PRIOR AUTHORIZATION POLICY

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

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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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of miglustat capsules is recommended in those who meet one of the following criteria:

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 RECOMMENDED FOR APPROVAL

Coverage of miglustat capsules is not recommended in the following situations:

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).

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

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.