PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Xenpozyme Prior Authorization Policy
- Xenpozyme™ (olipudase alfa-rpcp intravenous infusion – Genzyme)

REVIEW DATE: 09/13/2023

OVERVIEW

Xenpozyme, a hydrolytic lysosomal sphingomyelin-specific enzyme, is indicated for the treatment of **non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD)** in adult and pediatric patients.[1]

Disease Overview

ASMD is an autosomal recessive lysosomal storage disease that results from reduced activity of the enzyme acid sphingomyelinase (ASM), caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 gene.[1,2] ASM degrades sphingomyelin to ceramide and phosphocholine.[1] The deficiency of ASM causes an intra-lysosomal accumulation of sphingomyelin (as well as cholesterol and other cell membrane lipids) in various tissues. Xenpozyme provides an exogenous source of ASM. Xenpozyme is not expected to cross the blood-brain barrier or modulate the CNS manifestations of ASMD.

ASMD has historically been known as Niemann-Pick disease type A and/or B and is associated with a spectrum of disease phenotypes.[2] ASMD type B (also known as chronic visceral ASMD or Niemann-Pick type B disease) and ASMD type A/B (chronic neurovisceral ASMD, Niemann-Pick disease type A/B, or intermediate phenotype) have disease onset from childhood to early adulthood. ASMD type B has minimal to no CNS involvement, while ASMB type A/B has less severe neurologic manifestations than those observed in ASMD type A, which is fatal in early childhood. Visceral manifestations in ASMD include interstitial lung disease with decreased diffusing capacity of the lung, hepatosplenomegaly, progressive liver disease with cirrhosis or fibrosis, dyslipidemia, osteopenia, and thrombocytopenia. The leading causes of early mortality in adults with ASMD are lung disease/infections, liver failure, and bleeding.

Clinical Efficacy

The efficacy of Xenpozyme in adults and pediatric patients with ASMD was established in two pivotal trials (ASCEND and ASCEND-PEDS, respectively).[2,3] The pivotal trials enrolled patients with ASMD types B or A/B, but not type A. Eligible patients also had splenomegaly (spleen volumes ≥ 5 multiples of normal [MN] in pediatric patients and ≥ 6 MN in adults). In adults and children, Xenpozyme treatment improved spleen and liver volume as well as diffusing capacity of the lungs for carbon monoxide.

Guidelines

A consensus guideline for ASMD diagnosis has been developed by an international expert panel.[4] When there is a suspicion of ASMD, an ASM enzyme assay should be performed followed by gene sequencing if the enzymatic test is indicative of ASMD. Whenever possible, an enzyme assay for ASM and glucocerebrosidase activity should be performed in parallel to distinguish ASMD from Gaucher disease. Gene sequencing can be conducted after diagnosis based on ASM activity, but is not diagnostic on its own because of the high number of genetic variants of unknown significance. Biomarkers, while useful in disease monitoring, should not be considered sufficient for ASMD diagnosis (i.e., these include plasma chitotriosidase, plasma lyso-sphingolipids, and oxysterols). Physicians should perform clinical assessments to predict the phenotype and clinical course of the disease upon identification of sphingomyelin phosphodiesterase-1 (SMPD1) pathogenic variants of unknown pathogenicity in pediatric patients.

Safety

Xenpozyme has a Boxed Warning for hypersensitivity reactions, including anaphylaxis.[1] Prior to administration, pretreatment with antihistamines, antipyretics, and/or corticosteroids should be considered and appropriate medical measures, including cardiopulmonary resuscitation equipment should be readily available during Xenpozyme administration.

POLICY STATEMENT

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

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

1. **Acid Sphingomyelinase Deficiency (ASMD).** Approve for 1 year if the patient meets the following (A, B, C, and D):
   Note: ASMD has historically been known as Niemann-Pick Disease.
   - **A)** The diagnosis of ASMD meets ALL of the following (i, ii, and iii):
     - **i.** The diagnosis of ASMD has been established by acid sphingomylinase (ASM) enzymatic assay testing; AND
     - **ii.** The diagnosis of ASMD has been confirmed by mutation testing; AND
     - **iii.** A diagnosis of Gaucher disease has been excluded; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has ASMD type B; OR
     - **ii.** Patient has ASMD type A/B; AND
   - **C)** Patient has two or more non-central nervous system signs of ASMD type B or type A/B according to the prescriber; AND
     Note: Examples of non-central nervous system signs of ASMD type B or type A/B include but are not limited to hepatosplenomegaly, interstitial lung disease, decreased diffusing capacity of the lungs, progressive liver disease with cirrhosis or fibrosis, dyslipidemia, osteopenia, thrombocytopenia, anemia, leukopenia.
   - **D)** The medication is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xenpozyme is not recommended in the following situations:

1. **Acid Sphingomyelinase Deficiency (ASMD), Type A.** Xenpozyme is indicated for non-central nervous system manifestations of ASMD. Xenpozyme is not expected to cross the blood-brain barrier or modulate the central nervous system manifestations of ASMD.[1] Patients with ASMD type A were excluded from the pivotal trials with Xenpozyme.[2,3]

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. Xenpozyme™ intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; July 2023.
2. Wasserstein M, Lachmann R, Hollack C, et al. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results. *Genet Med*. 2022;24(7):1425-1436.
3. Diaz GA, Jones SA, Scarpa M, et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. *Genet Med.* 2021;23:154-1550.
4. Geberhiwot, T., Wasserstein, M., Wanninayake, S. et al. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann–Pick disease types A, B and A/B). *Orphanet J Rare Dis* 18, 85 (2023). Available at: https://doi.org/10.1186/s13023-023-02686-6. Accessed on: August 31, 2023.