kg/day, Oral route	DS	23	8 weeks	DS	xpt	
STP-1	BC.609	2012	2	STP open label add on (Japan)	DS efficacy	OL	STP 250 capsules or STP 250 mg powder for oral suspension ir (b) (4) Up to 50 mg/kg/day, Oral route	DS	33	16 weeks, OL extension	DS	xpt	
TAU-EAP (ATU de COHORTE)	BC.458	2007	2	OL add on STP, long term safety, EMA temp authorization	DS safety	OL	STP 250 and/or 500 mg capsules and STP 250 and 500 mg powder for oral suspension in (b) (4) 50-100 mg/kg/day, Oral route	DS	210	up to several years	DS	xpt	screened 272
STEV	BC.288	1997	3	single blind STP add on after baseline	DS efficacy	SB	STP 250 and 500 mg capsules and 100, 250, and 500 mg powder for oral suspension in (b) (4) 60 mg/kg/day for 28 days, then increased (as needed) up to 90 mg/kg/day for 56 days, Oral route	DS	25	12 weeks	DS	xpt	
STEV	BC.288	1997	3	single blind STP add on after baseline	non-DS efficacy	SB	same as DS	Refractory epilepsy, non-DS	202	12 weeks	POS, generalized	PDF- Written	
STILON	BC.387	2003	3	OL extension	OL Safety extension of STICAR, LENNOX, WOW, STEV, STISERV, STICLO	OL	STP 250 and/or 500 mg capsules or powder for oral suspension in (b) (4) Maximum dose: 4,000 mg/day, Oral route	DS	45	up to several years	DS	xpt	
STILON	BC.387	2003	3	OL extension	OL Safety extension of	OL	same as DS	non-DS	110	up to several	DS	xpt	xpt after

Study name	study number	Date*	category	type	objective	design	Test Product(s); Dosage Regimen; Route of Administration	population	n	duration	seizure type	Data presentation	comment
					STICAR, LENNOX, WOW, STEV, STISERV, STICLO					years			IR
DIAVEY	BC.627	2012	3	OL post marketing	DS safety, STP add on to AEDs	OL	STP 250 and 500 mg capsules and STP 250 and 500 mg powder for oral suspension in (b) (4) 50 mg/kg/day, Oral route	DS	153	up to several years	DS	xpt	
DIAVEY	BC.627	2012	3	OL post marketing	non-DS safety, STP add on to AEDs	OL	same as DS	non-DS	77	up to several years	POS, generalized epilepsy, LGS, multifocal, others	xpt	xpt after IR
Lennox-Gastaut	BC.274	1994	4	SB, ref period - PBO- add on to standard therapy	efficacy & safety of STP as add on	SB	STP 500 mg capsules and (b) (4) <29 kg: 2,000 mg/day, 29-<39 kg: 2,500 mg/day, >40 kg: 3,000 mg/day, Oral route	LGS	24	8 weeks	LGS	PDF- Written	
STICAR	BC.246	1990	4	add on to CBZ	efficacy	DB	STP 500 mg capsules 2,000 mg/day, Oral route	non-DS	62	8 weeks	epilepsy that is susceptible to carbamazepine, POS, 2nd generalized, absence, tonic, atonic, myoclonic	PDF- Written	
STISEVR	BC.484	2000	4	add on to CBZ	efficacy	SB-OL	STP 250 and 500 mg capsules and 100, 250, and 500 mg powder for oral suspension in (b) (4) 50 mg/kg/day then increased (as needed) up to 90 mg/kg/day, Oral route	non-DS	32	12 weeks	POS type 1-3	PDF- Written	

Study name	study number	Date*	category	type	objective	design	Test Product(s); Dosage Regimen; Route of Administration	population	n	duration	seizure type	Data presentation	comment
WOW	BC.276	1994	4	add on to CBZ	efficacy	OL	STP 500 mg capsules 3,000 mg/day, Oral route	non-DS	64	70 days	POS, generalized	PDF- Written	
martinez-Lage	BC.244	1986	4	titrate off of existing therapy after 8 week basal period to STP monotherapy	efficacy	OL	STP at least 1,800 mg/day as monotherapy, adjusted when biotherapy, Oral route	non-DS	31	8 weeks transition to STP monotherapy, 8 weeks STP alone	POS , CP or 2nd generalized	PDF- Written	
Courjon	BC.109	1976	4	refractory patients receiving "some form of treatment",	efficacy	OL	STP 50 and 100 mg capsules 200-300 mg/day (increased or decreased accordingly), Oral route	non-DS	135	1 month to more than 6 months	POS, primary generalized	PDF- Written	
Loiseau	BC.243	1984	4	withdrawal of background AED over 5 to 8 weeks, then 12 weeks STP monotherapy	efficacy	OL	Up to 1800mg/day, oral	non-DS	44	12 weeks	POS	PDF- Written	

*Date of last patient or study report date in cases where last patient recruitment date is not provided

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