CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Xenpozyme Utilization Management Medical Policy
- Xenpozyme™ (olipudase alfa-rpcp intravenous infusion – Genzyme)

REVIEW DATE: 09/02/2026

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 adults 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 ASMD 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.

Dosing Information

Dosing is weight-based.[1] For patients with a body mass index (BMI) of ≤ 30 kg/m^2, actual body weight is used. For patients with a BMI > 30 kg/m^2, adjusted body weight is used (adjusted body weight in kg = [actual height in meters]^2 x 30). Home infusion of Xenpozyme under the supervision of a healthcare provider may be considered for patients on a maintenance dose and who are tolerating the infusion well. The decision to have patients moved to home infusion should be made after evaluation and recommendation by a physician.

The recommended starting dose in adults is 0.1 mg/kg via intravenous (IV) infusion.[1] The dose is titrated every 2 weeks over a period of 14 weeks to a maintenance dose of 3 mg/kg every 2 weeks (Table 1). To reduce the risk of infusion-associated-reactions or elevated transaminase levels, the dose escalation regimen in Table 1 should be followed.

In pediatric patients, the recommended starting dose is 0.03 mg/kg via IV infusion. The dose is titrated every 2 weeks over a period of 16 weeks to a maintenance dose of 3 mg/kg every 2 weeks (Table 2). To reduce the risk of hypersensitivity and infusion-related reactions or elevated liver enzyme elevations levels, the dose escalation regimen outlined in Table 2 below should be followed.

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A dose is considered "missed" when it is not administered within 3 days of the scheduled date. Refer to Table 3 for missed doses.

Table 1. Xenpozyme Dose Escalation Regimen for Adults (≥ 18 Years of Age).[1]

First dose (Day 1/Week 0)	0.1 mg/kg
Second dose (Week 2)	0.3 mg/kg
Third dose (Week 4)	0.3 mg/kg
Fourth dose (Week 6)	0.6 mg/kg
Fifth dose (Week 8)	0.6 mg/kg
Sixth dose (Week 10)	1 mg/kg
Seventh dose (Week 12)	2 mg/kg
Eighth dose (Week 14)†	3 mg/kg (recommended maintenance dose)

† The dose escalation phase includes the first 3 mg/kg dose.

Table 2. Xenpozyme Dose Escalation Regimen for Pediatric Patients.[1]

First dose (Day 1/Week 0)	0.03 mg/kg
Second dose (Week 2)	0.1 mg/kg
Third dose (Week 4)	0.3 mg/kg
Fourth dose (Week 6)	0.3 mg/kg
Fifth dose (Week 8)	0.6 mg/kg
Sixth dose (Week 10)	0.6 mg/kg
Seventh dose (Week 12)	1 mg/kg
Eighth dose (Week 14)†	2 mg/kg
Ninth dose (Week 16) †	3 mg/kg (recommended maintenance dose)

† The dose escalation phase includes the first 3 mg/kg dose.

Table 3. Dosing Recommendations for Xenpozyme Missed Doses*.[1]

Consecutive Missed Doses In:	Escalation Phase	Maintenance Phase
1 missed dose	First dose after a missed dose: Administer last tolerated dose. Second and subsequent doses after missed dose: Resume dose escalation at next infusion according to Table 1 for adults or Table 2 for pediatric patients.	First and subsequent doses after missed dose: Administer maintenance dose.
2 consecutive missed doses	First dose after missed dose: Administer 1 dose below the last tolerated dose. Second and subsequent doses after missed dose: Resume dose escalation according to Table 1 for adults or Table 2 for pediatric patients.	First dose after missed dose: Administer 1 dose below the maintenance dose. Second and subsequent doses after missed dose: Resume the maintenance dose.
≥ 3 consecutive missed doses	For adults who have not completed the dose escalation phase: Reinitiate dose escalation regimen starting at 0.1 mg/kg and follow Table 1. For pediatric patients who have not completed the dose escalation phase: Reinitiate dose escalation regimen starting at 0.03 mg/kg and follow Table 2.	First and subsequent doses after missed doses: Restart dosing at 0.3 mg/kg and follow Table 1 for adults or Table 2 for pediatric patients. • For adults who have missed ≥ 3 consecutive doses in the maintenance phase during which sphingomyelin could have reaccumulated: The treating physician may consider resuming the dosing at 0.1 mg/kg and dose escalate according to Table 1. • For pediatric patients who have missed ≥ 3 consecutive doses in the maintenance phase during which sphingomyelin could have reaccumulated: The treating physician may consider resuming the dosing at 0.03 mg/kg and dose escalate according to Table 2.

*At scheduled infusion after a missed dose, if the dose administered is 0.3 mg/kg or 0.6 mg/kg, administer that dose twice as per Table 1 and 2.

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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 medical benefit coverage of Xenpozyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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:

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FDA-Approved Indication

1. **Acid Sphingomyelinase Deficiency (ASMD).** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   Note: ASMD has historically been known as Niemann-Pick Disease Type A and/or B.
   A) The diagnosis of ASMD meets ALL of the following (i, ii, and iii):
      i. The diagnosis of ASMD has been established by acid sphingomyelinase (ASM) enzymatic assay testing; AND
      ii. The diagnosis of ASMD has been confirmed by genetic testing demonstrating biallelic pathogenic variants in the sphingomyelin phosphodiesterase-1(*SMPD1*) gene; 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) According to the prescriber, patient has two or more non-central nervous system signs of ASMD type B or type A/B; 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.

   Dosing. Approve up to 3 mg/kg administered by intravenous infusion no more frequently than once every 2 weeks.
   Note: For patients with a body mass index (BMI) of ≤ 30 kg/m^2, actual body weight is used. For patients with a BMI > 30 kg/m^2, adjusted body weight is used. To calculate adjusted body weight, use the following equation: adjusted body weight in kg = (actual height in meters)^2 x 30.

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.[1] Xenpozyme is not expected to cross the blood-brain barrier or modulate the central nervous system manifestations of ASMD. 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.

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REFERENCES

1. Xenpozyme™ intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; December 2024.
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.* 2023 Apr;18(1):85.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Acid Sphingomyelinase Deficiency (ASMD):** For diagnosis, confirmation of a mutation was revised to more specifically state, "genetic testing demonstrating biallelic pathogenic variants in the sphingomyelin phosphodiesterase-1(*SMPD1*) gene".	09/25/2024
Annual Revision	No criteria changes.	09/17/2025
Annual Revision	No criteria changes.	09/02/2026

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