

Category:

Best Product for Orphan/Rare Diseases

Company Name:

Zevra Therapeutics

Product/Solution Name:

MIPLYFFA®

Compound/Tech Name:

arimoclomol

Trade Name:

MIPLYFFA®

Corporate Name:

arimoclomol

Date of Approval:

2024-09-20

Indications:

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

Therapeutic Areas:

- o Neurodegenerative diseases
- o Lysosomal storage disorders
- o Ultra-rare diseases

General Information File Document upload:

Background information and need for drug / device:

In September 2024, the FDA granted its first-ever approval to MIPLYFFA (arimoclomol) for the treatment of Niemann-Pick disease type C, which is an ultra-rare, progressive, neurodegenerative and ultimately fatal disorder. NPC is caused by mutations in the NPC1 or NPC2 genes, which are responsible for intracellular lipid transport. These genetic mutations result in the accumulation of unprocessed cholesterol and lipids in cells, leading to widespread cellular dysfunction. NPC affects both children and adults, presenting with a wide range of visceral, neurological, and psychiatric symptoms, including impairments in cognition, speech, swallowing, ambulation, and fine motor skills. Its clinical heterogeneity and diagnostic challenges contribute to significant delays in diagnosis and treatment.

With an estimated 900 individuals affected in the U.S., and only approximately 300-350 diagnosed, NPC represents an ultra-rare disease with significant unmet medical need. Historically, treatment options have been limited to supportive care and off-label use of miglustat, offering only modest symptomatic relief. The absence of an FDA-approved disease-modifying therapy left families and clinicians with few viable options.

MIPLYFFA, developed by Zevra Therapeutics, is an oral therapy, approved for use in combination with miglustat, represents a transformative advancement in the management of NPC. MIPLYFFA works by increasing the transcription of genes in the Coordinated Lysosomal Expression and Regulation (CLEAR) network, including NPC1 and NPC2. These increases in gene expression lead to improved cholesterol metabolism and lysosomal clearance through NPC-dependent and independent pathways, addressing the underlying cause of NPC and halting the progression of disease.

The approval of MIPLYFFA, which also previously received Orphan Drug designation by the FDA and Orphan Medicinal Product designation by the European Medicines Agency, was the result of years of dedicated research, clinical collaboration, and patient advocacy. MIPLYFFA's at-home dosing regimen, one capsule three times daily with or without food, with administration flexibility including water, food, or feeding tubes, adds to its accessibility and convenience for patients and caregivers.

Robust demand for MIPLYFFA reflects the meaningful clinical outcomes observed through more than 5 to 7 years of patient experience across >270 NPC patients through Zevra's phase 2/3 clinical trial (NCT02612129), Open-Label Extension study, Expanded Access Program (EAP: NCT04316637), and pediatric sub-study. It promises to be the cornerstone therapy for the NPC addressing the underlying cause of disease rather than merely treating its symptoms.

In parallel with MIPLYFFA's approval, Zevra launched AmplifyAssist, a comprehensive patient support program, and unveiled the "Learn NPC, Read Between the Signs" campaign on Rare Disease Day to aid in early recognition of this elusive disorder. To support Zevra's goal of providing access to as many people living with NPC as possible, the company has a global Expanded Access Program. Additionally, later this

year, Zevra is planning to submit a Marketing Authorization Application in Europe, where we estimate ~1,100 people are living with NPC. Importantly, Zevra's partnerships with multiple patient advocacy organizations have played a crucial role in amplifying the impact of MIPLYFFA, bringing hope to families and clinicians, and expanding access to this groundbreaking therapy.

Background File Document upload:

N/A

History of the development of the solution/product:

The development of MIPLYFFA is a testament to scientific persistence, translational research, and regulatory collaboration in the pursuit of a treatment for NPC, a progressive, ultra-rare neurodegenerative disorder with no previously approved therapies in the United States.

MIPLYFFA is shown to enter the cell and increase the translocation of transcription factors EB and E3 (TFEB & TFE3) from the cytosol to the nucleus, which upregulate the coordinated lysosomal expression and regulation (CLEAR) genes, including NPC1 & NPC2. The MIPLYFFA-induced increase in CLEAR gene expression results in increased NPC1 protein levels in the lysosomes, and other proteins supporting lysosomal function.

Ultimately this leads to a reduction of unesterified cholesterol in the lysosome. In animal NPC models, greater correction of aberrant lysosomal cholesterol trafficking was shown to correlate with the improvement of specific neurological behaviors, such as rearing and gait. MIPLYFFA targets the pathophysiology of NPC through NPC-dependent and independent mechanisms.

The pivotal Phase 2/3 randomized, double-blind, placebo-controlled trial enrolled 50 pediatric patients with NPC across multiple international sites. Participants received arimoclomol or placebo three times daily for 12 months, alongside standard of care, which could include miglustat. For all pivotal trial analyses performed using the validated primary endpoint 5-domain NPC Clinical Severity Scale (NPCCSS), arimoclomol demonstrated directionally consistent benefit over placebo that was both statistically significant and clinically meaningful. The 5-domain NPCCSS is a validated scale specific to NPC that measures 5 key neurological functions; speech, swallow, fine motor skills, ambulation, and cognition.

Despite these promising results, the FDA issued a Complete Response Letter in 2021. Following its acquisition of arimoclomol in 2022, Zevra Therapeutics re-engaged with regulators, reanalyzing the data using a rescored 4-domain scale, having undertaken further validation work on the swallow domain and focusing on the large group of patients co-administered with miglustat. This reconfirmed the therapeutic benefit of arimoclomol, with the estimated placebo-adjusted mean change from baseline at month 12 being -2.2-points, a statistically significant and clinically meaningful reduction in disease progression.

In 2024 The National Niemann-Pick Disease Foundation (NNPDF) spearheaded efforts

with six other NPC advocacy and research organizations to compile a petition of nearly 1,000 signatures from NPC patients, caregivers, and physicians with direct experience utilizing arimoclomol. The petition can be accessed on the NNPDF website [here](#). I encourage you to read the personal stories of people living with this devastating rare disease. These efforts culminated in FDA approval of MIPLYFFA, the first U.S.-approved treatment for NPC, for use in combination with miglustat in patients aged two years and older with neurological manifestations of the disease. This milestone reflected not only scientific achievement but also regulatory innovation, including the formation of the FDA's first Genetic Metabolic Diseases Advisory Committee (GeMDAC). The committee, comprising experts in medical genetics, metabolism, epidemiology, and other specialties, voted in favor of approval, concluding that MIPLYFFA's clinical and nonclinical data supported its effectiveness.

MIPLYFFA's approval marked a major milestone in rare disease therapeutics, demonstrating how targeting protein misfolding and lysosomal impairment can yield meaningful, disease-modifying outcomes for previously untreatable conditions.

Development File Document upload:

[Zevra Therapeutics Prix Galien Award Nomination_Final.docx](#)

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:

MIPLYFFA (arimoclomol) represents a groundbreaking, first-in-class, innovation in the treatment of Niemann-Pick disease type C (NPC), advancing the therapeutic landscape for lysosomal storage disorders (LSDs) through a novel disease modifying mechanism of action that penetrates the central nervous system (CNS), and direct addressing of disease pathophysiology.

MIPLYFFA enhances lysosomal function by activating transcription factors TFEB and TFE3 which upregulate the coordinated lysosomal expression and regulation (CLEAR) network, improving autophagy and cellular cholesterol clearance. By improving lysosomal function through NPC-dependent and independent pathways, MIPLYFFA directly addresses the pathophysiology of NPC and modifies disease progression. The approval of MIPLYFFA marked a paradigm shift from symptomatic management to disease modification in NPC. In the pivotal clinical trial, arimoclomol in combination with miglustat, stopped disease progression through the 12 month study period, as measured by -0.2 points of disease progression on the rescored 4-domain NPCSS, compared with 1.9 points of disease progression for patients treated with placebo and miglustat over the same period. Separation between MIPLYFFA with miglustat (-0.3) and placebo with miglustat (+0.4) can be seen as early as week 12. In the 4-year open label extension study, the on-label population's observed rate of disease progression was much slower than the 1.9 points per year of disease progression in the placebo group during the double-blind phase confirming MIPLYFFA's long-term effectiveness, safety, and durability for up to 5-years. For patients with a disease that previously

offered no FDA-approved treatment, this represents a transformational improvement in prognosis and quality of life.

MIPLYFFA is more than a treatment; it is a lifeline. It addresses NPC's core pathology where previous therapies failed, and its success redefines what's possible in rare disease drug development. The approval of MIPLYFFA not only brings hope to the NPC community but also opens new avenues for innovation across the entire field of lysosomal storage and neurodegenerative disorders.

For information on the proper administration of MIPLYFFA, refer to the Full Prescribing Information and Instructions for Use.

Innovation File Document upload:

N/A

Please provide appropriate references (PubMed, Abstract, Website):

PUBMED

1. Eugen Mengel a,* , Marc C. Patterson b , Rosalia M. Da Riolo c , Mireia Del Toro d , Federica Deodato e , Matthias Gautschi f , Stephanie Grunewald g , Sabine Weller Grønberg h , Paul Harmatz i , Julia B. Hennermann j , Bénédicte Héron k , Esther M. Maierl , Agathe Roubertie m , Saikat Santra n , Anna Tylki-Szymanska o , Lisa LaGorio p , Elizabeth Berry-Kravis q , Forbes D. Porterr , Beth Solomon s , Louise Himmelstrup t , Travis Mickle u , Sven Guenther u , Christine Í Dali t. Efficacy results from a 12-month double-blind randomized trial of arimoclomol for treatment of Niemann-Pick disease type C (NPC): Presenting a rescored 4-domain NPC Clinical Severity Scale. *Mol Genet Metab.* 2025 May;43(1):101233. Doi: /10.1016/j.ymgmr.2025.101233. Epub 2025 May 28.
2. Shammass H, Kloster Fog C, Klein P, Koustrup A, Pedersen MT, Bie AS, Mickle T, Petersen NHT, Kirkegaard Jensen T, Guenther S. Mechanistic insights into arimoclomol mediated effects on lysosomal function in Niemann-pick type C disease. *Mol Genet Metab.* 2025 May;145(1):109103. doi: 10.1016/j.ymgme.2025.109103. Epub 2025 Apr 2. PMID: 40215728.
3. Mengel E, Patterson MC, Da Riolo RM, Del Toro M, Deodato F, Gautschi M, Grunewald S, Grønberg S, Harmatz P, Héron B, Maier EM, Roubertie A, Santra S, Tylki-Szymanska A, Day S, Andreasen AK, Geist MA, Havnsøe Torp Petersen N, Ingemann L, Hansen T, Blaettler T, Kirkegaard T, Í Dali C. Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment. *J Inher Metab Dis.* 2021 Nov;44(6):1463-1480. doi: 10.1002/jimd.12428. Epub 2021 Sep 7. PMID: 34418116; PMCID: PMC9293014.
4. Patterson, M.C., Lloyd-Price, L., Guldberg, C. et al. Validation of the 5-domain

Niemann-Pick type C Clinical Severity Scale. *Orphanet J Rare Dis* 16, 79 (2021).
<https://doi.org/10.1186/s13023-021-01719-2>

5. Mengel E, Bembi B, Del Toro M, Deodato F, Gautschi M, Grunewald S, Grønborg S, Héron B, Maier EM, Roubertie A, Santra S, Tylki-Szymanska A, Day S, Symonds T, Hudgens S, Patterson MC, Guldborg C, Ingemann L, Petersen NHT, Kirkegaard T, Í Dali C. Clinical disease progression and biomarkers in Niemann-Pick disease type C: a prospective cohort study. *Orphanet J Rare Dis*. 2020 Nov 23;15(1):328. doi: 10.1186/s13023-020-01616-0. Erratum in: *Orphanet J Rare Dis*. 2021 Jun 1;16(1):246. doi: 10.1186/s13023-021-01855-9. PMID: 33228797; PMCID: PMC7684888.
6. Rakonczay Z Jr, Iványi B, Varga I, Boros I, Jednákovits A, Németh I, Lonovics J, Takács T. Nontoxic heat shock protein coinducer BRX-220 protects against acute pancreatitis in rats. *Free Radic Biol Med*. 2002 Jun 15;32(12):1283-92. doi: 10.1016/s0891-5849(02)00833-x. PMID: 12057766.
7. Kirkegaard T, Gray J, Priestman DA, Wallom KL, Atkins J, Olsen OD, Klein A, Drndarski S, Petersen NH, Ingemann L, Smith DA, Morris L, Bornæs C, Jørgensen SH, Williams I, Hinsby A, Arenz C, Begley D, Jäättelä M, Platt FM. Heat shock protein-based therapy as a potential candidate for treating the sphingolipidoses. *Sci Transl Med*. 2016 Sep 7;8(355):355ra118. doi: 10.1126/scitranslmed.aad9823. PMID: 27605553; PMCID: PMC6821533.
8. Fog CK, Zago P, Malini E, Solanko LM, Peruzzo P, Bornaes C, Magnoni R, Mehmedbasic A, Petersen NHT, Bembi B, Aerts JFMG, Dardis A, Kirkegaard T. The heat shock protein amplifier arimoclomol improves refolding, maturation and lysosomal activity of glucocerebrosidase. *EBioMedicine*. 2018 Dec;38:142-153. doi: 10.1016/j.ebiom.2018.11.037. Epub 2018 Nov 27. PMID: 30497978; PMCID: PMC6306395.
9. Shammass H, Kloster Fog C, Klein P, Koustrup A, Pedersen MT, Bie AS, Mickle T, Petersen NHT, Kirkegaard Jensen T, Guenther S. Mechanistic insights into arimoclomol mediated effects on lysosomal function in Niemann-pick type C disease. *Mol Genet Metab*. 2025 May;145(1):109103. doi: 10.1016/j.ymgme.2025.109103. Epub 2025 Apr 2. PMID: 40215728.
10. Abelleira Lastoria DA, Keynes S, Hughes D. Current and Emerging Therapies for Lysosomal Storage Disorders. *Drugs*. 2025 Feb;85(2):171-192. doi: 10.1007/s40265-025-02145-5. Epub 2025 Jan 18. Erratum in: *Drugs*. 2025 Apr 12. doi: 10.1007/s40265-025-02175-z. PMID: 39826077.

MEDICAL CONFERENCE PRESENTATIONS

21st Annual WORLDSymposium

- Efficacy Results from a 12-month Double-blind Randomized Trial of Arimoclomol for the Treatment of Niemann-Pick Disease Type C - Presenting a Rescored 4-domain NPC

Clinical Severity Scale

- Qualitative Assessment of the Validity and Standardization of the Swallow Domain in the 5-domain Niemann-Pick Disease Type C (NPC) Clinical Severity Scale (5DNPCCSS) And Analysis in an NPC Clinical Trial Data Set
- Arimoclomol Safety Profile in the Treatment of Niemann-pick Disease Type C In a Real-world Setting: Long-term Safety Data from an Expanded Access Program in the United States
- Long-term Efficacy and Safety Evaluation of Arimoclomol Treatment in Patients with Niemann-Pick Type C - Data From 48 Months Open Label Trial
- Safety of Arimoclomol in a Pediatric Sub-Study of Niemann-pick Disease Type C Patients Aged 6 To <24 Months at Study Enrollment
- Perseverance Is Key for Regulatory Success in Ultra-Rare Diseases - Key Learnings from Arimoclomol's Regulatory Journey
- Arimoclomol for the Treatment of Niemann-pick Disease Type C In a Real-world Setting: Long-term Data from an Expanded Access Program in the United States
- Arimoclomol Upregulates Expression of Genes Belonging to the Coordinated Lysosomal Expression and Regulation (CLEAR) Network
- Efficacy Results from A 12-month Double-blind Randomised Trial of Arimoclomol for Treatment of Niemann-Pick Disease Type C - Presenting A Rescored 4-domain NPC Clinical Severity Scale

The Child Neurology Society Annual Meeting

- Qualitative Assessment of the Validity and Standardization of the Swallow Domain in the 5-Domain Niemann-Pick disease type C (NPC) Clinical Severity Scale (5DNPCCSS)
- ## American Society of Human Genetics 2024 Annual Meeting

- Arimoclomol Upregulates Expression of Genes Belonging to the Coordinated Lysosomal Expression and Regulation (CLEAR) Network

Society for the Study of Inborn Errors of Metabolism (SSIEM) 2024 Annual Symposium

- Arimoclomol for the Treatment of NPC in a Real-World Setting: Long-Term Outcomes from an Expanded Access Program in the USA
- Arimoclomol Safety Profile in the Treatment of NPC in a Real-World Setting: Long-Term Data From an Expanded Access Program in the USA
- Long-term Efficacy and Safety Evaluation of Arimoclomol Treatment in Patients with Niemann Pick Type C - Data from 48 Months Open Label Trial
- Efficacy Results from a 12-month Double-blind Randomized Trial of Arimoclomol for Treatment of Niemann Pick Disease Type C - Presenting an Improved 4-Domain NPC Clinical Severity Scale

- Arimoclomol in adults with NPC in a real-world setting: Long-term data from an expanded access program in the USA

52nd Child Neurology Society Annual Meeting

- Evaluation of the Long-Term Effect of Arimoclomol in NPC - 48 Months Data from CT-ORZY-NPC-002
- Real World Data Collection in Niemann-Pick Disease Type C - Data from Expanded Access Program with Arimoclomol

The 19th Annual WORLDSymposium™

- Association Between NPC Severity Score Domains and Corresponding Items of the Performance-based Scale for the Assessment and Rating of Ataxia (SARA)
- Evaluation of the Long-Term Effect of Arimoclomol in NPC

NEWS RELEASES

- Zevra Launches New Disease State Awareness Campaign, 'Learn NPC, Read Between the Signs,' to Drive Early Recognition and Treatment of Niemann-Pick Disease Type C
- Zevra Therapeutics Announces U.S. Commercial Availability of MIPLYFFA™ (arimoclomol) for Treatment of Niemann-Pick Disease Type C
- Zevra Therapeutics' MIPLYFFA™ (arimoclomol) Receives U.S. FDA Approval as Treatment for Niemann-Pick Disease Type C
- FDA Advisory Committee Votes Favorably that the Data Support Arimoclomol as Effective Treatment for Patients with Niemann-Pick Disease Type C
- Zevra Announces FDA Advisory Committee Meeting to Review Arimoclomol for the Treatment of Niemann-Pick Disease Type C
- Zevra Therapeutics Provides FDA Update on the PDUFA Action Date for Arimoclomol as a Treatment for Niemann-Pick Disease Type C
- Zevra Therapeutics Receives FDA Acceptance of Resubmission of NDA for Arimoclomol as a Treatment for Niemann-Pick Disease Type C
- Zevra Therapeutics Announces Resubmission of Arimoclomol New Drug Application to the U.S. Food and Drug Administration

ADDITIONAL INFORMATION

- About MIPLYFFA
- Full Prescribing Information and Instructions for Use for information on the proper administration of MIPLYFFA
- FDA Approves First Treatment for Niemann-Pick Disease, Type C

IMPORTANT SAFETY INFORMATION

Before starting MIPLYFFA, tell your healthcare provider about all your medical conditions, including if you are pregnant or plan to become pregnant, breastfeeding or plan to breastfeed.

Tell your healthcare provider about all the medicines you take, including any prescription and over-the-counter medicines, vitamins, or herbal supplements.

MIPLYFFA may affect how other medicines work.

What are the possible side effects of MIPLYFFA?

MIPLYFFA may cause serious side effects including:

- Hypersensitivity reactions. Call your healthcare provider immediately if you get any of the following symptoms:
 - o urticaria (hives),
 - o shortness of breath,
 - o persistent cough, or
 - o facial swelling
- Harm to your unborn baby. If you are of childbearing age, take precautions to prevent pregnancy. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with MIPLYFFA.

- Infertility. MIPLYFFA may affect your ability to have children.

The most common side effects of MIPLYFFA in patients also taking miglustat include upper respiratory tract infection, diarrhea and decreased weight.

These are not all the possible side effects of MIPLYFFA. Call your HCP for medical advice about side effects. You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Drug Interactions: MIPLYFFA can cause side effects if used together with certain drugs called OCT2 substrates. Talk to your healthcare provider about any drugs that you may be taking for other conditions.

MIPLYFFA capsules for oral use are available in the following strengths in a 90-count bottle: 47 mg, 62 mg, 93 mg, and 124 mg.

For more information, please see the Prescribing Information, including Instructions for Use.

References File Document upload:

N/A