Pharmaceutical company request for oral testimony at the October 18, 2019 Idaho Medicaid Pharmacy & Therapeutics Committee meeting.

Submission # _02

Date request was received: _____10/28/2019

Drug: Diacomit (Stiripentol)

Therapeutic Drug Class: ___antiepileptic_

Pharmaceutical Company: __ BIOCODEX | USA

This request has been reviewed and denied for oral

testimony.

From: Eide, Tamara J.
To: Fox, Suzanne; Gennrich, Jane
Subject: FW: Biocodex Written Testimony- Diacomit (Stiripentol) [External Email]
Date: Monday, October 28, 2019 8:29:20 AM
Attachments: image002.png
image004.png
image006.png
BBD-00011 DIACOMIT Medicaid Formulary Ltr Final v3.pdf

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From: CHAMBERS Casey
Sent: Monday, October 28, 2019 7:57 AM
Subject: Biocodex Written Testimony- Diacomit (Stiripentol) [External Email]

Hi Tamara and the Idaho Medicaid Pharmacy & Therapeutics Committee-

I am writing on behalf of Biocodex to submit written testimony and also request the opportunity to testify during the upcoming P&T meeting regarding Diacomit (Stiripentol). Please find the attached written testimony for Diacomit (Stiripentol), along with a one page executive summary per Idaho Medicaid P&T policy.

If you have any questions or should you need anything additional, please do not hesitate to reach out.

Thank you,

Casey Chambers

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Executive Summary

DIACOMIT® (stiripentol) is an antiepileptic drug approved by the US Food and Drug Administration in 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.

Dravet syndrome is recognized as one of the most devastating forms of epilepsy in children, by its age of onset, clinical signs, dramatic disabilities, increased mortality rate, resistance to conventional anti-epileptic drugs, impact on the neuropsychological and motor development of the patient through adulthood, and its life-shortening consequence.

The 2 well-controlled, pivotal trials of stiripentol in Dravet syndrome patients (STICLO trials) showed a significant response rate from stiripentol combined with valproic acid and clobazam. Stiripentol has long-established efficacy data and over 25 years of clinical evidence associated with extensive data collection and analyses.

DIACOMIT is strongly recommended as an optimal second-line medication by the North America Consensus Panel Dravet syndrome guidelines, with the highest American Academy of Neurology class of evidence rating (level I).

Disease Description

Dravet syndrome is a rare, severe, life-threatening epileptic encephalopathy currently affecting around 2,800 children (from 2 to 18 years) in the United States. Dravet syndrome is associated with a genetic mutation, starts at the first year of life, and persists throughout the lifespan of a patient.

Dravet syndrome is one of the most medically intractable forms of epilepsy marked by frequent seizures of varying types and is often refractory to conventional anti-epileptic drugs. It is characterized by generalized clonic or tonic-clonic seizures, appearing during the first year of life in an otherwise normal infant, and which are later associated with myoclonus, atypical absences and partial seizures (Dravet et al. 2012). In most cases, the first seizures are associated with fever, are generalized, are often prolonged (can last over 20 minutes) and may evolve into *status epilepticus*. With time, seizures increase in frequency and become more likely to occur without fever.

Prognosis is poor: seizures respond poorly to conventional anti-epileptic drugs and most patients develop severe psychomotor retardation. Developmental delay becomes apparent within the second year of life and is followed by definite cognitive impairment and personality disorders. Dravet syndrome is a devastating condition characterized by the following impairments in almost all patients: cognitive and psychomotor development disturbances, intellectual impairment, problems with gait, sleep disturbances, and dependency on a caregiver in adulthood. The risk of premature death (21%) is significantly increased; the highest mortality is observed at ages 3-7 years, with the majority of cases being sudden unexpected death in epilepsy (SUDEP) followed by *status epilepticus* (Shmuely et al. 2016).

Dravet syndrome affects not only the patients, but also the caregivers and the family unit. Caring for a child with Dravet syndrome is associated with extremely heavy humanistic and economic burden. Children with Dravet syndrome require intensive care, including developmental assessments and interventions, individual help at school, respite care, and chronic care throughout adulthood. Episodes of *status epilepticus* require immediate transportation of the patient to the nearest hospital. The fear of *status epilepticus* and SUDEP is one of the most significant concerns of the Dravet syndrome children's parents. The care demands for their child are such that one parent usually cannot work, and family life may be very complex. It is estimated, that 66% of caregivers of patients with Dravet syndrome suffer from depression (Camfield et al. 2016, Villas et al. 2017).

DIACOMIT® (stiripentol) - Efficacy and Safety Data

Stiripentol is a structurally unique antiepileptic drug molecule, acting as a positive allosteric modulator of the gamma-aminobutyric acid GABA-A receptor.

Seizures are one of the typical clinical manifestations in patients with Dravet syndrome, and the major treatment goal is to reduce seizures with the highest morbidity. In this setting, stiripentol combined with clobazam and valproic acid demonstrated significant efficacy in Dravet syndrome in 2 randomized, pivotal phase III clinical trials (STICLO trials) (Chiron at al. 2000; Chiron 2005).

As summarized in the table below, after 8 weeks of treatment with stiripentol, 71% (STICLO France) and 67% (STICLO Italy) of the Dravet patients achieved at least a 50% reduction in seizure frequency (the primary endpoint). A 69% and a 74% mean reduction in seizure frequency was also observed in STICLO France and STICLO Italy respectively. Additionally, 43% (STICLO France) and 25% (STICLO Italy) of children on stiripentol versus none on placebo became completely free of clonic or tonic-clonic seizures after 8 weeks of treatment.

	STICLO France N=41		**STICLO Italy N=23**	
	Stiripentol N=21	**Placebo N=20**	**Stiripentol N=12**	**Placebo N=11**
Percentage change from baseline in seizure frequency				
n Mean ± SD Median Min – Max	20 -69 ± 42 -91 -100 – 28	16 7.6 ± 38 7.4 -75 – 65	11 -74 ± 27 -81 -100 – -33	9 -13 ± 62 -27 -87 – 140
p value	0.0002		0.0056	
Responder analysis				
No of responders/total (Responder Rate) [95% CI]	15/21 (71%) [52 – 91]	1/20 (5%) [0.0 – 15]	8/12 (67%) [40 – 93]	1/11 (9.1%) [0.0 – 26]
p value	<0.0001		0.0094	
Seizure-free patients				
No (%) of patients free of generalized tonic-clonic seizures/total	9/21 (42.9%)	0/20 (0.0%)	3/12 (25.0%)	0/11 (0.0%)
p value	0.0013		0.2174	

Regarding safety, in the STICLO trials the majority of the observed adverse events could be categorized as either neurological (sleepiness/drowsiness/somnolence) or gastrointestinal (loss of appetite, nausea, and loss of weight) in origin. Many of them were often due to associated anticonvulsant medicinal products such as clobazam and were managed through dose reduction of other antiepileptic drugs, with no impact on efficacy.

These efficacy and safety data were consistent within and across multiple studies conducted after the STICLO trials:

- Thanh et al. (2002) conducted an open-label study in 46 Dravet syndrome patients treated with stiripentol in France. On average, patients were treated with stiripentol for 3 years and efficacy results showed a statistically significant reduction of seizure frequency and duration compared to baseline ($P<0.001$).
- A multicenter, open-label safety clinical trial, conducted in 155 patients (STILON), of whom 45 had Dravet syndrome, showed that in Dravet patients, the antiepileptic efficacy of stiripentol was maintained over long-term treatment, up to several years with a satisfactory safety profile.
- Until the marketing authorization was granted in 2007, 210 Dravet patients were recruited in a multicenter Temporary Access Use - Extended Access Program which mainly focused on safety. During the trial, only 15 of 210 (7.1%) patients were prematurely withdrawn from the trial: 7 (3.3%) for lack of efficacy, 4 (1.9%) for other reasons, 1 (0.5%) for the occurrence of status epilepticus, and 3 (1.4%) for AEs. The most frequently reported AEs were decreased appetite, somnolence, agitation, sleep disorder, thrombocytopenia, hypotonia, and insomnia, the same as in the pivotal trials.
- As requested by the European Medicines Agency following stiripentol approval in 2007, a post-marketing survey (DIAVEY) was initiated to proactively collect Adverse Drug Reactions (ADRs) and safety information for patients newly prescribed stiripentol. 227 patients from 57 centers in 11 European countries were included, 152 Dravet syndrome and 75 with other epilepsies. 16 of the 152 (10.5%) Dravet patients were less than 1 year old, and all patients were included for several years (between 1 to 5 years). Study results did not show that stiripentol had a negative impact on the growth in height or weight of these patients. Biological abnormalities observed and possibly linked to stiripentol, such as modifications of the liver function parameters, leukopenia, neutropenia, and the rare risk of thrombocytopenia, were already known and addressed in the label.
- An open label, multicenter phase III trial in Dravet syndrome patients was conducted in Japan. At the end of a 12-week sort-term period, 66.7% of the patients were responders with a mean percent change from baseline in seizure frequency of -57 ± 30.9%. Response was maintained over 52 weeks, and no new safety concern was raised (Inoue et al. 2014; Inoue et al. 2015).
- In the USA, Wirrell et al. (2013) conducted a retrospective review of the efficacy and safety of stiripentol in Dravet patients. Data from 82 Dravet patients documented a responder rate of 63% with stiripentol added to valproic acid and clobazam. Furthermore, stiripentol was associated with marked reductions in the frequency of prolonged seizures, use of rescue medication and emergency room visits.

Recently, several published studies described the very long-term use of stiripentol in Dravet patients. Notably, Myers et al. (2018) evaluated the long-term use of stiripentol in children with Dravet syndrome in a 12-year observational cohort in the United Kingdom and Australia. Twenty-three of 41 patients treated with stiripentol during this observational period had a > 50% reduction in generalized tonic-clonic seizures. Importantly, of the 27 patients who had *status epilepticus* prior to stiripentol initiation, a > 50% decrease in *status epilepticus* was observed in 11 and 7 had no further episodes of *status epilepticus* after stiripentol initiation.

Also, in a long-term follow-up of a French cohort of 40 Dravet patients, all patients were still receiving stiripentol after a median duration of exposure of 18 years (range 3-24 years), with good tolerability, and the positive impacts of stiripentol on epilepsy were maintained as patients entered adulthood (Chiron 2018).

Overall, this extensive body of long-term data consistently demonstrated the maintenance of stiripentol efficacy over several years, even very long-term into adulthood, with a good safety profile. No discrepancy was observed between the studies regarding efficacy and safety data, despite the studies having been conducted in various countries (Europe, USA, Australia, …) and various populations (Caucasian, Asian).

Approaches to Treatment

A North America Consensus Panel established that current standard treatment options for Dravet syndrome in the US typically include the use of valproic acid and/or clobazam as first-line, followed by the combination of stiripentol with valproic acid and clobazam, or the off-label use of topiramate and a ketogenic diet as second-line treatment (Wirrell et al. 2017).

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

These recommendations are in line with a recent expert opinion by Brigo et al. (2018) and are consistent with the International League Against Epilepsy (ILAE) commission of pediatrics, which stated that stiripentol in combination with valproate and clobazam is recommended as the treatment and showed a consistent elevated responder rate (Wilmshurst et al. 2015).

Overall, stiripentol has been available under special access program in the US since 2000 and was approved for adjunctive treatment with clobazam and valproate in Dravet syndrome in 27 countries in the EU (January 2007), Canada (December 2012), Japan (September 2012), and Switzerland (2018). Since stiripentol was first launched in 2007, more than 2,300 patients have been exposed, and no significant safety signal has been reported to date.

Recent approval of stiripentol by the US FDA (August 2018) makes this treatment available to all US patients with Dravet syndrome. Stiripentol addresses key unmet medical needs in this poorly serviced population experiencing a catastrophic, life-threatening condition.

Stiripentol is available in capsule form for oral use and powder form for oral suspension, with both forms available in two different strengths: 250 mg and 500 mg. The daily dose of stiripentol is dependent on the patient's body weight and should target the recommended level of 50 mg/kg/day with a maximum recommended total dose of 3,000 mg/day

Economic Benefits

A health economic model was developed to conduct a cost-utility analysis of stiripentol in conjunction with clobazam and valproate (stiripentol+VPA+CLB) versus VPA+CLB alone for the treatment of Dravet syndrome patients. The model estimated the expected costs and quality-adjusted life-year (QALY) gains over a 15-year time horizon in a cohort of patients initially treated with VPA+CLB, whose seizures are not adequately controlled.

The model simulated the disease progression of Dravet syndrome patients through several health states defined by levels of reduction in seizure frequency (seizure free, not seizure free, and not adequately controlled). Additionally, the possibility of switching to a maintenance therapy and mortality were integrated in the model. A 3-month cycle length was adopted based on clinical practice and existing guidelines.

Results of the cost-utility analysis reveal that the stiripentol strategy is associated with a predicted gain of 0.164 QALYs at an additional cost of $15,749 over a 15-year time horizon, resulting in an incremental cost per QALY gained of $95,796. The difference in total costs between both strategies is mainly due to a higher drug costs of stiripentol+VPA+CLB compared to VPA+CLB ($236,991 versus $186,843), explained by the longer life expectancy, better seizure control (therefore, expected switches to maintenance therapy), and acquisition costs. The monitoring costs, costs of transportation, changing therapy costs, and costs associated to Status epilepticus management for stiripentol+VPA+CLB are lower than for VPA+CLB.

In general, the results are found to be sensitive to the patient starting age at stiripentol initiation (with higher starting ages leading to higher incremental cost-effectiveness ratios (ICERs)) and the cost of maintenance therapy for the VPA+CLB strategy.

Considering the Institute for Clinical and Economic Review's ultra-rare disease threshold of $500,000 per QALY, the probability of stiripentol+CLB+VPA being cost-effective against CLB+VPA is 88%.

From the societal perspective, accounting for indirect costs associated with caring for a Dravet syndrome child, caregiver time commitment results in indirect costs of $500,063 for stiripentol+VPA+CLB and $522,671 for VPA+CLB strategy; meaning stiripentol+VPA+CLB dominates VPA+CLB strategy (better health outcomes with a cost saving).

The model also predicts the impact of stiripentol on healthcare plan budgets for up to 5 years and considers a population of 9 Dravet syndrome patients in a health plan with 1,000,000 members. Stiripentol usage was assumed to range from 60% of patients in the first year to 90% of patients in year 5. The cumulative budget over 5 years is $908,308 without stiripentol and $1,026,490 with stiripentol, leading to a difference of $118,182 over 5 years. The incremental cost per member per month over 5 years is below 1 cent.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
No contraindications are listed.

WARNINGS & PRECAUTIONS

Somnolence
DIACOMIT can cause somnolence. Monitor patients for somnolence, particularly when DIACOMIT is used concomitantly with other CNS depressants or clobazam, which is also known to cause somnolence.

Decreased Appetite and Decreased Weight
DIACOMIT can cause decreases in appetite and weight. The growth and weight of pediatric patients treated with DIACOMIT should be carefully monitored.

Neutropenia and Thrombocytopenia
DIACOMIT can cause significant declines in neutrophil and platelet counts. Hematologic testing should be obtained prior to starting treatment with DIACOMIT and then every 6 months.

Withdrawal Symptoms
As with most antiepileptic drugs (AEDs), DIACOMIT should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus.

Risks in Patients with Phenylketonuria (PKU)
DIACOMIT powder for suspension contains phenylalanine, which can be harmful to patients with PKU. Before prescribing DIACOMIT powder for suspension to a patient with PKU, consider the total daily intake of phenylalanine from all sources, including DIACOMIT powder for suspension. DIACOMIT capsules do not contain phenylalanine.

Suicidal Behavior and Ideation
AEDs, including DIACOMIT, increase the risk of suicidal thoughts or behavior. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

ADVERSE REACTIONS
The most common adverse reactions that occurred in at least 10% of DIACOMIT-treated patients and more frequently than on placebo were somnolence, decreased appetite, agitation, ataxia, decreased weight, hypotonia, nausea, tremor, dysarthria, and insomnia.

PREGNANCY
There are no adequate data on the developmental risks associated with the use of DIACOMIT in pregnant women. Based on animal data, DIACOMIT may cause fetal harm.
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AEDs, such as DIACOMIT, during pregnancy. Physicians are advised to recommend that pregnant patients taking DIACOMIT enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (information at http://www.aedpregnancyregistry.org). This can be done by calling the toll-free number 1-888-233-2334, and must be done by patients themselves or their caregiver.

To report suspected adverse reactions, contact BIOCODEX at 1-866-330-3050 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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