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Policy Number: C9646-A

Zavesca (miglustat)

PRODUCTS AFFECTED

miglustat, Yargesa (miglustat), Zavesca (miglustat)
*Opfolda (miglustat) – SEE OPFOLDA MHI C27241-A

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Type 1 Gaucher disease, Niemann-Pick Disease

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. TYPE 1 GAUCHER DISEASE:

1. Documented diagnosis of mild to moderate* Type 1 Gaucher Disease (GD1)
   NOTE: **Severe type 1 Gaucher disease defined as hemoglobin concentration less than 9 g/dL, platelet count less than 50,000/mm3 (< 50 x 109/L) or active bone disease.1-3 The safety and efficacy of miglustat have not been established in individuals with severe type 1 GD defined as hemoglobin concentration less than 9 g/dL, platelet count less than 50,000/mm3 (< 50 x 109/L) or active bone disease.*
   AND
2. Documentation diagnosis was confirmed by Glucocerebrosidase activity in the white blood cells or skin fibroblasts less than or equal to 30% of normal activity OR Genotype testing indicating a mutation of two alleles of the glucocerebrosidase genome [DOCUMENTATION REQUIRED]
   AND
3. Documentation of symptomatic manifestations of Type 1 Gaucher Disease defined by at least ONE of the following signs and symptoms: Anemia, hepatomegaly, splenomegaly, skeletal disease (e.g., joint deterioration, pathological fracture, osteopenia, avascular necrosis, osteosclerosis, marrow infiltration, lytic lesions, or Erlenmeyer flask deformity), abdominal or bone pain, fatigue, exertional limitation, weakness, cachexia, OR thrombocytopenia
   AND
4. Documentation of rationale as to why enzyme replacement therapy [i.e., imiglucerase (Cerezyme), velaglucerase (Vpriv), taliglucerase (Elelyso)] is NOT a therapeutic option, such as but not limited to the following: Refractory or intolerant to enzyme replacement therapy, Allergic to components of, or hypersensitivity to enzyme replacement therapy or Poor venous access
   AND
5. Documentation of member's therapeutic goals based on their individual baseline symptoms (e.g., bone pain, fatigue, dyspnea, angina, abdominal discomfort), overall health, and quality of life

B. NIEMANN-PICK DISEASE:

1. Documented diagnosis of Niemann-Pick disease, type C
   AND
2. Documentation diagnosis was confirmed by genetic testing that identifies both disease-causing alleles in NPC1 or NPC2 [DOCUMENTATION REQUIRED]
   AND
3. Documentation of mild-to-moderate neurologic, psychiatric, or cognitive manifestations

CONTINUATION OF THERAPY:

A. TYPE 1 GAUCHER DISEASE:

1. Documentation of improvement in, or stabilization from, baseline based on member's therapeutic goals which may include any of the following: spleen volume, hemoglobin level, liver volume, platelet count (sufficient to decrease the risk of bleeding), growth, bone pain or crisis
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

B. NIEMANN-PICK DISEASE:

1. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified geneticist, metabolic specialist, hematologist, or physician experienced in the management of Gaucher Disease or Niemann-Pick disease. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
Mild-to-moderate Type 1 GD: 300 mg per day (3 capsules per day)
Niemann-Pick Type C disease: 600 mg daily (6 capsules per day)

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Agents for Gaucher Disease

FDA-APPROVED USES:
Indicated as monotherapy for treatment of adult patients with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (e.g., because of allergy, hypersensitivity, or poor venous access

COMPENDIAL APPROVED OFF-LABELED USES:
Niemann-Pick Disease

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Gaucher Disease (GD) is a rare, autosomal recessive, lysosomal storage disorder caused by mutations in the glucocerebrosidase gene, resulting in the accumulation of glucosylceramide in macrophage cells. GD is characterized by hepatosplenomegaly, thrombocytopenia and anemia, and is classified into 3 major types and2 subtypes. There are 3 subtypes based on characteristic patterns of clinical signs and age of onset, GD is subdivided into three main disease variants: type 1 (non-neuronopathic), type 2 (acute neuronopathic), and type 3 (subacute neuronopathic).

- Type 1 (nonneuronopathic form): bone disease and lack of primary central nervous system involvement
- Type 2 (acute neuronopathic form): severe neurologic impairment without bone involvement
- Type 3 (chronic or subacute neuronopathic form): neurologic impairment and bone disease subtype fetal or perinatal-lethal form: death in utero or shortly after birth

Type I Gaucher Disease (GD1) is an inherited disease caused by a functional deficiency of glucocerebrosidase, the enzyme that mediates degradation of the glycosphingolipid glucosylceramide. The failure to degrade glucosylceramide results in the lysosomal storage of this lipid material within tissue macrophages leading to widespread pathology. Macrophages containing stored glucosylceramide are typically found in the liver, spleen, and bone marrow and occasionally in the lung,

kidney, and intestine. Secondary hematologic consequences include severe anemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly. Skeletal complications include osteonecrosis and osteopenia with secondary pathological features. Common manifestations of GD include anemia, hepatomegaly, splenomegaly, thrombocytopenia, and skeletal abnormalities (bone pain, bone crisis, growth retardation, osteopenia).

The decision to treat with enzyme-replacement therapy (ERT) or substrate-reduction therapy (SRT) in nonneuronopathic (type 1) GD is based upon disease severity, as determined by the initial assessment, or significant disease progression, as established through regular follow-up. Goals of treatment are elimination or improvement of symptoms, prevention of irreversible complications, and improvement in overall health and quality of life. Additional goal in children is optimization of growth.

ERT (imiglucerase, velaglucerase, or taliglucerase) or SRT are preferred treatments for members with clinically significant manifestations of non- neuronopathic GD (Type 1). ERT is the standard of care and is recommended for symptomatic pediatric members and for members with severe manifestations of nonneuronopathic GD1. Available therapies for GD1include intravenous ERT (Cerezyme, VPRIV, and Elelyso) and oral substrate reduction therapy (Zavesca). Zavesca (miglustat) is the first oral substrate reduction therapy (SRT) for Gaucher's Disease, type 1.

- Type 1 Gaucher disease is caused by a functional deficiency of glucocerebrosidase, the enzyme that mediates the degradation of the glycosphingolipid glucosylceramide.
- Miglustat competitively and reversibly inhibits the enzyme needed to produce glycosphingolipids and decreases the rate of glycosphingolipid glucosylceramide formation. Glucosylceramide accumulates in type1 Gaucher disease, causing complications specific to this disease.
- The goal of treatment with miglustat is to reduce the rate of glycosphingolipid glucosylceramide biosynthesis so that the amount of glycosphingolipid substrate is reduced to a level which allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective (substrate reduction therapy).

Zavesca (miglustat) may be authorized for second-line treatment in Type I GD for adult members with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option, or for the treatment of the neurological manifestations of Niemann-Pick disease, type C when appropriate criteria are met.

- Miglustat should be considered an alternative to enzyme replacement therapy with beta- glucocerebrosidase (i.e., alglucerase or imiglucerase) in members with confirmed non-neuronopathic Gaucher's disease (GD).
- Miglustat appears less effective than enzyme infusions (particularly with respect to hematologic response) and may not be associated with clinically-relevant benefit in some members; the main goal of miglustat therapy, a significant reduction in stores of glucocerebroside (glucosylceramide), has not been addressed in available published clinical studies. As the primary studies in these members were uncontrolled, some benefits reported may have occurred in the absence of therapy. Although controlled studies in type 1 GD are difficult to perform, an additional study at least investigating effects of the drug on tissue or plasma glucocerebroside appears warranted

Niemann-Pick type C disease is a rare genetic lysosomal storage disorder that causes severe, progressive neurological symptoms. It is a very serious, life-threatening condition that can affect infants, children, and adults. NP-C is characterized by cellular accumulation of lipids, in particular unesterified cholesterol and glycosphingolipids, in many parts of the body including brain, liver and spleen.

The symptoms of NP-C are highly variable and classically present in mid-to-late childhood. Symptoms become progressively more severe and include: disturbance of voluntary rapid eye movements (supranuclear gaze palsy); difficulty in swallowing (dysphagia); slurred and irregular speech (dysarthria); lack of muscle control (ataxia); cognitive dysfunction with associated dementia and in some cases seizures, and sudden muscle weakness during moments of strong emotion such as laughter (gelastic cataplexy).

Lipid accumulation can also lead to an enlarged liver and/or spleen (hepatosplenomegaly).
Niemann-Pick disease (NPD), also called sphingomyelin-cholesterol lipidosis, is a group of autosomal recessive disorders associated with splenomegaly, variable neurologic deficits, and the storage of lipids including sphingomyelin and cholesterol. Niemann-Pick disease originally was defined in terms of its histology as a reticuloendotheliosis. It now is subdivided into two major categories.
Niemann-Pick disease type A (NPD-A) and type B (NPD-B) are allelic disorders caused by mutations in the sphingomyelin phosphodiesterase-1 gene (SMPD1), and characterized by a primary deficiency of acid sphingomyelinase activity. NPD-A is the severe, early-onset form, and NPD-B is the less severe, later- onset form. An intermediate phenotype between these two extremes has also been described.
Niemann-Pick disease type C is caused by mutations of the NPC1 and NPC2 genes that result in impaired cellular processing and transport of low-density lipoprotein (LDL)-cholesterol
Based upon the observation that glycolipids were increased in NPD-C cells, substrate reduction therapy with miglustat, an inhibitor of glycosphingolipids biosynthesis, was shown to decrease lipid storage, improve endosomal uptake, and normalize lipid trafficking in B lymphocytes [74]. However, it is unclear if miglustat reduces disease progression in NPD-C, and data are limited and conflicting: In a preliminary open-label randomized controlled trial, members ≥12 years old with NPD-C assigned to miglustat 200 mg three times daily (n = 20) demonstrated nonsignificant improvement in horizontal saccadic eye movement velocity (the primary outcome measure) at 12 months compared with members assigned to standard care (n = 9) [75]. The difference between groups was statistically significant after excluding members taking benzodiazepines. Improvement or stabilization with miglustat, statistically nonsignificant in most cases, was also seen in clinically relevant secondary outcome measures, including swallowing capacity, hearing acuity, and ambulation.
Early miglustat treatment did not prevent neurologic involvement in two children with NPD-C one a girl with early infantile onset and mild axial hypotonia who started treatment at age 7 months, and the second a boy with no neurologic symptoms who started treatment at age 19 months [76,77].

After the first seven and five years of therapy, respectively, both children remained without neurologic symptoms [76]. However, over the ensuing three years, the girl developed cognitive impairment, a cherry red spot, vertical gaze paresis, ataxia, dysmetria, and gelastic cataplexy, while the boy developed mild cognitive decline, hyperreflexia, and mild incoordination, but no gazeparesis.
Thus, miglustat may delay the progression of the neurologic manifestations of NPD-C in children without severe neurologic symptoms at the start of treatment. However, expert consensus guidelines note that miglustat should not be given to members who have no neurologic manifestations because some remain asymptomatic for long periods of time [79]. In accord with these guidelines, we suggest miglustat for members with NPD-C who have mild to moderate neurologic, psychiatric, or cognitive manifestations. Members and their families should be informed that the effectiveness of miglustat for NPD-C is unproven, and that the best attainable outcome of therapy is neurologic stabilization or a slower rate of neurologic disease progression. The available clinical studies suggest that miglustat has no benefit for cholestatic or systemic symptoms.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Zavesca (miglustat) products are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Zavesca (miglustat) include: No labeled indications.

Inconclusive or Non-Supportive Evidence
For GM2 gangliosidoses, such as Tay-Sachs disease and Sandhoff disease, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. (RG B) An open-label study of 5 children treated with 24 months of miglustat therapy reported significant deterioration in several neurologic endpoints, with some areas of cognitive

function remaining stable in 3 members. (14) (EG 2) A study of 30 adult members with late onset Tay-Sachs disease randomized members to miglustat or no treatment in a 2:1 fashion for 12 months, followed by a 24-month extension period. In terms of the primary outcomes of change in muscle and grip strength and the secondary outcomes of change in gait, balance, and overall disability, no measurable benefit was demonstrated in the treatment group at any time during the study period.

For *mucopolysaccharidosis type III*, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. A randomized double-blind placebo-controlled trial of 25 members reported that miglustat did not clinically improve standardized cognitive tests or sleep disturbances.

For t*ype 3 Gaucher disease*, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. A 24-month, phase II, open-label, randomized controlled trial with 30 members showed that miglustat had no significant benefits in terms of neurologic manifestations, although some improvement in pulmonary function was suggested.

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
migLUstat CAPS 100MG
Yargesa CAPS 100MG
Zavesca CAPS 100MG

REFERENCES

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information References	Q3 2025
REVISION- Notable revisions: Products Affected Required Medical Information Quantity Available Dosage Forms References	Q3 2024
REVISION- Notable revisions: Products Affected Diagnosis Required Medical Information Prescriber Requirements FDA-Approved Uses Available Dosage Forms References	Q3 2023
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Duration of Approval Prescriber Requirements Quantity Compendial Approved Off Labeled Uses Contraindications/Exclusions/Discontinuation	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file