Itvisma® (Onasemnogene Abeparvovec-Brve)

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➲ Instructions for Use

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Community Plan Policy

- Itvisma® (Onasemnogene Abeparvovec-Brve)

Application

UnitedHealthcare Commercial

This Medical Drug Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Drug Policy applies to Individual Exchange benefit plans.

Coverage Rationale

➲ See Benefit Considerations

Itvisma is proven and medically necessary for one treatment per lifetime for the treatment of spinal muscular atrophy (SMA) in patients who meet all of the following criteria:

- Submission of medical records (e.g., chart notes, laboratory values) confirming the mutation or deletion of genes in chromosome 5q resulting in one of the following:
  - Homozygous gene deletion or mutation of survival motor neuron 1 (*SMN1*) gene (e.g., homozygous deletion of exon 7 at locus 5q13); **or**
  - Compound heterozygous mutation of *SMN1* gene [e.g., deletion of *SMN1* exon 7 (allele 1) and mutation of *SMN1* (allele 2)]

  and
- Submission of medical records (e.g., chart notes, laboratory values) confirming that patient has 2 or 3 *SMN2* gene copies; **and**
- Patient is ≥ 2 years of age; **and**
- Patient is not dependent on **either** of the following:
  - Invasive ventilation or tracheostomy
  - Use of non-invasive ventilation beyond use for naps and nighttime sleep

  and
- Prescribed by a neurologist with expertise in the treatment of SMA; **and**
- Patient is not to receive routine concomitant SMN modifying therapy [e.g., Evrysdi (risdiplam), Spinraza (nusinersen)] (patient's medical record will be reviewed); **and**
- Patient does not have an elevated anti-AAV9 antibody titer above 1:50; **and**

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- Patient will receive prophylactic prednisolone (or glucocorticoid equivalent) prior to and following receipt of Itvisma in accordance with the U.S. Food and Drug Administration (FDA)–approved Itvisma labeling; **and**
- Patient will receive Itvisma as a single-dose intrathecal injection in accordance with the FDA-approved labeling; **and**
- Patient has never received gene therapy treatment [i.e., Zolgensma (onasemnogene abeparvovec-xioi), Itvisma] for SMA in the patient's lifetime; **and**
- Provider does not request a planned inpatient admission for the sole purpose of administering Itvisma; **and**
- Authorization will be issued for no more than one treatment per lifetime and for no longer than 45 days from approval

Additional Information Relevant to the Review Process but not Impacting the Determination of Medical Necessity

- Provider attests that the patient will be assessed via the Hammersmith Functional Motor Scale – Expanded (HFMSE) scale to establish a baseline functional assessment within the 2 weeks **prior** to Itvisma administration†; **and**
- Provider attests that the patient, while under the care of the provider, will be assessed by (HFMSE) during subsequent office visits†

†For quality purposes only, this information will not be considered as part of the individual coverage decision.

Itvisma is not proven or medically necessary for:

- The treatment of SMA for patients younger than 2 years of age; **or**
- SMA without chromosome 5q mutations or deletions; **or**
- The routine combination treatment of SMA with concomitant SMN modifying therapy

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies and guidelines may apply.

HCPCS Code	Description
J3405	Injection, onasemnogene abeparvovec-brve, per treatment

Diagnosis Code	Description
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
G12.1	Other inherited spinal muscular atrophy
G12.8	Other SMAs and related syndromes
G12.9	Spinal muscular atrophy, unspecified
G12.25	Progressive spinal muscle atrophy

Background

Spinal muscular atrophy (SMA) is a rare, autosomal recessive neurodegenerative disorder that affects the survival of motor neurons of the spinal cord. SMA is caused primarily by biallelic (homozygous) variants in the *SMN1* gene. The estimated annual incidence of SMA is 4-10 per 10,000 live births. Approximately 1/40 to 1/60 people are SMA carriers, equating to 3.5 to 5.2 million and 12 to 18 million individuals in the United States and Europe, respectively. SMA is characterized by the degeneration of motor neurons of the spinal cord, resulting in hypotonia and muscle weakness. Historically, SMA has been classified into five phenotypic subtypes (0-4) based on age of symptom onset and motor function achieved. The uncommon SMA type 0 phenotype has prenatal onset associated with decreased fetal movement, significant motor weakness, respiratory distress, difficulty feeding, contractures, and cardiac defects noted at birth. The most incident phenotype, type 1 SMA, occurs in approximately 60% of infants born with SMA with weakness during the first 6 months and never achieving independent sitting. SMA type 2 phenotype has been defined by weakness between 6 and 18 months of life after achieving independent sitting but not walking independently. Approximately 10% of individuals born with SMA presented with SMA type 3 and achieved walking independently with abnormal gait and were diagnosed after 18 months of age. An estimated < 1% of individuals with SMA present during adulthood (usually fourth decade) and are classified as type 4 or adult-onset SMA and have mild motor impairment. Although symptoms are milder and

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progression is slower, people with adult-onset SMA often experience a long process of testing and evaluations before diagnosis. Current literature indicates that the number of copies of the *SMN2* gene that a patient has is the best predictor of clinical phenotype. Individuals with more *SMN2* copies usually have a less severe form of SMA than those with fewer copies.

The active ingredient (drug substance) in Itvisma is identical to Zolgensma (onasemnogene abeparvovec-xioi) but formulated at a different concentration. Zolgensma is administered intravenously based on patient weight to pediatric patients less than 2 years of age with SMA due to bi-allelic mutations in the *SMN1* gene. Itvisma is a concentrated formulation in a smaller delivery volume, administered directly to the central nervous system via a single intrathecal injection independent of patient weight, which expands treatment options available to patients with SMA older than 2 years of age. The direct administration of Itvisma into the cerebrospinal fluid surrounding the spinal cord (site of action) allows for delivery to motor neurons with a lower dose of vector, without the need to adjust for the patient's body weight. This provides a treatment with rapid onset and direct targeting of the genetic root cause of SMA. By addressing the root cause of SMA, Itvisma restores SMN protein production and halts further disease progression.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Clinical Evidence

Prediction of SMA Phenotype Based on *SMN2* Copy Number

Historically, SMA was characterized by a classification system for describing age of symptom onset and maximum motor function achieved. This classification divides SMA into five types: Types 0, 1, 2, 3, and 4. Current literature indicates that the number of copies of the *SMN2* gene that a patient has is the best predictor of clinical phenotype, however the correlation is not absolute. Calucho et al. assessed the correlation of *SMN2* copy number to SMA phenotype in 3459 patients worldwide from reports published after 1999. Analysis of the North American cohort showed similar findings. Seventy-three percent of patients with 2 copies were diagnosed with type I SMA, accounting for 79% of all type I SMA cases. Patients with 3 copies of *SMN2* were the most numerous in the entire cohort accounting for approximately half of the cases. Fifteen percent of patients with 3 copies of *SMN2* were diagnosed with Type I SMA. Ninety-five percent of patients with type II SMA and 54% of patients with type III SMA had 3 copies or less of *SMN2*. Approximately 15% of patients in the worldwide cohort had 4 copies of *SMN2*. Patients with 4 copies of *SMN2* were highly unlikely to be diagnosed with type I SMA as greater than 99% of cases were diagnosed with non-type I SMA, with approximately 90% of patients with 4 *SMN2* copies developing type III SMA. Patients with 4 copies or more of *SMN2* accounted for 0.3% of all cases diagnosed with type I SMA and approximately 5% of all cases diagnosed with type II SMA.

Clinical Trial: Intrathecal OAV101 in Pediatric Patients With Type 2 SMA (STEER, NCT05089656)

The efficacy of Itvisma was evaluated in a Phase 3 randomized, double-blind, sham-controlled study (STEER; NCT05089656) in 126 patients with SMA aged 2 to less than 18 years who were treatment-naive, and able to sit but never able to walk independently. Patients were randomized to Itvisma or sham procedure as a one-time dose. The primary endpoint was the change from baseline in the Hammersmith Functional Motor Scale – Expanded (HFMSE) total score over 52 weeks. The HFMSE is a 33-item measure that assesses the motor functional abilities of children and adults with SMA. The maximum total score is 66 and higher scores indicate better motor function. The mean change from baseline in the HFMSE total score was 2.39 and 0.51 with Itvisma and sham, respectively (difference 1.88, 95% CI: 0.51, 3.25; p = 0.0074). The most common adverse reactions (≥ 10%) with Itvisma use were upper respiratory tract infection, upper gastrointestinal symptoms, pyrexia, and headache.

Clinical Trial: Intrathecal OAV101 in Patients With SMA Who Discontinued Treatment With Nusinersen or Risdiplam (STRENGTH, NCT05386680)

The safety of Itvisma was also evaluated in a Phase 3b, single-arm, open-label study (STRENGTH; NCT05386680) in 27 patients with SMA aged 2 to less than 18 years who had discontinued treatment with Evrysdi® (risdiplam) or Spinraza® (nusinersen), two chronic SMN-targeted therapies. Patients were able to sit independently but have never taken steps independently. The mean age at dosing was 7.4 years. The primary objective was to characterize the safety and

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tolerability of Itvisma and a secondary endpoint included the change in HFMSE over 52 weeks. As a secondary endpoint, the mean (standard deviation) change from baseline in HFMSE score at Week 52 was 0.17 (2.88) for patients treated with Itvisma (n = 21). The HFMSE demonstrated stabilization for the overall study population over 52 weeks.

Professional Societies

Health Care Provider Working Group

An SMA working group of American and European health care providers updated the SMA best practice recommendations for diagnosis through systematic literature review and sequential modified Delphi surveys and discussions. The health care provider working group (HCPWG), supported by Cure SMA, included 18 members plus 2 organizing and nonvoting Cure SMA staff members who moderated discussions and had no stake in the decisions. The HCPWG included 5 European physician neurologists, 12 U.S. physician neurologists, and 1 U.S. genetic counselor. All HCPWG members participated voluntarily without compensation. Included in their recommendations was a recommendation that SMA infants identified by NBS and before treatment initiation should be characterized by *SMN2* copy number, current motor function, age at symptom onset, and severity of symptoms. The classification of SMA severity based on SMA type has changed due to the effectiveness of SMN-enhancing treatments in tandem with early identification by NBS and urgent confirmatory diagnosis. Thus, the HCPWG discussed that classification of newborns by SMA type is not clinically meaningful for newly diagnosed infants with SMA and those treated early in their life with SMN-enhancing treatment(s). Because *SMN2* copy number is associated with disease phenotype, progression, and outcomes, determining the number of *SMN2* copies is urgent and should be included as a component of the confirmatory diagnostic testing to include both the number of *SMN1* and *SMN2* gene copies. In addition, based on consensus recommendations by U.S. clinicians to treat infants with 4 copies of *SMN2* urgently, distinguishing between 4 and 5 copies of *SMN2* is necessary.

2024 European Neuromuscular Expert Consensus Statement on Gene Replacement Therapy for Spinal Muscular Atrophy

In 2020, a group of 13 European neuromuscular experts, conveyed to help aid the rational use of Zolgensma and presented 11 consensus statements covering qualification, patient selection, safety considerations, and long-term monitoring after the European Medical Agency (EMA) approval of Zolgensma. After three years, a similar yet larger group of European experts assembled to assess the emerging evidence of onasemnogene abeparvovec's role in treating older and heavier SMA patients, integrating insights from recent clinical trials and real-world evidence. This effort resulted in 12 consensus statements, with strong consensus achieved on 9 and consensus on the remaining 3, reflecting the evolving role of onasemnogene abeparvovec in treating SMA. The following is a recommendation from the European expert panel that addressed intrathecal administration of onasemnogene abeparvovec:

- Consensus statement 5: Since the risk of gene therapy increases with the dose administered and since the dose is proportional with the weight and age, heavier and older patients should be treated very cautiously as the data available in these patients are very scarce. Treatment with other disease-modifying treatments or future intrathecal administration of onasemnogene abeparvovec if it shows an acceptable efficacy-safety ratio, should be considered as a valuable alternative, and discussed with parents.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Itvisma (onasemnogene abeparvovec-brve) is an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of spinal muscular atrophy (SMA) in adult and pediatric patients 2 years of age and older with confirmed mutation in *SMN1* gene.

References

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Policy History/Revision Information

Date	Summary of Changes
10/01/2026	**Coverage Rationale** • Revised coverage criteria; replaced criterion requiring "the patient is not to receive routine concomitant SMN modifying therapy [e.g., Evrysdi (risdiplam), Spinraza (nusinersen)] (patient's medical record will be reviewed *and any current authorizations for SMN modifying therapy will be terminated upon Itvisma approval*)" with "the patient is not to receive routine concomitant SMN modifying therapy [e.g., Evrysdi (risdiplam), Spinraza (nusinersen)] (patient's medical record will be reviewed)" **Supporting Information** • Updated *References* section to reflect the most current information • Archived previous policy version 2026D0142B

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its policies and guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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