09-J5000-04

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Subject: Arimoclomol (Miplyffa) Capsules

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DESCRIPTION:

Niemann-Pick disease type C (NPC) is a rare, progressive autosomal recessive lysosomal storage disorder which results in the accumulation of cholesterol and other fatty substances within various tissues of the body, including brain tissue. The clinical presentation of NPC varies based on age and may include visceral, neurologic, and psychiatric symptoms. Children with NPC 2 years of age and younger are classified as perinatal and early-infantile disease and present with liver disease and prolonged neonatal jaundice, hepatosplenomegaly, and developmental delay. Children with NPC aged 2 years to early adolescence are classified as late-infantile or juvenile-onset disease and present with neurological manifestations (e.g., clumsiness, progressive ataxia, dysarthria, dystonia), hepatomegaly or splenomegaly, and vertical supranuclear gaze palsy, which is considered the clinical hallmark of the disorder. Lastly, adolescents greater than 15 years old and adults are classified as adolescent/adult-onset disease and present with atypical psychotic disorder, progressive neurologic symptoms (e.g., ataxia, dystonia, dysarthria) and vertical supranuclear gaze palsy. Unfortunately, diagnosis may be delayed due to the variable age of onset and various symptoms.

Genetic testing is used to confirm the diagnosis through the *NPC1* gene (NPC type 1C) or *NPC2* gene (NPC type 2C) sequencing, two genes that are known to cause NPC. Biallelic variants in either of the two genes result in the same clinical disease. If two known or likely pathogenic alleles are present, then the diagnosis is confirmed. If sequencing shows two pathogenic alleles with 1 or 2 potential variants of unknown significance, then disease is possible and a filipin test is conducted. If the filipin test is highly positive with 'classical' staining or moderately positive with 'variant' staining, then NPC is considered confirmed, and if “mildly” stained, then it is likely not NPC but may be possible NPC heterozygote. Until recently, treatment options were limited and included miglustat (Yargesa, Zavesca) at 100 – 200 mg by mouth once to three times per day along with symptomatic management and the patient’s needs (e.g.,

physical and speech therapy). On September 20, 2024, the FDA approved arimoclomol (Miplyffa) for use in combination with miglustat for the treatment of neurological manifestations of NPC in adult and pediatric patients 2 years of age and older.

The safety and effectiveness of arimoclomol (Miplyffa) was assessed in a randomized, double-blind, placebo-controlled, 12-month trial in patients 2 to 19 years of age who had a molecularly confirmed diagnosis of NPC. Fifty patients were randomized 2:1 to treatment with weight-adjusted arimoclomol (Miplyffa) (31 to 124 mg) or placebo orally three times per day. The randomization was stratified by miglustat use status at baseline. Efficacy assessments, including the rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS) score, were performed at baseline and every 3 months until 12 months of treatment. The R4DNPCCSS is a measure of NPC disease progression that consists of the four items assessing ambulation, speech, swallow, and fine motor skills that patients with NPC and their caregivers and physicians have identified as most relevant with higher scores representing greater severity of disease. Of the patients enrolled in the study, 76% of the treatment arm and 81% of the placebo arm received miglustat six months or longer prior to the time of enrollment. For the subgroup of patients who also received miglustat at enrollment, the mean age was 11.6 years, the mean time since first NPC symptom was 8.5 years, and the mean age at onset of first neurological symptom was 4.9 years. In this subgroup, 56% of patients were females, 87% were Caucasian, 5% were Asian, 3% were native Hawaiian or other Pacific Islander, and 5% were unknown. The mean baseline R4DNPCCSS score was higher in the arimoclomol (Miplyffa) group (n=26; mean=8.9) than the placebo group (n=13; mean=7), with an overall mean R4DNPCCSS score of 8.3. In the arimoclomol (Miplyffa) group, four patients discontinued the study: 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. Table 1 lists the change from baseline in the R4DNPCCSS Score at Month 12 in patients 2 to 19 years of age with NPC (subgroup who also received miglustat).

Table 1: Change from Baseline in R4DNPCCSS Score at Month 12 in Patients 2 to 19 Years of Age with NPC (Subgroup Who Also Received Miglustat)

	R4DNPCCSS Score			
	Baseline		**Change from Baseline to Month 12**	
	Arimoclomol (Miplyffa) with miglustat (N=26)	Placebo with miglustat (N=13)	Arimoclomol (Miplyffa) with miglustat (N=22)	Placebo with miglustat (N=12)
Mean (SD)	8.9 (6.1)	7 (5.8)	-0.2 (1)	1.9 (3.4)
Median	7.5	5	0	1
LS Mean (SE)			-0.2 (0.5)	2 (0.7)
Placebo-subtracted Difference (95% CI) [a]			-2.2 (-3.8, -0.6)	

[a] Changes in R4DNPCCSS score from baseline to month 12 were compared using an analysis of variance (ANCOVA) model fitted with treatment and baseline R4DNPCCSS score as covariate

The most common adverse reactions with arimoclomol (Miplyffa) (reported in ≥ 15%) are upper respiratory tract, infection, diarrhea, and decreased weight.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of arimoclomol (Miplyffa) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is 2 years of age or older with a diagnosis of Niemann-Pick disease type C (NPC)
2. One of the following ("a" or "b"): - Laboratory documentation of the genetic testing results must be submitted
    a. Genetic test demonstrating biallelic known or likely pathogenic variants in the *NPC1* or *NPC2* gene
    b. Both of the following ("i" and "ii"):
        i. Genetic test demonstrating two pathogenic alleles with 1 or 2 potential variants of unknown significance in the *NPC1* or *NPC2* gene
        ii. Filipin test is highly positive with 'classical' staining or moderately positive with 'variant' staining
3. Prescribed in combination with generic miglustat (Yargesa, Zavesca) unless the member has a documented hypersensitivity or intolerance to miglustat – documentation must be provided
4. **NOT** being administered in combination with levacetylleucin (Aqneursa)
5. Negative pregnancy test prior to therapy initiation (only for women of reproductive potential)
6. Prescribed by a specialist who treats patients with NPC such as a neurologist, neuromuscular specialist, or geneticist.
7. Dose does NOT exceed 124 mg three times a day

Approval duration: 6 months

Arimoclomol (Miplyffa) is considered experimental or investigational for any other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcome.

Continuation of arimoclomol (Miplyffa) **meets the definition of medical necessity** for members meeting the following criteria:

1. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), OR the member has previously met ALL indication-specific initiation criteria.

2. Member has a clinical meaningful response (e.g., improvement, stabilization, and/or slowed decline in ambulation, speech, swallow, and fine motor skills) with no significant adverse drug reactions (e.g., severe hypersensitivity reactions) necessitating discontinuation of therapy.
3. Prescribed in combination with generic miglustat (Yargesa, Zavesca) unless the member has a documented hypersensitivity or intolerance to miglustat – documentation must be provided
4. **NOT** being administered in combination with levacetylleucin (Aqneursa)
5. Recent negative pregnancy test (only for women of reproductive potential)
6. Prescribed by a specialist who treats patients with NPC such as a neurologist, neuromuscular specialist, or geneticist.
7. Dose does NOT exceed 124 mg three times a day

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Arimoclomol (Miplyffa) is indicated for use in combination with miglustat for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients 2 years of age and older.
- The recommended oral dosage is based on the patient's actual body weight:
  - 8 kg to 15 kg, is 47 mg three times a day
  - > 15 kg to 30 kg, is 62 mg three times a day
  - > 30 kg to 55 kg, is 93 mg three times a day
  - > 55 kg, is 124 mg three times a day
- Arimoclomol (Miplyffa) may be administered with or without food and should be swallowed whole. If the patient has difficulty swallowing capsules, the capsule may be opened and sprinkles (entire contents) into 15 mL of water or apple juice or soft food (e.g., applesauce, pudding, or yogurt). The mixture should be stirred for 15 seconds, and the entire mixture immediately consumed. If administering via a feeding (nasogastric or gastric) tube, open the capsule and sprinkle the entire contents into 20 mL of water. Do not add the capsule contents to other liquids besides water. Stir the mixture for 15 seconds and administer the entire mixture immediately via feeding tube. Then flush the feeding tube with 5 mL of water after administration.
- Arimoclomol (Miplyffa) is an inhibitor of the organic cationic transporter 2 (OCT2) transporter and may increase the exposure of drugs that are OCT2 substrates. When arimoclomol (Miplyffa) is used concomitantly with OCT2 substrates, monitor for adverse reactions and reduce the dosage of the OCT2 substrate.

Dose Adjustments

- Dosage adjustments are required for patients with an eGFR ≥ 15 to < 50 mL/minute and are as follows:
  - 8 kg to 15 kg, is 47 mg two times a day
  - > 15 kg to 30 kg, is 62 mg two times a day
  - > 30 kg to 55 kg, is 93 mg two times a day
  - > 55 kg, is 124 mg two times a day
- Arimoclomol (Miplyffa) was not evaluated in patients with eGFR < 15 mL/minute.
- No dosage adjustments are needed for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). Arimoclomol (Miplyffa) has not been studied in patients with severe hepatic impairment (Child-Pugh Criteria C).

Drug Availability

- Arimoclomol (Miplyffa) capsules are supplied in 90-count bottles at the following strengths:
  - 47 mg (72542-147-01)
  - 62 mg (72542-162-01)
  - 93 mg (72542-193-01)
  - 124 mg (72542-124-01)

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Hypersensitivity Reactions:** Hypersensitivity reactions such as urticaria and angioedema have been reported in patients treated with arimoclomol (Miplyffa) during its clinical trial: two patients reported both urticaria and angioedema (6%) and one patient (3%) experienced urticaria alone. The reactions occurred within the first two months of treatment. Discontinue arimoclomol (Miplyffa) in patients who develop severe hypersensitivity reactions. If a mild or moderate hypersensitivity reaction occurs, stop arimoclomol (Miplyffa) and treat promptly. Monitor the patient until signs and symptoms resolve.
- **Embryofetal Toxicity:** Based on findings from animal reproduction studies, arimoclomol (Miplyffa) may cause embryofetal harm when administered during pregnancy. In animal reproduction studies, oral administration of arimoclomol to pregnant rats and rabbits resulted in post-implantation loss and structural abnormalities in offspring. These occurred at exposures equal to or greater than 10- and 5-fold, for rats and rabbits respectively, the human exposure at the maximum recommended

human daily dose of 372 mg. Advise pregnant females of the potential risk to the fetus. Consider pregnancy planning and prevention for females of reproductive potential.

- **Increased Creatinine without Affecting Glomerular Function:** Across clinical trials of arimoclomol (Miplyffa) consisting of patients with NPC, 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 arimoclomol (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 arimoclomol (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 arimoclomol (Miplyffa) discontinuation.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

E75.242	Niemann-Pick disease type C

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: The following National Coverage Determination (NCD) was reviewed on the last guideline revised date: Self-administered Drug List (A54770). No Local Coverage Determination (LCD) was found at the time of the last guideline revised date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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3. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2024. URL http://www.dynamed.com. Accessed 9/29/24.
4. Miplyffa (arimoclomol) [package insert]. Celebration, FL: Zevra Therapeutics, Inc.; September 2024.
5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 2024 Sept 29]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/09/24.

GUIDELINE UPDATE INFORMATION:

01/01/25	New Medical Coverage Guideline: Arimoclomol (Miplyffa) capsules for use in combination with miglustat for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients 2 years of age and older.