Drug Monograph

Drug/Drug Class:	**Diacomit® (stiripentol) oral capsule and powder / Anticonvulsant Agent**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Diacomit is available in capsule form and powder for oral suspension, both in 250 mg and 500 mg strengths. Biocodex, 1 Avenue Blaise Pascal, 60000 Beauvais France.
Summary of Findings:	In two randomized, double-blind, multicenter, placebo-controlled clinical trials (N=64), Diacomit showed improved efficacy versus placebo at reducing mean frequency of generalized clonic or tonic-clonic seizures. During the two-month trial the most common adverse reactions with Diacomit were somnolence, decreased weight, agitation, decreased appetite, agitation, and hypotonia. Patients should be monitored closely for somnolence, decreased appetite and weight, neutropenia and thrombocytopenia, and suicidal behavior and ideation while taking Diacomit.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-Preferred Agent ☒ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2,3]

Dravet syndrome, sometimes referred to as myoclonic epilepsy of infancy, is a rare epilepsy disease that most commonly presents in infancy or early childhood. Prevalence of Dravet syndrome is 1 in over 15,000 and over 80% of cases have a mutation in the SCN1A gene. Dravet syndrome can cause a multitude of symptoms including prolonged and frequent seizures, development issues, and sensory disorders. Treatment options are very limited for this disease and focus on care for the individual and the use of medications to treat the seizures. In 2018 the FDA approved the first treatment option in the form of Epidiolex.

Dosage Form(s) [1]

Diacomit is available in both capsule form and powder for oral suspension, both in 250 mg and 500 mg strengths.

Manufacturer [1]

Biocodex, 1 Avenue Blaise Pascal, 60000 Beauvais France.

Indication(s) [1]

Diacomit is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

The exact mechanism of action for Diacomit is unknown. Possible mechanisms of action include direct effects mediated through the gamma-aminobutyric acid $(GABA)_A$ receptor and indirect effects involving inhibition of cytochrome P450 activity leading to increased levels of clobazam.

Pharmacokinetics:

	Diacomit
Volume of Distribution	Protein binding 99%
Metabolism	Cytochrome P450
Excretion	Urine 73%, feces 18% (unchanged)
Half-life	4.5 – 13 hours

STICLO France and STICLO Italy

STUDY DESIGN	Two, double-blind, randomized, placebo-controlled, multicenter clinical trials (study 1 N=41 and Study 2 N=23).
INCLUSION CRITERIA	Patients must be 3 years to less than 18 years of age, have Dravet syndrome and be inadequately controlled on clobazam and valproate with at least 4 generalized clonic or tonic-clonic seizures per month despite optimized therapy.
EXCLUSION CRITERIA	The study excluded patients that did not meet the inclusion criteria.
TREATMENT REGIMEN	Patients eligible for the study were enrolled in a 1-month baseline in which they continued to take the antiepileptic treatment. After 1-month patients were randomized to receive either Diacomit at 50 mg/kg/day in divided doses with no dose titration or placebo. The 2-month studies had a primary endpoint of the responder rate as defined by a patient who experienced a greater than 50% decrease in the frequency of generalized clonic or tonic-clonic seizures during the double-blind treatment period compared to the 4-week baseline period.
RESULTS	Both studies showed a significantly greater responder rate compared to placebo (Study 1 p-value 0.0094 and Study 2 p-value[b] <0.001). In Study 1, 71% of patients receiving Diacomit were considered responders compared to 5% of patients receiving placebo. In Study 2, 67% of patients receiving Diacomit were considered responders compared to 9.1% of patients receiving placebo. In Study 1, 43% of patients reported no generalized clonic or tonic-clonic seizures for the duration of the study and 25% in Study 2. Diacomit also showed improvement for reduction in mean frequency of generalized clonic or tonic-clonic seizures.
SAFETY	The most common adverse reactions were somnolence, decreased weight, agitation, decreased appetite, agitation, and hypotonia. Two patients discontinued therapy, one had an adverse reaction of status epilepticus and the second had drowsiness, balance impaired and sialorrhea.

Contraindications (1)

- Diacomit has no known contraindications per prescribing information.

Warnings and Precautions (1)

- Somnolence**:** Somnolence was seen in 67% of treated patients (compared to 23% in placebo) and may require dose reduction. Clobazam can also cause somnolence therefore

clobazam doses may also need to be reduced.

- Decreased Appetite and Decreased Weight**:** Pediatric patient growth should be carefully monitored and may need dose reductions.
- Neutropenia and Thrombocytopenia**:** Diacomit can cause a significant decline in neutrophil count and platelet count. Hematologic testing should be obtained prior to starting and every 6 months thereafter.
- Withdrawal Symptoms**:** Diacomit should generally be withdrawn gradually to minimize the risk of increased seizure frequency and status epilepticus.
- Risks in Patients with Phenylketonuria**:** Diacomit powder for suspension contains phenylalanine, which can be harmful to patients with phenylketonuria (PKU).
- Suicidal Behavior and Ideation**:** Patients should be monitored for the emergence or worsening of depression, suicidal thought or behavior and/or any unusual changes in mood or behavior.

Adverse Effects [(1)]

Most common, ≥ 2%	Diacomit 50 mg/kg/day	Placebo
Somnolence	67%	23%
Decreased Weight	27%	6%
Decreased Appetite	46%	10%
Agitation	27%	16%
Nausea	15%	3%
Dysarthria	12%	0

Drug Interactions [(1)]

- Effect of Diacomit on Other Drugs**:** Diacomit is both an inhibitor and inducer of several metabolic pathways therefore dose adjustment may be possible for CYP1A2, CYP2B6, CYP2C8, CYP2C19 and P-glycoprotein and Breast Cancer Resistance Protein substrates.
- Effect of Other Drugs on Diacomit**:** Concomitant use of strong inducers with Diacomit should be avoided, or dosage adjustments should be made. CYP1A2, CYP3A4 or CYP2C19 inducers may lead to decreased Diacomit concentrations.
- CNS Depressants and Alcohol**:** Concomitant use Diacomit with other CNS depressants, including alcohol, may increase the risk of sedation and somnolence.

Dosage and Administration [(1)]

Diacomit has a recommended oral dosage of 50 mg/kg/day to be administered in 2 or 3 divided doses. When an exact dosage is not available, labeling recommends rounding up to the nearest possible dosage. The maximum recommended total dosage is 3000 mg/day. Diacomit capsules should be swallowed whole with a glass of water and during a meal. The powder for oral suspension should be mixed with 100 mL of water and taken immediately after mixing

during a meal. Once complete, 25 mL of water should be added to the glass and drank to ensure all the medication is administered.

Cost

BRAND NAME	MANUFACTURER	STRENGTH	DOSE	APPROXIMATE COST/MONTH*
Diacomit	Biocodex	250 mg, 500 mg Capsule or Powder for suspension	50 mg/kg/day in 2 or 3 divided doses	$1,166.67
Epidiolex	Greenwich Biosciences	100 mL bottle containing 100 mg of cannabidiol	2.5 mg/kg twice daily	$555.75

* Wholesale Acquisition Cost (based on a 30 kg patient)

Conclusion

The exact mechanism of action for Diacomit is unknown. Possible mechanisms of action include direct effects mediated through the gamma-aminobutyric acid $(GABA)_A$ receptor and indirect effects involving inhibition of cytochrome P450 activity leading to increased levels of clobazam. Diacomit is approved for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam. In two randomized, double-blind, multicenter, placebo-controlled clinical trials (N=64), Diacomit showed improved efficacy versus placebo at reducing mean frequency of generalized clonic or tonic-clonic seizures. During the two-month trial the most common adverse reaction with Diacomit were somnolence, decreased weight, agitation, decreased appetite, agitation, and hypotonia. Patients should be monitored closely for somnolence, decreased appetite and weight, neutropenia and thrombocytopenia and suicidal behavior and ideation while taking Diacomit.

Recommendation

The Division recommends adding this drug to the current 15 day quantity limitation fiscal edit and to the current psychotropic polypharmacy clinical edit.

References

1) Product Information: Diacomit™ (stiripentol), Biocodex, 1 Avenue Blaise Pascal, 60000 Beauvais France.
2) Dravet Syndrome Information Page March 27, 2019 National Institute of Neurological Disorders and Stroke.
3) What is Dravet Syndrome? Dravet Syndrome Foundation June 2019.

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