

## Update

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**On May 24, 2019, ICER issued an addendum to its Final Evidence Report on treatments for spinal muscular atrophy (SMA).**

This update reflected the FDA approval of Zolgensma, as well as new clinical trial data for Zolgensma that suggest a substantial benefit for individuals with presymptomatic SMA, and at least a small benefit for individuals with Type II SMA. Stakeholders may prefer to consider the economic analyses of Drug X presented in the report when assessing the value of Zolgensma. Value-based price benchmarks for Drug X would range from \$1.1 to \$1.9 million (prices to reach \$100,000 to \$150,000 per QALY gained) and from \$1.2 to \$2.1 million (prices to reach \$100,000 to \$150,000 per life year gained). Additional details can be found in the full Final Evidence Report. No other portions of this Report at a Glance have been updated.

## Summary

### WHAT IS SPINAL MUSCULAR ATROPHY?

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disease. In its most common form, Type I SMA (~60% of cases), symptoms begin in infancy. Affected children never sit up, and they rapidly develop difficulty swallowing and breathing, eventually requiring feeding tubes and mechanical ventilation. Without treatment, children typically die by age 2.

Later-onset SMA (Types II and III SMA) presents in later infancy and childhood. Although patients may be able to sit (Type II) or walk (Type III), without treatment, these abilities usually deteriorate over time, and lifespan is shortened.

With genetic screening at birth, individuals can be identified with pre-symptomatic SMA. Depending on the number of copies of a related gene, the type of SMA and prognosis for these individuals can be predicted with some degree of accuracy, but there is greater uncertainty for those infants who are expected to manifest Type II or Type III SMA.

### TREATMENT OPTIONS

Spinraza® (nusinersen, Biogen Idec.) is administered by spinal injection every four months. It works by modifying a gene (*SMN2*) to work more like the missing gene (*SMN1*) that is responsible for SMA. Zolgensma® (onasemnogene abeparvovec, Novartis AG/AveXis) is an emerging gene therapy that replaces the gene that codes for *SMN1*. It is under regulatory review with a decision expected by May 2019.

### EFFECTIVENESS AND VALUE

#### Spinraza

Spinraza has been evaluated in randomized controlled trials (RCTs) for patients with Type I-III SMA and for presymptomatic individuals. Spinraza is not a cure but reduces mortality and improves motor function substantially for Type I SMA and demonstrates small to moderate improvements for Types II and III.

Spinraza has also demonstrated improved mortality and motor outcomes in presymptomatic populations. Spinraza's cost effectiveness is best when used for presymptomatic infants, but at its current price it far exceeds commonly accepted thresholds. Using either a cost per quality-adjusted life year (QALY) or cost per life-year gained (LYG) basis for calculation, ICER's value-based price benchmark for Spinraza is \$36,000-\$65,000 (cost/QALY) or \$41,000-\$72,000 (cost/LYG).

#### Zolgensma

As of this date, Zolgensma has only been evaluated through a single-arm study of 12 patients with Type I SMA. At 2 years follow-up, no patients have shown deterioration of motor function. ICER's value-based price benchmark for Zolgensma used for Type I SMA is \$310,000-\$900,000 (cost/QALY) or \$710,000-\$1.5 million (cost/LYG).

### POLICY RECOMMENDATIONS

- To align reasonably with the benefits for patients and families, the price for Spinraza should be far lower than it is, and the price for Zolgensma should be lower than the hypothetical \$4-5 million price the manufacturer has suggested could be justified. To achieve the needed balance between incentives for innovation and health system affordability, all manufacturers should exercise their monopoly pricing power responsibly, setting prices that do not exceed a reasonable cost-effectiveness threshold.
- Payers should negotiate outcomes-based contracts under which a substantial portion of treatment cost is at risk should patients not receive adequate clinical benefit. Outcomes measures should extend beyond death and permanent ventilation, which might not be able to capture near-term lack of benefit for some Type I patients and are inadequate measures for treatment of later-onset or presymptomatic patients.

## Clinical Analyses

### KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

	Spinraza		Zolgensma
	Type I, Presymptomatic*	Later onset	Type 1
Survival	↑	↔ <sup>‡</sup>	↑
Avoidance of Permanent Ventilation	↑	Not reported	↑
Motor function (CHOP-INTEND, HINE-2, HFMSE)	↑	↑	↑
Motor Milestones	↑	↔ <sup>‡</sup>	↑

\*Data for presymptomatic population only available from conference abstracts

<sup>‡</sup>No deaths were reported

<sup>‡</sup>Differences in motor milestones between Spinraza and sham groups were not statistically significant

### HARMS

#### Spinraza

Treatment-related adverse events were rare in all Spinraza trials and never higher than those receiving sham treatment. The most commonly reported adverse events were related to the lumbar puncture procedure (e.g., fever, headache, vomiting, and back pain).

#### Zolgensma

The first treated infant showed signs of liver inflammation after infusion. Subsequently, all patients received oral prednisolone treatment for 30 days, starting the day before treatment. No infants suffered clinical sequelae but three children showed signs of liver inflammation despite prophylactic prednisolone, one of whom received additional treatment with prednisolone.

## Clinical Analyses (continued)

### SOURCES OF UNCERTAINTY

**Generalizability of trial results:** For both interventions, the narrow eligibility criteria of trials and small number of participants (especially for Zolgensma) raises concerns about generalizability of results to the wider population of patients with SMA (e.g., those who are more severely affected, initiate treatment later, experience comorbidities such as scoliosis).

**Long-term effects:** There is a lack of long-term safety and efficacy data on both interventions. For Spinraza, there is uncertainty in the long-term harms of repeated spinal injections in patients, particularly as they age or progress along the disease course. For Zolgensma, there is uncertainty in the durability of a gene therapy. To date, there has not been a waning of treatment effects, and longer-term studies will provide additional evidence.

**Evidence limitations in presymptomatic SMA:** In presymptomatic patients, the current evidence base consists of single-arm, uncontrolled study of Spinraza. The study is ongoing with interim results only available from conference presentations. A single-arm study of Zolgensma has started, but no results have been presented to date.

**Comparisons between Spinraza and Zolgensma:** Because of the differences in enrolled populations in the Type I SMA studies, it is not recommended to directly compare the results of Spinraza and Zolgensma.

### ICER EVIDENCE RATINGS

**How strong is the evidence that Spinraza and Zolgensma improve outcomes in patients with SMA compared to supportive care?**

Population	Spinraza	Zolgensma
Infantile-Onset (Type I)	Superior – High certainty of a substantial net health benefit versus supportive care*	Superior – High certainty of a substantial net health benefit versus supportive care*
Later-Onset (Type II and III)	High certainty of at least a small net health benefit	Insufficient – no studies identified
Presymptomatic	High certainty of at least a small net health benefit	Insufficient – no studies identified

\*See the full ICER report for additional rationale behind the decision to give Spinraza and Zolgensma the same evidence rating for Type I SMA

## Economic Analyses

### LONG-TERM COST-EFFECTIVENESS

Do these treatments meet established thresholds for long-term cost-effectiveness?

	Spinraza		
	Infantile-Onset (Type I)	Later-Onset (Type II/III)	Presymptomatic
Cost per QALY gained	\$1,112,000	\$8,156,000	\$709,000
Cost per LY gained	\$590,000	Dominated	\$652,000

QALY: quality-adjusted life year; LY: life year

#### Spinraza

At its estimated net cost per package of \$127,500, **Spinraza does not meet the commonly-used thresholds of \$50,000 to \$150,000 per quality-adjusted life year (QALY) gained or per life-year (LY) gained**, when compared to best supportive care (BSC) in any SMA population.

#### Zolgensma

Zolgensma's price is currently unknown, as the FDA has yet to issue an approval decision, so we have only reported threshold prices (see below). Results generated with a placeholder price of \$2 million can be found in the full report.

## Economic Analyses (continued)

### VALUE-BASED PRICE BENCHMARKS

What is a fair price for Spinraza and Zolgensma based on their value to patients and the health care system?

	Spinraza	Zolgensma
Current List Price	\$375,000*	N/A
Population	Presymptomatic SMA	Infantile-Onset (Type I SMA)
Annual Prices to Achieve \$100,000 to \$150,000 per QALY Gained <sup>†</sup>	\$36,400-\$64,800 (83%-90% discount) <sup>‡</sup>	\$310,000-\$899,000 <sup>§</sup>
Annual Prices to Achieve \$100,000 to \$150,000 per LYG <sup>†</sup>	\$41,400-\$72,300 (81%-89% discount) <sup>‡</sup>	\$710,000-\$1.5 million <sup>§</sup>
Is the Current Net price within range?	<b>NO</b>	--

QALY: quality-adjusted life year, LYG: life-year gained

\*Annual wholesale acquisition cost (WAC) for treatment in years 2+, not including any discounts, rebates, or mark-up. Price for year 1 is double the listed value due to the required loading dose.

<sup>†</sup>Threshold prices include any potential provider mark up. Prices for Spinraza are for years 2+; year 1 price is double the listed values.

<sup>‡</sup>Discount calculated from a year 2+ annual cost of \$382,500, which includes an assumed provider mark up

<sup>§</sup>One-time cost for Zolgensma

For treatments of ultra-rare disorders, insurers and other decisionmakers often give added weight to contextual considerations that lead to acceptance of prices higher than those that would meet traditional cost-effectiveness ranges. Therefore, ICER's report also includes multiple threshold price analyses for both drugs, ranging from \$50,000-\$500,000 per QALY and per LYG.

### POTENTIAL SHORT-TERM BUDGET IMPACT

**How many patients could be treated with Zolgensma at different price points before crossing ICER's \$991 million budget impact threshold?**

We estimated the potential budgetary impact of using Zolgensma to treat patients diagnosed with SMA Type I in the US. **At price points including our placeholder price (\$2 million), and the prices to reach \$150,000/QALY (\$899,000) or \$100,000/QALY (\$310,000), all eligible patients could be treated without exceeding the budget impact threshold.**

We did not estimate the budget impact of Spinraza because it has already been in use in the US marketplace for over a year.

## Summary of Votes

### CLINICAL EVIDENCE

The New England CEPAC unanimously found the evidence sufficient to show a net health benefit in infantile-onset SMA for both Spinraza and Zolgensma versus supportive care alone. The Council additionally found the evidence sufficient to show a net health benefit in the later-onset

(unanimous vote) and presymptomatic (10/12) patient populations for Spinraza. Evidence was not sufficient to distinguish between Spinraza and Zolgensma (0/12), nor was the evidence for Zolgensma found to be sufficient to show a net health benefit in presymptomatic patients (0/12).

### OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

Before voting on value, Council members considered other benefits and contextual considerations that may not be captured by the clinical evidence. Council members recognized that both treatments would reduce broader family or caregiver burden, as SMA is a condition that impacts all aspects of home life including marriage and dynamics among siblings. Both treatments may also help caregivers return to work and patients return to or participate more fully in schools and communities. The Council also acknowledged that the availability of these treatments has revolutionized the infrastructure of care for patients and families with SMA, including by establishing a case for newborn screening so that affected individuals can be

treated before symptoms develop. Council members unanimously recognized the reduced complexity of Zolgensma versus Spinraza, as it offers a one-time dose.

One potential disadvantage associated with these treatments is that may create or widen health disparities across socioeconomic, geographic, racial, or ethnic groups. This is because the therapies will primarily be available at academic medical centers, which may be difficult for some patients to travel to, while other families may not be aware that effective treatments now exist. The advent of infant screening for SMA may address these potential disparities.

### LONG-TERM VALUE FOR MONEY

#### Spinraza: Low Long-Term Value for Money

The Council acknowledged the substantial benefits of treatment with Spinraza and the relevance of “other benefits” and “contextual considerations,” but the price was judged as too high in relation to a broad view of benefits. The Council voted unanimously that Spinraza represents a **low long-term value for money** even for presymptomatic SMA.

#### Zolgensma

Voting on long-term value for money was not performed given the launch price is currently unknown.

## Policy Recommendations

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The New England CEPAC participated in a moderated policy discussion that included physicians, patient advocates, manufacturer representatives, and payer representatives. None of the resulting policy statements should be taken as a consensus view held by all participants. For a more detailed discussion, please see the [full report](#).

### For Plan Sponsors and Payers

- Given the uncertainty regarding the benefit of these treatments in some patient subpopulations and their high cost, it is reasonable for insurers to implement prior authorization criteria to ensure prudent use of these treatments.
- Payers should respond to all prior authorization requests within 48 hours and resolve any authorization challenges as soon as possible.
- Payers should negotiate outcomes-based contracts under which a substantial portion of treatment cost is at risk should patients not receive adequate clinical benefit. Outcomes measures should extend beyond death and permanent ventilation, which might not be able to capture near-term lack of benefit for some Type I patients and are inadequate measures for treatment of later-onset or presymptomatic patients.

### For Patient Advocacy Organizations

- Patient organizations should view their longer-term mission in support of patients to include active engagement with manufacturers to demand reasonable value-based pricing of the therapies that patients and their families helped bring to the market.

### For Manufacturers

- To align reasonably with the benefits for patients and families, the price for Spinraza should be far lower than it is, and the price for Zolgensma should be lower than the hypothetical \$4-5 million price the manufacturer has suggested could be justified. To achieve the needed balance between incentives for innovation and health system affordability, all manufacturers should exercise their monopoly pricing power responsibly, setting prices that do not exceed a reasonable cost-effectiveness threshold.
- Biogen's high-quality clinical trials of Spinraza should provide a model for others investigating treatments for ultra-rare conditions.

## Policy Recommendations (continued)

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### For Clinical Specialty Societies

- Individual clinicians and clinical specialty societies should work to address insurance barriers to inappropriate care, be vocal witnesses to the negative effects of excessive prices on patients and their families, integrate considerations of value into clinical guidelines, and work towards a health system that improves access and affordability while continuing to incentivize innovation.

### For Researchers

- Researchers should develop better measures of motor functioning that capture interim movement milestones such as finger strength that are meaningful to patients and clinicians.
- Registries such as those maintained by Cure SMA should be used to address remaining uncertainties in the evidence base.

## About ICER

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The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website ([www.icer-review.org](http://www.icer-review.org)).