Medical Policy Bulletin

Title:
olipudase alfa-rpcp (Xenpozyme™)
Policy #:
MA08.154a

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

MEDICALLY NECESSARY
INITIAL THERAPY
Olipudase alfa-rpcp (Xenpozyme) is considered medically necessary and, therefore, covered for individuals with acid sphingomyelinase deficiency (ASMD) when all of the following criteria are met, including dosing and frequency requirements listed in Attachment A:

- Diagnosis of non–central nervous system manifestations of ASMD type B or type A/B is confirmed by one of the following:
  - Molecular genetic testing that reveals biallelic pathogenic variants in the *SMPD1* (sphingomyelin phosphodiesterase-1) gene
  - Residual acid sphingomyelinase activity that is less than 10% of controls (in peripheral blood lymphocytes or cultured skin fibroblasts)
- Prescribed by, or in consultation with, a metabolic disease specialist, geneticist, or a specialist in the treatment of lysosomal storage disorders

CONTINUATION THERAPY
Continuation of olipudase alfa-rpcp (Xenpozyme) is considered medically necessary and, therefore, covered for individuals who have a documentation of a positive clinical response to therapy (e.g., decrease in spleen size, decrease in liver size, increase in platelet count, improved lung function)

NOT MEDICALLY NECESSARY

When molecular genetic testing does not reveal a genetic etiology for ASMD type B or type A/B (e.g., results of

testing show established benign variation(s), lack of biallelic pathogenic variation, or wild-type genotype in the *SMPD1*gene), olipudase alfa-rpcp (Xenpozyme) is considered not medically necessary and, therefore, not covered because the available published peer-reviewed literature does not support its use in the treatment of this disease.

EXPERIMENTAL/INVESTIGATIONAL

All other uses for olipudase alfa-rpcp (Xenpozyme) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

DOSING AND FREQUENCY REQUIREMENTS

Refer to Attachment A for dosing and frequency requirements for olipudase alfa-rpcp (Xenpozyme).

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of olipudase alfa-rpcp (Xenpozyme). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of olipudase alfa-rpcp (Xenpozyme) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member’s dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct post-payment review and audit procedures for any claims submitted for olipudase alfa-rpcp (Xenpozyme).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the service.

When coverage of olipudase alfa-rpcp (Xenpozyme) is requested outside of the Dosing and Frequency Requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

Guidelines

There is no Medicare coverage determination addressing olipudase alfa-rpcp (Xenpozyme); therefore, the Company policy is applicable.

BLACK BOX WARNINGS

Refer to the specific manufacturer's prescribing information for any applicable Black Box Warnings.

BENEFIT APPLICATION

Subject to the applicable Evidence of Coverage, olipudase alfa-rpcp (Xenpozyme) is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria and Dosing and Frequency Requirements listed in this medical policy are met.

For Medicare Advantage members, certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when olipudase alfa-rpcp (Xenpozyme) is covered under a member's medical benefit (Part B benefit). It does not address instances when olipudase alfa-rpcp (Xenpozyme) is covered under a member's pharmacy benefit (Part D benefit).

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Olipudase alfa-rpcp (Xenpozyme) was approved by the US Food and Drug Administration (FDA) on August 31, 2022 for the treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric individuals.

PEDIATRIC USE

The safety and effectiveness of olipudase alfa-rpcp (Xenpozyme) for the treatment of non-central nervous system manifestations of ASMD have been established in pediatric individuals down to birth. Use of olipudase alfa-rpcp (Xenpozyme) for this indication is supported by evidence from an adequate, and well-controlled trial in adults with supportive efficacy, safety, and tolerability data in pediatric patients. Compared to adults, a higher percentage of pediatric individuals experienced treatment related serious adverse reactions, anaphylaxis, hypersensitivity reactions, and infusion-associated reactions that occurred within 24 hours of infusion. Two pediatric individuals, an 18 month old receiving olipudase alfa-rpcp (Xenpozyme) and a 16 month old with ASMD type A that received a version of olipudase alfa manufactured from a different process developed anaphylaxis.

Description

Acid sphingomyelinase deficiency (ASMD) (historically known as Niemann-Pick disease [NPD] types A and B) is a rare, progressive, genetic lysosomal storage disease that results from reduced activity of the enzyme, acid sphingomyelinase (ASM), caused by pathogenic variants in the sphingomyelin phosphodiesterase-1 (*SMPD1*) gene. ASM breaks down a complex lipid called sphingomyelin that accumulates in the liver, spleen, lung, and brain. The deficiency of ASM causes an intra-lysosomal accumulation of sphingomyelin (as well as cholesterol and other cell membrane lipids) in various tissues. The diagnosis is confirmed when molecular genetic testing identifies both disease-causing alleles in *SMPD1* or when residual ASM activity in peripheral blood leukocytes or cultured skin fibroblasts is less than 10 percent of controls. ASMD has an autosomal recessive pattern of inheritance, and the birth prevalence is estimated at 0.4–0.6/100,000. The most common clinical presentation for individuals with any form of ASMD is hepatosplenomegaly.

- NPD-A (infantile neurovisceral AMSD): The most severe form of ASMD characterized by rapidly progressive disease where there is little to no residual ASM activity. Individuals present with hepatosplenomegaly, interstitial lung disease, feeding difficulties, dyslipidemia, loss of early motor skills in the first few months of life, and may develop macular cherry-red spot. This subtype occurs with greater frequency in individuals of Ashkenazi Jewish descent. Death typically occurs before 2 or 3 years of age.
- NPD-A/B (chronic neurovisceral ASMD): The intermediate form of ASMD whose onset is during childhood. Individuals have a less severe, slower progression of neurological symptoms and prolonged survival compared to infantile neurovisceral ASMD. Ataxia, gross motor delays, and learning disabilities are commonly seen. Progressive multisystem disease manifestations are similar to or more severe than those observed in chronic visceral ASMD. Premature death from liver and respiratory disease (age at death ranges from childhood to adulthood).
- NPD-B (chronic visceral ASMD): Later onset (childhood/adulthood) and less severe than NPD-A, with a good prognosis for survival into adulthood. Common clinical features in childhood include delayed growth and puberty, fatigue, and bone and joint pain. Most individuals with NPD-B have no neurologic abnormalities. Other abnormalities include dyslipidemia, osteopenia, and decreased platelet and white blood cell counts. Pulmonary function may worsen over time, and interstitial lung disease and pulmonary infections are common. The natural history is one of progressive hypersplenism and gradual deterioration of pulmonary function. Individuals may have a normal life span or die prematurely from disease complications that include respiratory failure, liver failure, and/or hemorrhage.

Olipudase alfa-rpcp (Xenpozyme) was approved by the US Food and Drug Administration (FDA) on August 31, 2022, for the treatment of non–central nervous system manifestations of ASMD in adult and pediatric individuals. Olipudase

alfa-rpcp (Xenpozyme) is an enzyme-replacement therapy that reduces sphingomyelin accumulation. It is not expected to cross the blood-brain barrier or modulate the CNS manifestations of ASMD. Prior to the approval of olipudase alfa-rpcp (Xenpozyme), the only option for treatment was supportive care (e.g., physical therapy, occupational therapy, nutritional support, supplemental oxygen, sedatives, transfusion of blood products, cholesterol-reducing agents).

PEER-REVIEWED LITERATURE

SUMMARY

Adult Individuals

The safety and efficacy of olipudase alfa-rpcp (Xenpozyme) was demonstrated in a multicenter, randomized, double-blinded, placebo-controlled, repeat-dose phase II/III trial (Trial 1: Wasserstein 2022: ASCEND trial) in 31 adults with ASMD (clinical diagnosis consistent with ASMD type B and A/B). Individuals received either olipudase alfa-rpcp (Xenpozyme) (dose escalation, then maintenance dose of 3 mg/kg) or placebo as an intravenous infusion once every 2 weeks. The trial was divided into two consecutive periods: a randomized, placebo-controlled, double-blinded primary analysis period (PAP) that lasted to Week 52, followed by an extension treatment period (ETP) for up to 4 years. Individuals randomly assigned to the placebo arm in the PAP crossed over to receive olipudase alfa-rpcp (Xenpozyme) treatment in the ETP to reach the targeted dose of 3 mg/kg, while individuals in the original olipudase alfa-rpcp (Xenpozyme) arm continued treatment. Individuals enrolled in the trial had a diffusion capacity of the lungs for carbon monoxide (DLco) ≤70% of the predicted normal value and a spleen volume ≥6 multiples of normal (MN) measured by magnetic resonance imaging (MRI). Five males and 13 females with a median age of 34 years (range, 18–66) were included in the placebo arm and eight males and five females with a median age of 34 years (range, 20–59) were included in the olipudase alfa-rpcp (Xenpozyme) arm. Key efficacy endpoints included assessment of % predicted DLco, spleen volume, liver volume and platelet count. At Week 52 during the PAP, an increase of 21% in the mean percent change in % predicted DLco was observed in the olipudase alfa-rpcp (Xenpozyme) arm compared to the placebo arm (P=0.0003), demonstrating a clinically significant improvement in lung function. A reduction in spleen volume of 39% was observed in the olipudase alfa-rpcp (Xenpozyme) arm compared to the placebo arm (P<0.0001). The changes in % predicted DLco and spleen volume were noted at Week 26 of treatment, the first post-dose endpoint assessment. A decrease in mean liver volume and an increase in mean platelet count were noted in the olipudase alfa-rpcp (Xenpozyme) arm compared to the placebo arm at Week 52 (P<0.0001 and P=0.0280, respectively). The most common adverse reactions that occurred were headache and cough.

Seventeen of 18 individuals previously receiving placebo and 13 of 13 individuals previously treated with olipudase alfa-rpcp (Xenpozyme) for 52 weeks (in the PAP) started or continued treatment with olipudase alfa-rpcp (Xenpozyme), respectively, for up to 4 years. At Week 104, individuals initially randomly assigned to placebo had received olipudase alfa-rpcp (Xenpozyme) for 52 weeks and demonstrated the following percent changes in clinical parameters from baseline (before first administration of olipudase alfa-rpcp [Xenpozyme]): 26.8% increase in predicted DLco, 36.5% reduction in spleen volume, 29.5% reduction in liver volume, and 19.5% increase in platelet count. Individuals in the previous olipudase alfa-rpcp (Xenpozyme) group demonstrated improvement from baseline to Week 104 in the following parameters: 34.1% predicted DLco; 48.3% reduction in spleen volume, 31.7% reduction in liver volume, and 24% increase in platelet count.

Pediatric Individuals

The use of olipudase alfa-rpcp (Xenpozyme) for this indication is supported by evidence from an adequate and well-controlled trial (Trial 1) in adults with supportive efficacy, safety, and tolerability data in pediatric patients (Trial 2 and Trial 3).

Compared with adults, a higher percentage of pediatric individuals experienced treatment-related serious adverse reactions, anaphylaxis, hypersensitivity reactions, and infusion-associated reactions that occurred within 24 hours of infusion. An 18 month old receiving olipudase alfa-rpcp (Xenpozyme) and a 16 month old with ASMD type A that received a version of olipudase alfa manufactured from a different process developed anaphylaxis. The most common adverse reactions in pediatric individuals were pyrexia, cough, diarrhea, and rhinitis.

<u>64 Weeks Safety, 52 Weeks Efficacy</u>
Olipudase alfa-rpcp (Xenpozyme) was evaluated in a multicenter, open-label, repeated-dose trial (Trial 2: Diaz 2021 ASCEND-Peds). Olipudase alfa-rpcp (Xenpozyme) was administered intravenously once every 2 weeks (by dose escalation, then maintenance dose of 3 mg/kg) for 64 weeks in eight pediatric individuals aged less than 18 years (seven individuals from 2 to <12 years old, and one individual <2 years old) with a clinical diagnosis consistent

with ASMD type B and A/B. Participants had a spleen volume of 5 or greater MN measured by MRI and height Z-score less than or equal to −1. Exploratory efficacy endpoints resulted in improvements in the following: 46.7% reduction in spleen volume, 38.1% reduction in liver volume, 45.9% mean percent change in % predicted DLco, 37.6% increased in mean platelet counts, and an increase in mean change in height Z-score of 0.5 at Week 52 as compared to baseline.

Long-term trial: 2.5 to 3.2 years
The eight pediatric individuals 2 to less than 12 years of age from Trial 2 continued treatment in an open-label long-term trial (Trial 3) and were treated with olipudase alfa-rpcp (Xenpozyme) for 2.5 to 3.2 years. Efficacy analyses showed continued improvements in the three individuals evaluated for % predicted DLco, six individuals evaluated for platelet counts, and all eight individuals evaluated for spleen and liver volumes, compared to baseline, during the additional 6 months extension. In addition, the height Z-score increased by 1.3 from baseline when evaluated through 24 months of olipudase alfa-rpcp (Xenpozyme) treatment. Bone age, as assessed by hand x-ray, was delayed by a mean of 26.4 months at baseline in the seven pediatric individuals enrolled in Trial 2 with a bone age measured at Month 24 in Trial 3. The bone age improved to within a mean of 12 months of the chronological age when assessed at Month 24 in these seven individuals.

OFF-LABEL INDICATION

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

References

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
E75.241 Niemann- Pick disease type B

E75.244 Niemann- Pick disease type A/B

HCPCS Level II Code Number(s)
J0218 Injection, olipudase alfa-rpcp, 1 mg

Revenue Code Number(s)
N/A

Policy History

MA08.145a

12/15/2025	This policy has been reissued in accordance with the Company's annual review process.
05/07/2024	This version of the policy will become effective 05/07/2024. The following new policy has been developed to communicate the Company's coverage criteria for olipudase alfa-rpcp (Xenpozyme™).

Version Effective Date:
12/15/2025
Version Issued Date:
12/15/2025
Version Reissued Date:

N/A