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Onasemnogene abeparvovec-brve

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and

effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

Coverage

Onasemnogene abeparvovec-brve (Itvisma®) **may be considered medically necessary** when **all** the following criteria are met:

1. Individuals are 2 years of age and older with spinal muscular atrophy with confirmed mutation in SMN1 gene:
   a. Deletion of both copies of the SMN1 gene; OR
   b. Compound heterozygous mutations of the SMN1 gene (defined below):
      i. Pathogenic variant(s) in both copies of the SMN1 gene;
      ii. Pathogenic variant in 1 copy and deletion of the second copy of the SMN1 gene;
2. Documentation of baseline liver assessment such as aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin, and prothrombin time;
3. Individual can sit (per clinical protocol sit = ability to sit up straight with head erect for at least 10 seconds without using arms or hands to balance or support head position);
4. The individual does not have advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence);
5. Negative baseline titers for anti-adeno-associated virus serotype 9 (AAV9) antibody;
6. Individual has not previously received onasemnogene abeparvovec-xioi (Zolgensma).

Repeat treatment or ante-partum use of onasemnogene abeparvovec-brve (Itvisma®) **is considered experimental, investigational, and/or unproven.**

Concurrent use of onasemnogene abeparvovec-brve (Itvisma®) with nusinersen and/or risdiplam **is considered experimental, investigational, and/or unproven**.

Use of nusinersen and/or risdiplam after administration of onasemnogene abeparvovec-brve (Itvisma®) **is considered experimental, investigational, and/or unproven.**

Onasemnogene abeparvovec-brve (Itvisma®) **is considered experimental, investigational and/or unproven** for all other non-U.S. Food and Drug Administration (FDA) approved indications.

Policy Guidelines

The U.S. Food and Drug Administration (FDA) has issued a black-box warning for onasemnogene abeparvovec-brve due to the risk of acute serious liver injury and elevated aminotransferases. Individuals with pre-existing liver impairment may be at higher risk.

Liver function (clinical exam, aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin, prothrombin time), platelet counts, and troponin-I levels should be monitored as per the prescribing label.

Where feasible, the individual's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following onasemnogene abeparvovec-brve infusion.

Per the FDA label, the safety and effectiveness of Itvisma have not been established in pediatric patients younger than 2 years of age.

Description

Spinal Muscular Atrophy

Spinal muscular atrophy is a rare autosomal recessive genetic disorder caused by homozygous deletions or variants in the *SMN1* gene located on chromosome 5. This gene produces the "survival of motor neuron" protein (*SMN1*), which is essential for motor neuron functioning. In 95% of cases of spinal muscular atrophy, there is a homozygous deletion of exon 7 in the *SMN1* gene. The remaining 5% of cases are compound heterozygotes for *SMN1* exon 7 deletions and small intragenic variants. (2) Due to absent or low levels of the survival motor neuron 1 protein, motor neurons in the spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk affecting the ability to crawl, walk, sit up, and control head. In more severe cases, feeding, swallowing, and breathing are affected as well. The exact role of the survival motor neuron protein in motor neurons has not been completely elucidated, and levels of the survival motor neuron protein required for optimal functioning are unknown. (3)

There is wide phenotypic heterogeneity in spinal muscular atrophy, as summarized in Table 1. This is due to the presence of *SMN2*, a modifying/backup gene, also located on chromosome 5, which is 99% identical to *SMN1*. However, 70% to 90% of the *SMN2* compensatory protein produced by this gene is defective and unstable due to the lack of exon 7. (4) The number of copies of the *SMN2* gene varies widely (range, 0-6), resulting in a less severe form of spinal muscular atrophy among those with more copies of the *SMN2* gene and vice-versa. (5) The relation between the *SMN2* copy number and spinal muscular atrophy phenotype is summarized in Table 2. These data were generated from DNA samples of 375 patients with spinal muscular atrophy who previously had been classified as follows: 188 with spinal muscular

atrophy type I, 110 with spinal muscular atrophy type II, and 77 with spinal muscular atrophy type III. (6)

Table 1. Characteristics and Subtypes of Spinal Muscular Atrophy

Type of SMA	Age at Symptoms Onset	Life Span	Highest Motor Milestone Achieved	*SMN2* Copy Number[a]
Type 0 (antenatal-onset SMA)	Prenatal	<6 months	Little ability to move and may be unable to breathe and swallow independently.	1
Type I (infantile SMA or Werdnig-Hoffman disease)	0-6 months	<2 years without respiratory support	Never rolls or sits unsupported.	2
Type II (intermediate SMA or Dubowitz disease)	<18 months	>2 years; ≈70% alive at 25 years of age	Sits independently once properly positioned; sometimes stands but never able to walk.	3 or 4
Type III (Kugelberg-Welander disease)				
Subtype IIIa	>18 months to 3 years	Similar to that of the general population	Sits, stands, and walks independently until puberty; many no longer walk after puberty. Never runs or jumps well.	3 or 4
Subtype IIIb	>3 years	Similar to that of the general population	Sits, stands, and walks independently until puberty; many no longer walk after puberty. Walks, runs, jumps, and can participate in sports.	4
Type IV (adult-onset SMA)	>21 years	Similar to that of the general population	Similar to that of the general population.	4-8

Adapted from the Muscular Dystrophy Association (n.d.), (7) National Organization for Rare Disorders (2024), (8) Zerres et al. (1995), (9) Finkel et al. (2014), (10) and Rudnik-Schoneborn et al. (2001). (11)
SMA: spinal muscular atrophy.

[a] Quantitative analysis of *SMN2* copies in 375 patients showed that 80% of SMA type I carry 1 or 2 *SMN2* copies, 82% with SMA type II carry 3 *SMN2* copies, and 96% with SMA type III carry 3 or 4 *SMN2* copies. (6)

Among 113 patients with SMA type I, 9 with 1 *SMN2* copy lived <11 months, 88 of 94 with 2 *SMN2* copies lived <21 months, and 8 of 10 with 3 *SMN2* copies lived 33 to 66 months. (12)

Table 2. Relation Between *SMN2* Copy Numbers and Spinal Muscular Atrophy Phenotype

Type of SMA	Percent With 1 *SMN2* Copy	Percent With 2 *SMN2* Copies	Percent With 3 *SMN2* Copies	Percent With 4 *SMN2* Copies
Type I	6.9	73.4	19.7	0
Type II	0	10.9	81.8	7.3
Type III	0	3.9	50.6	45.5
	Probability[a] of SMA Type I	**Probability[a] of SMA Type II**	**Probability[a] of SMA Type III**	
1 *SMN2* copy	99.9	0	0	
2 *SMN2* copies	97.3	2.7	0	
3 *SMN2* copies	7.2	82.8	10.0	
4 *SMN2* copies	1.6	14.8	83.6	

Adapted from Feldkötter et al. (2002). (6)
SMA: spinal muscular atrophy.
[a] Probability that an unaffected child who has been tested after birth and has been found to carry a homozygous *SMN1* deletion will develop SMA type.

Diagnosis

Spinal muscular atrophy can be diagnosed using multiple molecular genetic testing techniques such as multiplex ligation-dependent probe amplification or quantitative polymerase chain reaction or a comprehensive next-generation sequencing-based approach. Individuals are classified as having spinal muscular atrophy if they have a homozygous deletion of the *SMN1* gene or a homozygous absence of the *SMN1* gene due to gene conversion (i.e., *SMN1* gene conversion to *SMN2* gene) or a compound heterozygote variant in the *SMN1* gene. Individuals are defined as carriers if they have 1 copy of the *SMN1* gene on 1 chromosome and no copies on the other or 2 copies of the *SMN1* gene on 1 chromosome and no copies on the other. Assessing *SMN2* copy numbers as part of a diagnostic workup is important because it can provide critical information on disease progression and assist in possible clinical trial enrollment or treatment.

Because spinal muscular atrophy symptom onset may occur shortly after birth to months to years later, estimating the incidence and prevalence of spinal muscular atrophy subtypes is difficult. The incidence, as reported in the literature, is more precisely a birth prevalence rate, which is estimated between 9.1 and 10 per 100,000 live births, (13, 14) which translates to 500 new spinal muscular atrophy cases annually.

Treatment

Medical management of spinal muscular atrophy patients includes respiratory, nutritional, and musculoskeletal supportive care. Respiratory management includes airway clearance, antibiotic treatment of infections, noninvasive and invasive ventilation. Nutritional management includes changing food consistency, gastrostomy tube feeding, and dietician assessment. Musculoskeletal supportive care includes a variety of interventions such as equipment for

mobility, teaching self-care and function, physiotherapy, spinal surgery, posture and pain management, regular exercise, and scoliosis surgery. The type and extent of supportive care can affect survival in infant-onset disease (e.g., gastrostomy feeding and noninvasive/invasive ventilation).

Onasemnogene abeparvovec-brve is a single-dose intrathecal injection for adult and pediatric individuals ages 2 and older with a confirmed mutation in *survival motor neuron 1* (*SMN1*) gene.

Regulatory Status
On November 24, 2025, the U.S. Food and Drug Administration (FDA) approved onasemnogene abeparvovec-brve (Itvisma®) for the treatment of spinal muscular atrophy (SMA) in adult and pediatric patients 2 years of age and older with confirmed mutation in *survival motor neuron 1* (*SMN1*) gene. (1, 15)

Rationale

This policy is based on the U.S. Food and Drug Administration label for onasemnogene abeparvovec-brve (Itvisma®).

Onasemnogene abeparvovec-brve (Itvisma®) (1)
The efficacy of Itvisma was evaluated in a randomized, double-blind, sham-controlled study (Study 1; NCT05089656). The study enrolled patients with spinal muscular atrophy (SMA) who were treatment-naive, and able to sit but never able to walk independently. Patients with elevated (reference to > 1:50) baseline serum anti-AAV9 antibody titer were excluded.

A total of 136 patients were randomized in 3:2 ratio to receive either Itvisma at a dose of 1.2 x 10^{14} vg by single lumbar intrathecal injection or sham procedure. Randomization was stratified by age and pre-treatment Hammersmith Functional Motor Scale – Expanded (HFMSE) score at screening. A total of 126 patients received the assigned treatment and were included in the efficacy evaluation.

The demographic characteristics of the population were as follows: the mean age was 6 years (range, 2 to 17 years), 62 patients (49%) were male, 74 patients (59%) were Asian, 14 patients (11%) were White, 9 patients (7%) were Black or African American, and 7 patients (6%) were American Indian or Alaska Native, 22 patients (18%) were of “unknown” race. One hundred and twenty-two patients (97%) had confirmed biallelic deletion (0 copies) of the *SMN1* gene, while 4 patients (3%) had 1 copy. Patients' highest motor function ever achieved were as follows: 66 patients (52%) sitting without support, 33 patients (26%) standing with assistance, 24 patients (19%) walking with assistance, and 3 patients (2%) standing independently. At baseline, the mean HFMSE total score was 17.97 (range 1.0 - 41.0) and 18.17 (range 2.0 - 42.5) in the Itvisma-treated group and sham group, respectively.

The primary endpoint was the change from baseline in HFMSE total score at the end of follow-up, defined as the average of the Week 48 and Week 52 assessment, in Itvisma compared to sham. The HFMSE evaluates motor function in patients with SMA who have limited ambulation, comprising of 33 graded items that assess various motor skills ranging from sitting to using the stairs. Each item is scored from 0-2, with a maximum total score of 66. Higher scores indicate better motor function.

The efficacy results from Study 1 are summarized in Table 3 below.

Table 3. Efficacy Results from the Study 1 (n=126)

Endpoint	Itvisma (N=75)	Sham (N=51)	Treatment Difference Itvisma-Sham (95% CI)	p-value
Mean change from baseline in HFMSE total score at the end of follow-up[1,2,3]	2.39 (0.439)[4]	0.51 (0.532)[4]	1.88 (0.51 – 3.25)	0.0074

CI: confidence interval; HFMSE: Hammersmith Functional Motor Scale – Expanded.
[1] Assessed using the Full Analysis Set (FAS) population, which included all participants who were dosed with Itvisma (n=75) or who underwent sham procedure (n=51). The follow-up period was defined as the average of the Week 48 and Week 52 assessment.
[2] Least squares (LS) mean.
[3] Estimated using a linear mixed model repeated measures (MMRM) model with the observed change from Baseline in HFMSE total score at all post-baseline visits as the dependent variable. The fixed effects included treatment, visit, treatment by visit interaction, the strata, and the baseline HFMSE total score as covariate. An unstructured covariance matrix was used.
[4] Standard error of the mean (SEM)

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J3405

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. Package Insert and Information for Patients. Highlights of Prescribing Information. Itvisma® (onasemnogene abeparvovec-brve). Revised November 2025. Available at: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/itvisma> (accessed January 8, 2026).

Other:

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15. Novartis. Novartis receives FDA approval for Itvisma®, the only gene replacement therapy for children two years and older, teens, and adults with spinal muscular atrophy (SMA). Available at: <https://www.novartis.com> (accessed January 14, 2026).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
07/01/2026	New medical document. Onasemnogene abeparvovec-brve (Itvisma®) may be considered medically necessary when all the following criteria are met: 1. Individuals are 2 years of age and older with spinal muscular atrophy with confirmed mutation in SMN1 gene: a. Deletion of both copies of the SMN1 gene; OR b. Compound heterozygous mutations of the SMN1 gene (defined below): i. Pathogenic variant(s) in both copies of the SMN1 gene; ii. Pathogenic variant in 1 copy and deletion of the second copy of the SMN1 gene; 2. A baseline liver assessment such as aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin, and prothrombin time; 3. Individual can sit (per clinical protocol sit = ability to sit up straight with head erect for at least 10 seconds without using arms or hands to balance or support head position); 4. The individual does not have advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence); 5. Negative baseline titers for anti-adeno-associated virus serotype 9 (AAV9) antibody; 6. Individual has not previously received onasemnogene abeparvovec-xioi (Zolgensma). Repeat treatment or ante-partum use of onasemnogene abeparvovec-brve (Itvisma®) is considered experimental, investigational, and/or unproven. Concurrent use of onasemnogene abeparvovec-brve (Itvisma®) with nusinersen and/or risdiplam is considered experimental, investigational, and/or unproven. Use of nusinersen and/or risdiplam after administration of onasemnogene abeparvovec-brve (Itvisma®) is considered experimental, investigational, and/or unproven. Onasemnogene abeparvovec-brve (Itvisma®) is considered experimental, investigational and/or unproven for all other non-FDA approved indications.