PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Substrate Reduction Therapy – Miglustat Prior Authorization Policy
- Zavesca® (miglustat capsules – Actelion, generic)

REVIEW DATE: 05/07/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Miglustat capsules (Zavesca, generic), a glucosylceramide synthase inhibitor, is indicated as monotherapy for the treatment of mild to moderate **Gaucher disease type 1**, in adults for whom enzyme replacement therapy is not a therapeutic option (e.g., due to allergy, hypersensitivity, or poor venous access).[1]

Disease Overview

Gaucher disease is caused by a deficiency in the lysosomal enzyme β-glucocerebrosidase.[2] This enzyme is responsible for the breakdown of glucosylceramide into glucose and ceramide. In Gaucher disease, deficiency of the enzyme β-glucocerebrosidase results in the accumulation of glucosylceramide substrate in lysosomal compartment of macrophages, giving rise to foam cells or "Gaucher cells." Miglustat is a specific inhibitor of the enzyme glycosylceramide synthase, which is responsible for producing the substrate glucosylceramide.[1] By

functioning as a substrate reduction therapy, miglustat allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective.

Other Uses with Supportive Evidence
Although not FDA approved, miglustat has been used off-label for the treatment of Niemann-Pick disease Type C (NPC). NPC is an autosomal recessive, slowly progressive ultra-rare, lysosomal storage disorder.[3] It is caused by variants in either the *NPC1* (90% to 95%) or *NPC2* (5%) gene and yields deficient function of the corresponding proteins that normally bind and transport cholesterol.[4] Essentially, NPC results from a combination of toxic lipid accumulation in the lysosomes and a relative deficiency of necessary cholesterol in the rest of the cell. The lysosomal dysfunction in NPC leads to an accumulation of lipids in the brain, liver, and spleen. The clinical manifestations vary with age of onset and range from a neonatal rapidly progressive fatal disorder to an adult-onset chronic neurodegenerative disease.[5] Consensus clinical management guidelines for NPC have been developed by the International Niemann-Pick Disease Registry (INPDR) project (2018). Molecular genetic analysis of the *NPC1* and *NPC2* genes are required to confirm the diagnosis of NPC. It is recommended that all patients with a confirmed diagnosis of NPC should be considered for miglustat. However, miglustat is not recommended in patients with profound neurological disease since assessment of improvement with therapy would not be feasible.

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

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is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. **Gaucher Disease Type 1.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) The diagnosis is established by ONE of the following (i or ii):
      i. Demonstration of deficient beta-glucocerebrosidase activity in leukocytes or fibroblasts; OR
      ii. Molecular genetic test showing biallelic pathogenic glucocerebrosidase *(GBA)* gene variants; AND

B) The medication is prescribed by or in consultation with a geneticist, endocrinologist, metabolic disorder subspecialist, or a physician who specializes in the treatment of Gaucher disease or related disorders.

Other Uses with Supportive Evidence

2. **Niemann-Pick Disease Type C (NPC).** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 2 years of age; AND
   B) The diagnosis is established by a molecular genetic test showing biallelic pathogenic variants in either the *NPC1* or *NPC2* gene; AND
   C) The medication is prescribed by or in consultation with a geneticist, endocrinologist, metabolic disorder subspecialist, or a physician who specializes in the treatment of NPC or related disorders.

CONDITIONS NOT COVERED

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is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Concomitant Use with Other Approved Therapies for Gaucher Disease**. Concomitant use with other treatments approved for Gaucher disease has not been evaluated. Of note, examples of medications approved for Gaucher disease include Cerezyme (imiglucerase intravenous infusion), Elelyso (taliglucerase alfa intravenous infusion), Vpriv (velaglucerase alfa intravenous infusion), and Cerdelga (eliglustat capsules).

REFERENCES

1. Zavesca® capsules [prescribing information]. South San Francisco, CA: Actelion; August 2022.
2. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18:441.
3. Patterson M. Niemann-Pick disease type C. 2000 Jan 26 [updated 2020 Dec 10]. In: Adam MP, Ardinger HH, Pagon RA, et al., Washington, Seattle; 1993-2021.
4. Berry-Kravis E. Nieman-Pick disease type C: diagnosis, management and disease-targeted therapies in development. *Semin Pediatric Neurol.* 2021;31:100879.
5. Geberhiwot T, Moro A, Dardis A, et al; on behalf of the International Niemann-Pick Disease Registry (INPDR). Consensus clinical management guidelines for Niemann-Pick disease type C. *Orphanet J Rare Dis.* 2018;13:50.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/10/2023

Annual Revision	**Gaucher Disease Type 1:** Confirmation of a genetic mutation in the glucocerebrosidase gene was rephrased to more specifically state, "genetic test documenting biallelic pathogenic glucocerebrosidase *(GBA)* gene variants".	05/29/2024
Selected Revision	**Conditions Not Covered** **:** Concomitant use with other approved therapies for Gaucher disease was added.	08/14/2024
Selected Revision	**Gaucher Disease Type 1:** For confirmation by genetic testing, the term "documenting" was rephrased to "showing". **Niemann-Pick disease Type C:** This was added as a new condition of approval.	10/30/2024
Annual Revision	No criteria changes.	05/07/2025