PDL DRUG REVIEW

Proprietary Name: Miplyffa®
Common Name: arimoclomol
PDL Category: Neurologics

Comparable Products	Preferred Drug List Status
Aqneursa	Non-Preferred

Pharmacology/Usage: The mechanism(s) by which arimoclomol, the active ingredient of Miplyffa®, exerts its clinical effects is not known.

Indication: For use in combination with miglustat for the treatment of neurological manifestations of Niemann-Pick disease type C (NPD-C) in adult and pediatric patients 2 years of age and older.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal reproduction studies, Miplyffa® may cause embryofetal harm when administered during pregnancy. There are no available data on use in pregnant females to assess a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Advise pregnant females of the potential risk to the fetus. The safety and efficacy of use have not been established in pediatric patients younger than 2 years of age.

Dosage Form: Capsules: 47mg, 62mg, 93mg, and 124mg.

Recommended Dosage: The recommended dosage of Miplyffa®, in combination with miglustat, for patients with an actual body weight of:

- 8kg to 15mg, is 47mg TID.
- >15kg to 30kg, is 62mg TID.
- >30kg to 55kg, is 93mg TID.
- >55kg, is 124mg TID.

Miplyffa® can be administered with or without food. Swallow capsules whole. However, for patients who have difficulty swallowing capsules, administer Miplyffa® in one of two ways, including either as oral administration or as feeding tube administration (nasogastric or gastric tube). For oral administration, open the capsule and sprinkle the entire contents into 15ml of water or apple juice or 15ml of soft food (e.g., applesauce, pudding, or yogurt).

If a dose of Miplyffa® is missed, advise the patient to skip the missed dose and to resume taking the prescribed dose at the next scheduled time.

The recommended dosage of Miplyffa®, in combination with miglustat, in patients with an eGFR ≥50ml/minute is the same as the recommended dosage in patients with normal renal function. For patients with an eGFR ≥15 to <50ml/minute, the recommended oral dosage of Miplyffa®, in combination with miglustat, for patients with an actual body weight of:

- 8kg to 15mg, is 47mg BID.
- >15kg to 30kg, is 62mg BID.
- >30kg to 55kg, is 93mg BID.

- >55kg, is 124mg BID.

Drug Interactions: Arimoclomol is an inhibitor of the organic cationic transporter 2 (OCT2) transporter and may increase the exposure of drugs that are OCT2 substrates. When Miplyffa® is used concomitantly with OCT2 substrates, monitor for adverse reactions and reduce the dosage of the OCT2 substrate.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Miplyffa® with miglustat) minus reported % incidence for placebo with miglustat. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included upper respiratory tract infection (16%), diarrhea (0%), decreased weight (15%), decreased appetite (12%), tremor (12%), urticaria (12%), headache (4%), lower respiratory tract infection (4%), and seizure (4%).

Hypersensitivity reactions have been reported in patients treated with Miplyffa® during Trial 1: two patients reported both urticaria and angioedema (6%) and one patient (3%) experienced only urticaria. The reactions occurred within the first two months of treatment. Discontinue Miplyffa® in patients who develop severe hypersensitivity reactions. If a mild or moderate hypersensitivity reaction occurs, stop Miplyffa® and treat promptly. Monitor the patient until signs and symptoms resolve.

Across clinical trials of Miplyffa®, consisting of patients with NPD-C, healthy subjects, and patients with other diseases, there were mean increases in serum creatinine of 10% to 20% compared to baseline. These increases occurred mostly in the first month of Miplyffa® treatment and were not associated with changes in glomerular function. The increases in serum creatinine may be due to inhibition of renal tubular secretion transporters. During Miplyffa® treatment, use alternative measures that are not based on creatinine to assess renal function such as BUN, cystatin C, or measured GFR. Increases in creatinine reversed upon Miplyffa® discontinuation.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Zevra Therapeutics, Inc.

Analysis: The safety and efficacy of Miplyffa® were assessed in Trial 1, a randomized, double-blind, placebo-controlled trial of 12 months duration that included patients 2 to 19 years of age who had a molecularly confirmed diagnosis of NPD-C. Fifty patients were randomized to treatment with weight-adjusted Miplyffa® or placebo orally three times per day. In this study, 76% in the Miplyffa® group and 81% in the placebo group received miglustat 6 months or longer prior to the time of enrollment. For the subgroup who also received miglustat at enrollment, the mean age was 11.6 years, the mean time since first NPD-C symptom was 8.5 years, and the mean age at onset of first neurological symptom was 4.9 years. In this subgroup, 56% were female, 87% were white, and the mean baseline rescored 4-domain NPD-C Clinical Severity Scale or R4DNPCCSS score was higher in the Miplyffa® group (N=26, mean 8.9) than the placebo group (N=13, mean 7), with an overall mean R4DNPCCSS score of 8.3.

Efficacy assessments, including the R4DNPCCSS score, were performed at baseline and every 3 months until 12 months of treatment. The R4DNPCCSS is a measure of NPD-C disease progression that consists of the four items assessing ambulation, speech, swallow, and fine motor skills that patients with NPD-C and their caregivers and physicians have identified as most relevant with higher scores representing greater severity of disease.

In the Miplyffa® group, 4 patients discontinued the study, including one patient due to consent withdrawal and three patients due to adverse reactions. In the placebo group, one patient discontinued the study due to an adverse event.

The table below, adapted from the prescribing information, presents the changes from baseline in R4DNPCCSS score at month 12 in patients 2 to 19 years of age with NPD-C who also received miglustat.

	R4DNPCCSS Score			
	Baseline		Change from baseline to month 12	
	Miplyffa® with miglustat	Placebo With miglustat	Miplyffa® with miglustat	Placebo with miglustat
N	26	13	22	12
Mean	8.9	7	-0.2	1.9
Median	7.5	5	0	1
Least Squares (LS) Mean			-0.2	2
Placebo-subtracted difference			-2.2	

There were not sufficient data to determine the effectiveness of the use of Miplyffa® without miglustat for the treatment of neurological manifestations in patients with NPD-C.

Place in Therapy: Miplyffa® is indicated for use in combination with miglustat for the treatment of neurological manifestations of Niemann-Pick disease type C (NPD-C) in adult and pediatric patients 2 years of age and older. NPD-C is a rare autosomal recessive disorder that results in progressive neurological symptoms and organ dysfunction. To date, there is supportive treatment for physical manifestations of the disease through physical therapy.[4] The current treatment comparator is Aqneursa®, which was recently approved by the FDA (09/24). To date, there is no comparator trial between Aqneursa® and Miplyffa®. Each drug trial also looked at different functional scoring criteria outcomes.

The efficacy of Miplyffa® was established in a randomized, double-blind, placebo-controlled, 12-month trial that included 50 patients with a molecularly confirmed diagnosis of NPD-C. Efficacy assessments included the R4DNPCCSS score, with higher scores representing greater severity of disease. The least square mean change from baseline to month 12 was -0.2 with Miplyffa® plus miglustat as compared with 2 with placebo plus miglustat.

Per the full-text study by Mengel et al[2], the primary endpoint of the trial discussed above was the change from baseline in NPD-C severity at 12 months as assessed by the 5-domain NPD-C Clinical Severity Scale (5DNPCCSS). The fully validated 5-domain NPCCSS includes the domains determined to be most clinically relevant to patients, caregivers, and clinicians: ambulation, cognition, fine motor skills, speech, and swallowing. The total score ranges from 0 to 25, with a higher score indicating more severe clinical impairment. Results suggested for this primary endpoint, at month 12, the mean change was 0.76 for arimoclomol as compared with 2.15 for placebo, corresponding to a significant treatment effect in favor of arimoclomol of -1.40 ($p=0.046$). Furthermore, in the subgroup analysis of patients ≥4 years of age (N=44) and patients receiving concomitant miglustat (N=39), the treatment effect within each subgroup was increased ($p<0.05$).

Per the manufacturer, due to recommendations from the FDA, the 5DNPCCSS was amended to a R4DNPCCSS by making two functional changes. The cognition domain was removed from the scoring, due to concerns relating to cognition assessment in as 12-month study timeframe. In addition, the swallow domain was updated. The scoring system thus ranges from 0-20 for the R4DNPCCSS.[3]

Summary

It is recommended that Miplyffa® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Miplyffa [package insert]. Celebration, FL: Zevra Therapeutics, Inc; 2024.
[2] Mengel E, Patterson MC, Da Riol RM, et al. Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind, randomized, placebo-controlled, multinational phase 2/3 trial of a novel treatment. *J Inherit Metab Dis*. 2021; 44(6): 1463-1480.
[3] Information on Miplyffa Safety and Efficacy from the Pivotal Clinical Trial. From Zevra Therapeutics Medical Information, requested October 2024.
[4] UpToDate online. Overview of acid sphingomyelinase deficiency and Niemann-Pick disease type C. Accessed February 2025.

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