Drug Coverage Policy

Effective Date 12/1/2025
Coverage Policy Number IP0500
Policy Title ..... Xenpozyme

Enzyme Replacement Therapy – Xenpozyme

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.

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 pat. enic 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.

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.

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.

Coverage Policy

POLICY STATEMENT
Prior Authorization is required for 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.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

Xenpozyme is considered medically necessary when the following criteria are met:
FDA-Approved Indication

1. **Acid Sphingomyelinase Deficiency (ASMD).** Approve for 1 year if the patient meets **ALL** 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 the following (i, ii, and iii):
      i. The diagnosis of ASMD has been established by acid sphingomyelinase (ASM) enzymatic assay testing **[documentation required]**; AND
      ii. The diagnosis of ASMD has been confirmed by genetic testing demonstrating biallelic pathogenic variants in the sphingomyelin phosphodiesterase-1 (*SMPD1*) gene **[documentation required]**; AND
      iii. According to the prescriber, 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.
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, 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 Covered

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

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] Individuals with ASMD type A were excluded from the pivotal trials with Xenpozyme.[2,3]

Receipt of sample product does not satisfy any criteria requirements for coverage.

Coding Information

Note:
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0218	Injection, olipudase alfa-rpcp, 1 mg

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* 18, 85 (2023). Available at: https://doi.org/10.1186/s13023-023-02686-6. Accessed on: September 11, 2024.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes	12/15/2024
Annual Revision	**Policy Title:** **Updated** from "Olipudase alfa-rpcp" to "Enzyme Replacement Therapy-Xenpozyme". **Updated** policy template. **Removed** "documented" language throughout coverage policy criteria and replaced with bracketed *documentation required* after applicable criteria. **Updated** diagnostic criteria to require enzymatic assay testing and to screen a diagnosis of Gaucher disease ruled out.	12/1/2025

The policy effective date is in force until updated or retired.