APPENDICES

Onasemnogene Abeparvovec-xioi (Zolgensma) for Spinal Muscular Atrophy

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The Medicaid Evidence and Review of Cost Initiative (MERCI) describes policy considerations for drugs approved by the US Food and Drug Administration (FDA) through the accelerated approval pathway. This document is the appendix of a brief titled *Onasemnogene Abeparvovec-xioi (Zolgensma) for Spinal Muscular Atrophy*. The brief and these associated appendices provide the following information: estimated prevalence of target diagnoses (the accelerated approval drug's indication[s]) among Medicaid members; Medicaid members who received this treatment; and estimated drug costs for state Medicaid programs, including a breakdown of state and federal funds using the Federal Medical Assistance Percentage (FMAP).

APPENDIX A

METHODS

Data Sources

Researchers from the Center for Evidence-based Policy (Center) used the Centers for Medicare & Medicaid Services (CMS) Transformed Medicaid Statistical Information System (T-MSIS) Analytic Files (TAF) as the primary data source for drug indication cohort identification, prevalence estimates, and medication uptake. The TAF are a research-optimized version of state-submitted T-MSIS data, which include information on Medicaid and Children's Health Insurance Program (CHIP) enrollment, demographics, health care service use, and payments, all anchored in enrollment and claims records. State-submitted T-MSIS data are processed by the University of Minnesota Research Data Center and then compiled for use as national data files.

We obtained TAF demographic and enrollment data, along with inpatient, other service, and pharmacy claims data for years 2019 through 2021 for all Medicaid and CHIP members aged 0 to 64 years, excluding those with any months of dual enrollment in both Medicaid and Medicare. Using these criteria, we were not able to obtain data from Alabama or Utah, which do not submit claim information related to dual-enrollment status using this method. Sources used to inform cohort definitions, drug indication, and drug identification included peer-reviewed literature, grey literature sources, and publicly available databases.

The TAF data are subject to quality concerns. To identify data quality or usability issues affecting internal analytical validity, we used the Medicaid Data Quality (DQ) Atlas as a reference.[1] In general, a state was eliminated from analysis if the DQ Atlas identified a state's data as "unusable" for a topic, variable, or year. If a state's data were of "high concern," we investigated to determine the reason behind the rating and made a topic-specific or variable-specific judgment about inclusion or exclusion for analysis; we made decisions on whether to include, with a bias toward underreporting (as opposed to overreporting). We used 3 distinct methods to address large-scale data quality issues during initial data processing, as described below.

Member Demographic Identification and State Assignment

Members have 2 identifiers in the TAF: a primary identifier assigned during processing at the University of Minnesota Research Data Center that compiles claims across states for individual members, and a member-specific identifier (MSIS ID) assigned by the state (plus the identifying state). Ninety-seven percent of members had primary identifiers. For the remaining 3%, we used the combination of MSIS ID and state code. A very small proportion of members with primary identifiers had multiple enrollment records, sometimes with differing state codes and demographic information. Those members were assigned a state code based on the highest frequency and consistency of the following attributes, in order: state of residence, state with the highest proportion of claims, and state

with the longest period of enrollment. If there were ties among states for a member, we randomly assigned them to one of the states in which they had claims.

Differences in demographic information for members with multiple enrollment records were similarly reconciled. In the case of multiple records with missing demographic information, missing values were imputed from records assigned to the member in other states, or the most frequently reported characteristic was assigned. Race and ethnicity were the most commonly missing characteristics; age and sex were rarely missing in this dataset.

Mississippi Member Identification and Claims

Data linking of Mississippi claims records to member enrollment records was considered unusable by the DQ Atlas for 2019 to 2021.[1] Any members with claims submitted in Mississippi were assigned to that state for drug indication prevalence reporting. Further, the only demographic information that we could identify for members from Mississippi was birth date, from submitted claims. We could not use sex or race and ethnicity information in the enrollment files for these members. Only the following data are included from Mississippi:

- Number of people with drug indication, if no demographic information other than age is required for cohort inclusion
- A breakdown of members with a particular drug indication by age (sample size permitting)
- Comorbidities and health care service use for members with the drug indication, and matched comparisons when matching is based only on age
- Drug uptake, if applicable

In the case that other demographic characteristics are required for cohort inclusion (e.g., sex), members from Mississippi were not included.

Illinois Claims

Illinois claims data are known to be reported with multiple records per care episode, or "claim families," which in other states would be aggregated into a single claim record. Methods for including Illinois claims were applied according to TAF technical guidance resources and recommendations.[2]

Reporting of Data

Adhering to CMS reporting rules, we reported member counts in any subgroup only when the group size was at least 11. We reported rates and percentages when the group size on the numerator was at least 11 and the denominator group size was at least 50. If there were any race or ethnicity groups with 10 or fewer people, then the largest group was only reported when total of the unreported group sizes was greater than 10.

Prevalence Estimates

To estimate the number of members who were potentially eligible for this treatment in 2021, we first identified all nondually eligible members who were younger than 2 years of age at any point in 2021. These are the members who were enrolled in 2021 and had their 2nd birthday any time after the first day of the 2021, including those who were born during that year. We then identified members with spinal muscular atrophy (SMA) based on having at least 1 inpatient claim or 2 outpatient claims with an ICD-10 (International Classification of Diseases, 10th revision) diagnosis code of G12.0, G12.1, G12.8, or G12.9. We excluded a small number of members (n < 11) who had their first SMA claim after their 2nd birthday.

Matched Comparison Group

We used a matched-comparison method to analyze health care service use between members with the drug indication (under the age of 2 years and with SMA) and the Medicaid population at large. We performed 1-to-3 exact matching between members with and without the drug indication, based on member state, sex, age in years, and race and ethnicity groups, when available. If we identified more than 3 exact matches for a member with the drug indication, we chose 3 at random.

Health Care Service Use

We compared health care service use outcomes (hospitalizations and emergency department [ED] visits), measured in both SMA and matched comparison groups, between January 1, 2021, and December 31, 2021. We identified hospitalizations in the inpatient files as episodes of care based on unique admission date. Unique discharge dates were used in the case of missing admission dates. We identified ED visits in both inpatient and outpatient files using revenue center codes 450 through 459 and 981, and service date. The ED visits we report include visits that resulted in an admission.

Medication Uptake

Medication uptake was calculated as the proportion of estimated number of members with Zolgensma's indication with any identified claim for the drug. We identified Zolgensma claims based on the procedure code J3399 or the National Drug Codes (NDCs) listed below in outpatient and inpatient claims:

71894-0120-02	71894-0126-04	71894-0132-06	71894-0138-08
71894-0121-03	71894-0127-05	71894-0133-07	71894-0139-09
71894-0122-03	71894-0128-05	71894-0134-07	71894-0140-09
71894-0123-03	71894-0129-05	71894-0135-07	71894-0141-09
71894-0124-04	71894-0130-06	71894-0136-08	
71894-0125-04	71894-0131-06	71894-0137-08	

Cost Estimates

The cost estimates represent the projected annual total national costs associated with covering Zolgensma for treatment of Medicaid members with SMA. We modeled the costs based on the SMA prevalence and drug uptake in the TAF Medicaid claims data and the estimated incidence of eligible Medicaid members based on rates of SMA incidence, SMA types, and Medicaid enrollment reported elsewhere, as well as current wholesale acquisition cost for the drug and statutorily required rebate percentages. We modified the uptake rates observed in 2021, assuming the uptake increased by 15% since then based on the trends observed in 2019 to 2021. All model inputs and justifications are summarized in Exhibit A.

EXHIBIT A

Cost modeling inputs

Input name	Input	Source	Sensitivity analysis bounds
Prevalence and uptake[a]			
Prevalence of drug indication (with SMA, aged under 2 years)	472	Data	354 to 590
Uptake	18.3%	Data	10% to 40%
Incidence			
Number of births annually	3.6 million	CDC[3]	3.2 million to 4 million
Incidence rate for SMA	1 in 14,694 births	Belter et al. 2024[4]	1 in 20,000 to 1 in 10,000 births
Percentage of SMA types I and II	87%	Lally et al. 2017[5]	60% to 90%
Percentage enrolled in Medicaid	40%	KFF[6]	30% to 80%
Price			
Current annual drug cost (WAC), $	$2,391,706	IPD Analytics[7]	--
Federal rebates[b]	23.1%	SSA §1927(c)(1)(B)(i)[8]	--

Notes. [a] Includes estimated patient populations in Alabama, Mississippi, and Utah. [b] Do not include state-negotiated supplemental rebates.

Abbreviations. CDC: Centers for Disease Control and Prevention; SMA: spinal muscular atrophy; SSA: Social Security Administration; WAC: wholesale acquisition cost.

The 3 states excluded from the analyses due to data availability (Alabama, Mississippi, and Utah) are included in the national cost estimates, using the estimated prevalence and uptake rates set at the average rates observed in other states.

With a focus on direct drug costs, we did not include the costs of drug dispensing, administration, and monitoring. We also did not include any cost offsets associated with replacement of treatment-as-

usual, costs associated with adverse events, or cost implications of treatment effectiveness in terms of reduced health care service use or mortality.

We performed sensitivity analyses using Monte Carlo simulations that considered uncertainty in the model inputs, then we reported the range that contained 95% of the simulated cost values as the confidence bounds for our cost estimate. We considered possible error in estimating the number of members eligible for treatment due to known data quality issues in some states (i.e., overreporting in Massachusetts and New Jersey, and underreporting in Rhode Island) and the limitations of identifying young patients with limited claim history. We considered wide confidence bounds around the uptake rate and other incidence-related inputs.

For the state and federal breakdown of the costs, we first calculated the percentage of the members with the drug indication in CHIP and Medicaid enrollment categories. We then calculated the average FMAP rates across states weighted by the number of potentially eligible members in each enrollment category in each state, and applied the corresponding federal matching rates to the relevant portion of the total costs for Medicaid and CHIP members.[9] For states with unusable data quality for identifying enrollment eligibility category, we used the average rates for other states.

For our per-member per-month cost estimates in each state, we used the member-month counts reported in the 2023,[10] excluding any dually enrolled members.[11]

Limitations

Our cost estimates are based on the prevalence of SMA and uptake of Zolgensma we identified in the claims data. The accuracy of our analysis depends on the completeness and reliability of the claims and the treatment codes recorded in the inpatient and outpatient claims (e.g., diagnosis and procedure codes, NDCs) as well as enrollment and demographic information (e.g., dual-enrollment, date of birth) provided for each member.

For the states excluded due to data availability, our cost estimates assume that SMA prevalence and treatment uptake in these states are similar to what is observed in other states. Our cost estimates do not include supplemental rebates, and the estimated total cost is broken down by state and federal share without any consideration for third-party liability or other insurance payments.

APPENDIX B

DEMOGRAPHIC INFORMATION

EXHIBIT B

Availability of demographic information for Medicaid members included in analyses, 2021

	With SMA	%	Without SMA	%
Total	*459*	-	*5,948,018*	-
Sex available	454	98.9	5,947,784	100.0
Sex missing[b]	5	1.1	234	< 1
Race or ethnicity available	253	55.1	3,466,822	58.3
Race or ethnicity not reported[a]	92	20.0	1,218,566	20.5
Race or ethnicity missing[b]	114	24.8	1,262,630	21.2

Notes. [a] We did not report race or ethnicity data from states with unusable or high-concern data quality for race or ethnicity information, including Arizona, Connecticut, District of Columbia, Iowa, Louisiana, Massachusetts, New York, Oregon, Rhode Island, South Carolina, Tennessee, and Wyoming. [b] Missing in states for which sex or race and ethnicity data is reported.
Abbreviations. SMA: spinal muscular atrophy.

APPENDIX C

BASELINE CHARACTERISTICS OF TRIAL PARTICIPANTS

Who Participated in the Studies Used to Approve Zolgensma?

The 2 studies used to support full approval primarily included participants younger than 6 months who had been diagnosed with symptomatic or presymptomatic spinal muscular atrophy (SMA) type 1; while 1 study included patients up to 9 months of age, all participants had to have experienced symptoms before 6 months of age.[12,13]

Exhibit C provides a summary of participants in the studies used to approve Zolgensma.

EXHIBIT C

Baseline characteristics of participants in Study 1 (STR1VE) and Study 2[12,13]

Participant Characteristic	Study 1 (STR1VE)[a]	Study 2[b]	
		Cohort 1	Cohort 2
No. of participants	22	3	12
Age in months	3.7 (1.6)	6.3 (5.9 to 7.2)	3.4 (0.9 to 7.9)
Sex, n (%)			
Female	12 (55)	2 (67)	7 (58)
Male	10 (45)	1 (33)	5 (42)
Race, n (%)			
Asian	2 (9)	0	0
Black	3 (14)	0	0
White	11 (50)	3 (100)	11 (92)
All other race	6 (27)	0	1 (8)
Ethnicity, n (%)			
Hispanic or Latino	4 (18.2)	0	2 (16.7)
Not Hispanic or Latino	18 (81.8)	3 (100)	10 (83.3)
Other characteristics			
Age at symptom onset, months	1.9 (1.2)	1.7 (1.0 to 3.0)	1.4 (0 to 3.0)
Age at diagnosis, days	56.1 (98.6)	33 (4 to 85)	60 (0 to 136)
Baseline score on CHOP INTEND scale	32.0 (9.7)	16 (6 to 27)	28 (12 to 50)

Notes. [a] Data are means (SD) unless specified. [b] Data are means (range) unless specified. This information is taken from the trial publications and ClinicalTrials.gov trial registry records and may vary to that reported in the prescribing label.
Abbreviations. CHOP INTEND: The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

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