PRIOR AUTHORIZATION POLICY

POLICY: Niemann-Pick Disease Type C – Miplyffa Prior Authorization Policy
- Miplyffa™ (arimoclomol capsules –Zevra)

REVIEW DATE: 10/30/2024

OVERVIEW

Miplyffa is indicated in combination with miglustat for the treatment of neurological manifestations of **Niemann-Pick disease type C (NPC)** in patients ≥ 2 years of age.[1]

The FDA concluded that data are insufficient to determine the effectiveness of Miplyffa without miglustat for the treatment of neurological manifestations in patients with NPC.[1]

Disease Overview

NPC is an autosomal recessive, progressive lysosomal storage disorder.[5] NPC is considered an ultra-rare disease with an estimated incidence of 1 in 100,000 live births; however, this is thought to underestimate individuals with later onset disease.[4-6] NPC is caused by mutations in NPC1 (90% to 95%) or NPC2 (5%) that yield deficient function of the corresponding proteins that normally bind and transport cholesterol.[6] The lysosomal dysfunction in NPC leads to an accumulation of lipids in the brain, liver, and spleen.

The presentation of NPC is heterogeneous characterized by visceral, neurological, or psychiatric symptoms that may present at any age with variable rates of progression.[4] Patients have difficulties with walking, swallowing, speaking, concentration, and/or memory. The age of onset of neurological symptoms predicts the severity of the disease and determines life expectancy; NPC is classified according to the age of onset of neurological manifestations. Three forms of NPC are described: 1) visceral-neurodegenerative (< 2 years [early infantile]); 2) neurodegenerative (2 to 6 years [late infantile] and 6 to 15 years [juvenile]; and 3) psychiatric-neurodegenerative (> 15 years [adults]). Patients with infantile and juvenile-onset NPC are usually severely impacted by the disease; however, patients with adolescent- or adult-onset NPC likely make up the largest patient group in terms of prevalence (estimated to be ≥ 20%). The spectrum of NPC ranges from a neonatal rapidly progressive fatal disorder to an adult-onset chronic neurodegenerative disease. In addition, atypical presentations (fatal systemic perinatal form and initial systemic disease) constitute a small, but significant, proportion of cases.

Clinical Efficacy

The efficacy of Miplyffa was evaluated in one Phase II/III, randomized, double-blind, placebo-controlled, multicenter, pivotal study in patients ≥ 2 to ≤ 18 years of age with genetically confirmed NPC (n = 50).[2] The confirmed diagnosis of NPC met one of the following: 1) genetically confirmed mutation in both alleles of NPC1 or NPC2; OR 2) mutation in only one allele of NPC1 or NPC2 plus either positive filipin staining or elevated cholestane-triol level (> 2 times the upper limit of normal). Patients had at least one neurological sign of NPC and the ability to walk independently or with assistance. Concurrent use of miglustat was allowed; 78% of patients were taking miglustat. The mean age was 11.1 years. The mean age of first neurological symptom was 5.1 years; 48% of patients had late infantile-onset NPC (2 to < 6 years of age), 34% of patients had juvenile-onset NPC (6 to 15 years of age), and 16% of patients had early infantile-onset NPC (3 months to < 2 years of age). No patients with adult-onset NPC (age > 15 years at first neurological symptom) were enrolled. The primary efficacy endpoint was the change in NPC disease severity from baseline to Month 12 assessed by the 5-domain NPC Clinical Severity Scale (NPCCSS) score (5 domains: ambulation, cognition, fine motor skills, speech, and swallowing; scores range from 0 to 25, higher scores indicate more severe clinical impairment). The mean baseline 5-domain NPCCSS scores

were 12.1 points and 9.4 points in the Miplyffa and placebo groups, respectively. ***Results.*** At Month 12, the mean change from baseline on the 5-domain NPCCSS score significantly favored Miplyffa vs. placebo in the overall population (mean +0.76 points vs. +2.15 points, respectively; difference -1.40 points; P = 0.046); difference corresponds to a 65% reduction in annual disease progression. The treatment effect of Miplyffa (vs. placebo) on the 5-domain NPCCSS score was enhanced in the subgroups of patients ≥ 4 years of age (n = 44) [mean change +0.40 vs. +2.20, respectively; difference -1.80 points; P = 0.016; 103% reduction in annual disease progression] and in patients taking miglustat (n = 39) [mean change -0.06 points vs. +2.01 points, respectively; difference -2.06; P = 0.006; 82% reduction in annual disease progression]. There was no significant difference between Miplyffa and placebo in the proportion of responders (stable or improved 5-domain NPCCSS scores) [50.0% vs. 37.5% of patients, respectively]. Further, a similar proportion of patients had a 2-point (or greater) worsening on the 5-domain NPCCSS at Month 12 (~44% of patients). At Month 12, there were no significant differences between Miplyffa and placebo for secondary endpoints.

Data from the 4-year open-label extension (5 years of exposure to Miplyffa) have been presented (unpublished); 29 patients (71%) completed the open-label extension.[3] Generally, the severity of disease progressed slowly over the open-label extension in a stepwise pattern. In patients who continued Miplyffa from the pivotal trial, the mean change in the 4-domain NPCCSS score (4 domains: ambulation, speech, swallowing, and fine motor; scores range from 0 to 20, higher scores indicate more severe clinical impairment) for each year in the open-label extension was variable and showed an initial worsening (4-domain NPCCSS +1.4 points for the first 1 year of the open-label extension [Months 12 to 24]). The mean year-to-year change in the 4-domain NPCCSS score for the following 3 years (Years 2, 3, and 4) was +1.1 points, +0.3 points, and +0.8 points, respectively. The increase in disease progression during the first 1-year of the open-label extension was attributed to a small number of patients who were not taking miglustat and had rapid disease progression.

Guidelines

Consensus clinical management guidelines for NPC have been developed by the International Niemann-Pick Disease Registry (INPDR) project (2018).[4] Disease-modifying therapy is discussed; however, Miplyffa is only mentioned as an agent in development. Optimal disease management includes a multidisciplinary team (e.g., primary care physician, metabolic disease specialist, neurologist, psychiatrist, anesthesiologist, neuro-ophthalmologist, neuropsychologist, speech and language therapist, occupational and physical therapists, nutritionist, gastroenterologist, social worker, genetic counselor) based in a specialty care center. The mainstay of therapy is symptom management with disease-modifying agents when available. Patients should be assessed for growth and developmental delay, mobility, swallowing and diet, speech, spasticity, bowel and bladder dysfunction, cataplexy, mental well-being, hypersalivation/drooling, and hearing.

Regarding disease-modifying therapies, all patients with a confirmed diagnosis of NPC should be considered for miglustat (strength of recommendation: 2; level of evidence C; 13% of experts completely agree, 38% mostly agree, 13% partially agree, 25% mostly disagree, and 13% completely disagree).[4] However, there are several instances in which miglustat is not recommended: patients who are pre-symptomatic or have only spleen or liver enlargement, those with advanced neurological disease (e.g., inability to ambulate without a wheelchair, complete lack of verbal communication, swallowing difficulties profound enough to require tube feeding through a percutaneous gastrostomy) or dementia (e.g., need for 24-hour care), and patients with another life-threatening illness with estimated lifespan < 1 year (noted not to be based on evidence). Note: In the US, miglustat is indicated as monotherapy for the treatment of adults with mild/moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option.[8] However, in other countries, it is approved for the management of neurologic manifestations of NPC.[5]

Treatment goals should be established at diagnosis and reviewed regularly (generally every 6 to 12 months) and aimed at improving or maintaining the physical and psychosocial well-being of the patient.[4]

NPC Diagnosis

When NPC is clinically suspected, diagnosis can be confirmed by the combination of biochemical and molecular genetic studies.[4] In any individual in whom the diagnosis of NPC is considered based on their clinical manifestations and/or abnormal biomarker profile genetic testing for NPC genes should be conducted to confirm the diagnosis. Mutation analysis of NPC1 and NPC2 genes is mandatory to confirm the diagnosis of NPC. It is also the only reliable method to diagnose NPC carriers within a family and the highly preferred strategy for prenatal diagnosis. The identification of two alleles with known disease-causing mutations in either NPC1 or NPC2 gene confirms the diagnosis of NPC. Approximately 700 NPC1 variants have been reported among which around 420 are considered pathogenic, with only a limited number being common (p.I1061T, pP1007A) or recurrent mutations. Interpretation of new missense and splicing mutations should be undertaken with caution and their pathogenicity must be verified. The presence of very severe mutations (frameshift, nonsense, large deletion) in both alleles often results in early-infantile neurological disease (with a higher risk of severe, possibly fatal, systemic disease). Approximately 26 pathogenic NPC2 mutations have been described. Most are frameshift of nonsense as well as large deletion variants that leads to a severe clinical phenotype. Among the missense mutations in NPC2, two variants (p.V39 M and p.P120S) have been associated with the juvenile or adult forms of the disease. More patients from North Africa, Italy, and Turkey have been identified with NPC2 mutations.

The filipin test is no longer considered a first-line test for the diagnosis of NPC; however, it remains a very useful diagnostic tool in uncertain cases where biomarkers and/or molecular analysis provide inconclusive results and to assess the pathogenicity of novel genetic variants. This assay needs to be performed on cultured fibroblasts from skin biopsies; it is invasive and has a long turnaround time. Further the assay is technically challenging, labor intensive, and is only performed in specialized laboratories. If only one pathogenic mutation is identified by molecular analysis of NPC1 and NPC2, filipin testing should be performed.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Miplyffa. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Miplyffa as well as the monitoring required for adverse events and long-term efficacy, approval requires Miplyffa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Miplyffa is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Niemann-Pick disease type C.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy: Approve if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Patient has one or more neurological symptom(s) of Niemann-Pick disease type C; AND
       Note: Examples of neurologic symptoms of Niemann-Pick disease type C include loss of motor function, swallowing, and speech and cognitive impairment.
     - **iii.** Patient can walk independently or with assistance; AND
     - **iv.** The diagnosis is established by a genetic test showing biallelic pathogenic variants in either the NPC1 gene or NPC2 gene; AND
     - **v.** Patient does NOT have adult-onset Niemann-Pick disease type C; AND
       Note: Adult-onset NPC is defined as the age of the first neurological symptom occurring > 15 years of age.
     - **vi.** The patient meets ONE of the following (a or b):
       - **a)** The medication will be taken in combination with miglustat; OR
       - **b)** According to the prescriber, patient is unable to take miglustat; AND
     - **vii.** The medication is prescribed by or in consultation with a geneticist, endocrinologist, metabolic disorder subspecialist, neurologist, or a physician who specializes in the treatment of Niemann-Pick disease type C or related disorders.
   - **B)** Patient is Currently Receiving Miplyffa. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient does NOT have adult-onset Niemann-Pick disease type C; AND
       Note: Adult-onset Niemann-Pick disease type C is defined as the age of the first neurological symptom occurring > 15 years of age.
     - **ii.** The patient meets ONE of the following (a or b):
       - **a)** The medication will be taken in combination with miglustat; OR
       - **b)** According to the prescriber, patient is unable to take miglustat; AND
     - **iii.** According to the prescriber, patient has derived benefit from treatment defined as disease stabilization, slowed progression, or improvement; AND
     - **iv.** The medication is prescribed by or in consultation with a geneticist, endocrinologist, metabolic disorder subspecialist, neurologist, or a physician who specializes in the treatment of Niemann-Pick disease type C or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Miplyffa is not recommended in the following situations:

1. **Amyotrophic Lateral Sclerosis.** Arimoclomol did not improve efficacy outcomes relative to placebo in patients with amyotrophic lateral sclerosis. A multinational, randomized, double-blind, placebo-controlled, parallel group trial assessed the efficacy of arimoclomol (400 mg three times daily) vs. placebo in adults with amyotrophic lateral sclerosis (n = 245).[10] The primary outcome was the Combined Assessment of Function and Survival (CAFS) rank score over 76 weeks of treatment. At Week 76, the CAFS score did not differ between arimoclomol and placebo groups (mean 0.51 vs 0.49, respectively; P = non-significant). Proportions of participants who died were similar between the

treatment groups (18% [n = 29/160] and 23% [n = 18/79] of patients in the arimoclomol and placebo groups, respectively). Most deaths were due to disease progression.

2. **Combination use with Aqneursa (levacetylleucine granules).** Aqneursa is indicated for the treatment of neurological manifestations of Niemann-Pick disease Type C in patients ≥ 15 kg.[11] There are no data available regarding combination use of Aqneursa and Miplyffa.

3. **Gaucher Disease.** A Phase II study with arimoclomol in patients with Gaucher disease type 1 or 3 was terminated; the Coronavirus disease-19 pandemic prevented the ability to assess the trial objective.[7] Additional data are needed to determine if arimoclomol is beneficial in patients with Gaucher disease type 1 or 3.

4. **Inclusion Body Myositis.** Arimoclomol did not improve efficacy outcomes relative to placebo in patients with inclusion body myositis. A multicenter, randomized, double-blind, placebo-controlled trial assessed the efficacy of arimoclomol (400 mg three times daily) vs. placebo in adults with inclusion body myositis fulfilling the European Neuromuscular Center research diagnostic criteria 2011 (n = 152).[9] The primary endpoint was the change from baseline to Month 20 in the Inclusion Body Myositis Functional Rating Scale (IBMFRS) total score. At Month 20, the mean IBMFRS change from baseline was not significantly different between arimoclomol and placebo (-3.26; 95% confidence interval: -4.15, -2.36; P = non-significant).

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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