Evrysdi 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
4/1/2023	8/1/2022

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Evrysdi® (risdiplam) Powder for oral solution	The 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 an autosomal recessive neurodegenerative disorder, caused by bi-allelic loss or dysfunction of the survival motor neuron (SMN) gene. The two versions of SMN, SMN1 and SMN2, differ by only five nucleotides. SMN1 produces a full-length transcript that encodes functional SMN protein. About 94% of SMA patients have a homozygous deletion of SMN1 exon 7. SMN1 can be absent because of deletion or SMN1-to-SMN2 conversion. The SMN1 and SMN2 genes are all located at 5q13.2, an unstable chromosomal region that is prone to deletion, duplication, and gene conversion. A single nucleotide transition in SMN2 exon7 relative to SMN1 causes most of the SMN2 pre-mRNA to lack exon 7 and encode nonfunctional SMNΔ7 protein. However, about 10% of SMN2 pre-mRNA is normal and can be translated into full-length SMN protein. (5) Insufficient levels of the survival motor neuron protein result in a loss of motor neurons of the brainstem and spinal cord, progressive muscular atrophy, and weakness. SMA has an incidence of approximately 1 in 10,000 live births and a carrier frequency of approximately 1 in 54. 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 gene 2 (SMN2), which produces a small, insufficient amount of SMN protein.(2) The SMA type 1 (SMA1) phenotype is the most severe, and accounts for 60% of SMA patients.(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(4)

SMA Type	Age of Onset	Highest Achieved Motor Function	Natural Age of Death	Typical Number of SMN2 Copies[5]
0	Prenatal/fetal	None	Less than 6 months	1
1	Less than 6 months	Sit with support only	Less than 2 years	1-3

2	6-18 months	Sit independently	Greater than 2 years	2-3
3	Greater than 18 months	Walk independently	Adulthood	3-4
4	Adult (20s-30s)	Walk through adulthood	Adulthood	Greater than or equal to 4

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 (≥ 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), Hammersmith Functional Motor Scale – Expanded (HFMSE), six-minute walk test (6MWT), 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 FDA-approved therapies for SMA, Zolgensma and Spinraza. Zolgensma is a gene therapy product dosed once via intravenous infusion.(6) Spinraza affects splicing of the SMN2 gene 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)

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 in 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 contraindications or boxed warnings.(1)

REFERENCES

Number	Reference
1	Evrysdi Information. Genentech, Inc. September 2022.
2	Al-Zaidy S, Pickard AS, Kotha K, et. al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. Pediatric Pulmonology 2019;54:179-185.
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. B<C Musculoskelet Disord. 2015; 16(1):11.
6	Zolgensma Prescribing Information. AveXis, Inc. May 2019
7	Spinraza Prescribing Information. Biogen. June 2019
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
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. doi:10.3233

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Preferred Status	Effective Date
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	Days Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date
Evrysdi	Risdiplam For Soln	0.75 MG/ML	240.0	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 is age 2 months to less than or equal to 25 years at the time of approval **AND** 2. Genetic testing confirms diagnosis of classic (5q) spinal muscular atrophy (SMA), including loss of, or defect in, the *SMN1* gene (NOTE: laboratory documentation must be provided) **AND** 3. Genetic testing confirms less than or equal to 4 copies of the *SMN2* gene (NOTE: laboratory documentation must be provided) **AND** 4. The patient does not have advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence [defined as invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in absence of an acute reversible illness, excluding perioperative ventilation]) **AND** 5. The patient does NOT have any serious concomitant illness (e.g., severe liver or kidney disease, symptomatic cardiomyopathy, acute viral infection) **AND** 6. The patient will NOT be using the requested agent in combination with nusinersen (Spinraza) or onasemnogene abeparvovec (Zolgensma) **AND**

Module	Clinical Criteria for Approval
	7. If the patient has been previously treated with nusinersen (Spinraza), use of nusinersen (Sprinraza) will be discontinued 4 months before treatment with risdiplam (Evrysdi) is started **AND** 8. If the patient has been previously treated with onasmnogene abeparvovec (Zolgensma), the patient has NOT achieved the expected benefit from gene therapy, as demonstrated by the inability to achieve and sustain a CHOP INTEND score of more than 40 points within 3 months of gene therapy **AND** 9. The prescriber is a neurologist or the prescriber has consulted with a neurologist **AND** 10. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months **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 positive clinical response with the requested agent (e.g., improvement in motor function or stabilization of motor function loss) **AND** 3. The patient does not have advanced SMA (e.g. complete paralysis of limbs, permanent ventilator dependence [defined as invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in absence of an acute reversible illness, excluding perioperative ventilation]) **AND** 4. The patient does NOT have any serious concomitant illness (e.g., severe liver or kidney disease, symptomatic cardiomyopathy, acute viral infection) **AND** 5. The patient will NOT be using the requested agent in combination with nusinersen (Spinraza) or onasemnogene abeparvovec (Zolgensma) **AND** 6. The prescriber is a neurologist or the prescriber has consulted with a neurologist **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**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) is greater than 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