Risdiplam Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
04-01-2024	08-01-2022

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Evrysdi® (risdiplam) Powder for oral solution	Treatment of spinal muscular atrophy (SMA) in pediatric and adult patients		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Spinal Muscular Atrophy	Spinal muscular atrophy (SMA) is the second most common autosomal recessive neurodegenerative disorder, caused by bi-allelic loss or dysfunction of the survival motor neuron 1 (SMN1) gene.(2,11) SMA is characterized by dysfunction and then loss of the alpha motor neurons in the spinal cord that causes progressive muscle atrophy and weakness.(10) The SMN1 and SMN2 genes are all located on chromosome 5q13.2, an unstable chromosomal region that is prone to deletion, duplication, and gene conversion. There are two forms of survival motor neuron (SMN), SMN1 and SMN2, that differ by only five nucleotides.(5) SMN1 is the primary gene responsible for functional production of SMN protein. SMN1 produces a full-length transcript that encodes functional SMN protein.(3) SMN1 can be absent because of deletion or SMN1-to-SMN2 conversion.(5) The most common mutation causing SMA is a homozygous deletion of the SMN1 exon 7.(11) SMN2 preferentially excludes exon 7 during splicing and, as a result, produces only a small fraction of functional SMN protein as compared with SMN1.(3) Because SMN2 produces a reduced number of full-length transcripts, the number of SMN2 copies can modify the clinical phenotype and is an essential predictive factor.(3,11) About 94% of SMA patients have a homozygous deletion of SMN1 exon 7. SMA has an incidence of approximately 1 in 10,000 live births and a carrier frequency of approximately 1 in 54.(3) SMA is classified into four subtypes (1-4) based on age of onset of symptoms and motor milestone achievement. This variability in the clinical phenotype is largely a result of the number of copies of the survival motor neuron 2 (SMN2) gene. The SMA type 1 (SMA1) phenotype is the most severe.(2) The presence of two copies of SMN2 is associated with SMA1. Infants with SMN1 bi-allelic deletions and two copies of SMN2 have a 97% risk of SMA1.(3) Clinical Classification of SMA(11)

SMA Type	Number of SMN2 Copies	Percent of Cases	Age of Onset	Highest Achieved Motor Function	Natural Age of Death Prior to Disease Modifying Therapy
0	1	Rare, less than 1%	Prenatal, at birth	Non-sitter, no head control	Death within weeks of birth
1	1-2	45%	0-6 months	Non-sitter	Death by age 2
2	3	20%	6-18 month	Sit independently, never stands or ambulates	Most alive at 25 years
3	3-4	30%	3a: 18 months-3 years 3b: 3-30 years	Ambulates independently	Normal lifespan
4	Greater than or equal to 4	Less than 5%	Greater than 30 years	Ambulates independently	Normal lifespan

The onset of symptoms for SMA1 occurs shortly after birth and prior to six months of age with a clinical hallmark of the inability to achieve independent sitting.(2) A historical cohort showed that the median age at symptom onset among infants with the disease was 1.2 months (range, 0 to 4 months).(3) Infants with SMA1 rapidly lose motor function and ultimately succumb to respiratory complications often within the first year of life. Studies of SMA1 infants with two SMN2 copies offered standard of care showed a median age of death or permanent ventilation (greater than or equal to 16h/day for at least 14 consecutive days) that ranged from 8 to 10.5 months.(2) Patients with SMA1 do not achieve major milestones in function and have a decline in function, as measured on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scale, which ranges from 0 to 64, with higher scores indicating better motor function. In a historical analysis of 34 patients with SMA1, all but one of the patients did not reach a score of at least 40 after 6 months of age. In another cohort, CHOP-INTEND scores decreased by a mean of 10.7 points from 6 months to 12 months of age.(3)

Molecular genetic testing is the standard tool for diagnosis of SMA. Genetic testing for homozygous deletion will confirm the disease in 95% of patients. Essentially all other patients with SMN-related SMA will be compound heterozygotes with a single SMN1 deletion and a mutation in the other SMN1 copy.(4) Guidelines recommend use of age-appropriate testing to advise initiation and follow-up of drug therapy in SMA patients. They acknowledge that the tests vary in availability, physician expertise and preference, and the patient's ability, based on age, to participate. The function assessments that were considered for use in SMA patients were CHOP-INTEND, Hammersmith Infant Neurological Examination (HINE-2), Hammersmith Functional Motor Scale-Expanded (HFMSE), six-minute walk test (6MWT), Revised Upper Limb Module (RULM) test, and Bayley Scales of Infant and Toddler Development (BSID). Risdiplam efficacy trials utilized Bayley Scales of Infant and Toddler development, Third Edition (BSID-III), and Motor Function Measurement score (MFM32).(10)

In addition to risdiplam, there are two additional FDA-approved therapies for SMA, Zolgensma and Spinraza. Zolgensma is an SMN1 gene transfer via adenovirus vector dosed once via intravenous infusion.(6,11) Spinraza, a modified antisense oligonucleotide the binds SMN2 mRNA to modify splicing, causing an increase in SMN

	protein production. Spinraza is administered as an intrathecal injection dosed every four months after completing a loading dose series.(7,11)
Efficacy	Risdiplam modifies pre-mRNA splicing of SMN2, increasing the production of SMN2. Risdiplam's New Drug Application included two clinical trials: FIREFISH (NCT02913482) and SUNFISH (NCT02908685). FIREFISH was an open-label, multi-center clinical study to assess the safety, tolerability, pharmacokinetic, pharmacodynamics, and efficacy of risdiplam in infants with Type 1 SMA. It consisted of an exploratory dose finding segment and a confirmatory segment that investigated risdiplam for 24-months. Primary outcome measures were finding the recommended segment 2 dose of risdiplam, and in segment 2, finding the percentage of infants who are sitting without support at 12-months of treatment, assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler development, Third Edition (BSID-III). Inclusion criteria included a clinical history of Type 1 SMA with onset after 28 days but prior to three months, a confirmed diagnosis of 5q-autosomal SMA, and having two SMN2 gene copies. Exclusion criteria included concomitant or previous administration of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier, or gene therapy, patients that were hospitalized for a pulmonary event within the last two months, requiring invasive ventilation or tracheostomy, and patients with unstable GI, renal, hepatic, endocrine, or cardiovascular disease.(8) SUNFISH was a multi-center, double-blind, placebo-controlled, Phase II/III study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in adult and pediatric participants with Type 2 and Type 3 SMA. There were two segments to the study: a 12-week exploratory dose finding segment and a 24-month confirmatory segment. Outcome (motor function) was assessed by the 32-item Motor Function Measure score (MFM32). At one year, risdiplam treatment led to clinically meaningful improvement, with an average increase in MFM36 score of 1.36, compared with an average 0.19 decrease in MFM32 score for the placebo group. The inclusion criteria for segment 2 were patients with Type 2 or 3 SMA (with a confirmed diagnosis of 5q-autosomal recessive SMA) that were non-ambulatory and a negative blood pregnancy test. Exclusion criteria included concomitant or previous administration of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier, or gene therapy, patients that were hospitalized for a pulmonary event within the last two months, unstable GI, renal, hepatic, endocrine, or cardiovascular disease considered to be clinically significant by the investigator, or requirement of invasive ventilation or tracheostomy.(9)
Safety	Risdiplam has no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Evrysdi prescribing information. Genentech, Inc. March 2023.
2	Al-Zaidy S, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatr Pulmonol.* 2019;54(2):179-185.
3	Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene Replacement Therapy for Spinal Muscular Atrophy. *N Engl J Med* 2017;377:1713-22.
4	Arnold WA, Kassar D, Kissel JT. Spinal Muscular Atrophy: Diagnosis and Management in a New Therapeutic Era. *Muscle Nerve* 2015 Feb;51(2):157-167. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4293319/
5	Fang P, Li L, Zeng J, et al. Molecular Characterization and Copy Number of SMN1, SMN2 and NAIP in Chinese Patients with Spinal Muscular Atrophy and Unrelated Healthy Controls. *BMC Musculoskelet Disord.* 2015;16(1):11.
6	Zolgensma Prescribing Information. Novartis Gene Therapy, Inc. February 2023.
7	Spinraza Prescribing Information. Biogen. February 2023.
8	Investigate Safety, Tolerability, PK, PD and Efficacy of Risdiplam (RO7034067) in Infants With Type 1 Spinal Muscular Atrophy (FIREFISH). https://clinicaltrials.gov/ct2/show/NCT02913482

Number	Reference
9	A Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam (RO7034067) in Type 2 and 3 Spinal Muscular Atrophy (SMA) Participants (SUNFISH). https://clinicaltrials.gov/ct2/show/NCT02908685
10	Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. *J Neuromuscul Dis*. 2018;5(2):145-158.
11	Keinath MC, Prior DE, Prior TW. (2021). Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. *The application of clinical genetics,* 14, 11-25. https://doi.org/10.2147/TACG.S239603

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Evrysdi	risdiplam for soln	0.75 MG/ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Evrysdi	Risdiplam For Soln	0.75 MG/ML	240	mLs	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Evrysdi	risdiplam for soln	0.75 MG/ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Evrysdi	Risdiplam For Soln	0.75 MG/ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of Spinal Muscular Atrophy (SMA) type 1, 2, or 3 **AND** 2. The patient's diagnosis was confirmed by genetic testing confirming the mutation or deletion of genes in chromosome 5q (medical records required) **AND** 3. The patient has had at least ONE of the following baseline (prior to starting therapy with the requested agent) functional assessments based on patient age and motor ability: A. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) B. Hammersmith Infant Neurological Examination (HINE-2) C. Hammersmith Functional Motor Scale-Expanded (HFMSE) D. Six-minute walk test (6MWT) E. Bayley Scales of Infant and Toddler Development (BSID) F. Motor Function Measurement score (MFM32) G. Revised Upper Limb Module (RULM) test **AND** 4. The patient does NOT require invasive ventilation or tracheostomy **AND** 5. The patient has not received gene therapy for the requested indication (e.g., Zolgensma [onasemnogene abeparvovec-xioi]) **AND** 6. If the patient has used Spinraza (nusinersen) in the last four months, they will complete a four-month washout period between the last Spinraza (nusinersen) dose and the initiation of therapy with the requested agent **AND** 7. The patient will NOT be using the requested agent in combination with Spinraza (nusinersen) **AND** 8. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 9. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had improvements or stabilization from baseline (prior to starting therapy with the requested agent) with the requested agent as indicated by one of the following functional assessments based on patient age and motor ability: A. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) B. Hammersmith Infant Neurological Examination (HINE-2) C. Hammersmith Functional Motor Scale-Expanded (HFMSE) D. Six-minute walk test (6MWT) E. Bayley Scales of Infant and Toddler Development (BSID) F. Motor Function Measurement score (MFM32) G. Revised Upper Limb Module (RULM) test **AND** 3. The patient does NOT require invasive ventilation or tracheostomy **AND** 4. The patient has not received gene therapy for the requested indication (e.g., Zolgensma [onasemnogene abeparvovec-xioi]) **AND** 5. The patient will NOT be using the requested agent in combination with Spinraza (nusinersen) **AND**

Module	Clinical Criteria for Approval
	6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** 12 months