Medicaid Drug Cap Initiative:

Nusinersen (Spinraza®)

Presentation for

Drug Utilization Review Board

July 23, 2020

Purpose

- Spinraza® has been identified as contributing to pharmacy expenditures exceeding the Medicaid Drug Cap as defined in NYS Public Health Law, article 2-A, title 2 section 280.

- To evaluate the utilization of Spinraza® (nusinersen) across the entire New York State (NYS) Medicaid population including the fee-for-service (FFS) program and managed care organizations (MCOs).

- To assist in the formulation of a target manufacturer supplemental rebate amount for Spinraza®.

Spinraza®: Background

Agent	Dosage formulation/ Strength	Manufacturer
Spinraza® (nusinersen)	•Injection for intrathecal use •12 mg/5 mL (2.4 mg/1 mL) single-dose vial	Biogen

- Food and Drug Administration (FDA) approval:
  - Date: December 2016
  - Indication: Treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

- Nusinersen is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide.

Nusinersen: Background

SMA

- SMN protein deficiency leads to motor neuron degeneration, muscle atrophy.

SMN Protein

- Production depends on SMN1 gene on chromosome 5q13.
- In SMA, SMN1 gene mutations reduce functional protein expression.

Nusinersen Mechanism of Action

- Paralogous SMN2 gene also codes for SMN protein but produces very little functional SMN protein due to aberrant splicing.
- Nusinersen modifies the SMN2 pre-messenger RNA splicing, resulting in the creation of functional full-length SMN protein.

Nusinersen Dosing

- 1 dose of nusinersen: 12 mg/5 mL via intrathecal injection.

- Initiation: 4 loading doses (LD)
  - 3 doses at 14 day intervals; fourth dose 30 days after third.
- Maintenance dose (MD): 1 dose every 4 months.

Nusinersen: Background

- Information related to the following will not be discussed during the presentation but details are available in the report:
  - Contraindications;
  - Warnings and precautions;
  - Adverse events;
  - Drug interactions; and
  - Special populations.

Legislative Overview by Subsection

- Medicaid drug cap law:
  - Law lists factors the Board may consider when formulating drug rebate recommendation.
  - Presentation reviews findings related to each item.

In formulating a recommendation concerning a target rebate amount for a drug, the drug utilization review board may consider:

(i) Publicly available information relevant to the pricing of the drug;

Public Drug Pricing Information

WAC for Initial Year of Nusinersen Therapy

Year 1	WAC ($) 12 mg/5 mL dose*	WAC Total ($)*
Loading Dose 1 (Day 0)	$127,500	$510,000
Loading Dose 2 (Day 14)		
Loading Dose 3 (Day 28)		
Loading Dose 4 (Day 58)		
Maintenance Therapy (Day 180)	$127,500	$255,000
Maintenance Therapy (Day 300)		
TOTAL WAC FOR YEAR 1 OF THERAPY		**$765,000**

Note: The wholesale acquisition cost (WAC) is an estimate of the manufacturer's list price for a drug to wholesalers or direct purchasers, but does not include discounts or rebates.

*WAC as of February 2020. Source eMedNY.
WAC=wholesale acquisition cost.

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Public Drug Pricing Information

WAC for Maintenance Year of Nusinersen Therapy

Year of Maintenance Therapy	WAC ($) 12 mg/5 mL dose*	WAC Total ($)*
Maintenance Therapy Dose 1	$127,500	$382,500
Maintenance Therapy Dose 2		
Maintenance Therapy Dose 3		
ANNUAL MAINTENANCE WAC		**$382,500**
WAC for First 2 Years of Therapy		**$1,147,500**

*WAC as of February 2020. Source eMedNY.
WAC=wholesale acquisition cost.

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In formulating a recommendation concerning a target rebate amount for a drug, the drug utilization review board may consider:

- **(ii) Information supplied by the department relevant to the pricing of the drug;**
  - The department will provide the DURB with information relevant to the pricing of Spinraza® (nusinersen) at today's executive session.

In formulating a recommendation concerning a target rebate amount for a drug, the drug utilization review board may consider:

(iii) Information relating to value-based pricing

Value-Based Pricing

- The Institute for Clinical and Economic Review (ICER) will provide an economic review related to the value-based pricing of Spinraza® (nusinersen).

Nusinersen Coverage: Medicaid Programs

- NYS Medicaid (MCOs and FFS): covered as a medical benefit.
- Review of 7 other state Medicaid programs:
  - Coverage criteria were available for 5 states: California, Florida, Illinois, Massachusetts, and Texas.
  - Criteria for nusinersen initiation:
    - Confirmation of SMA diagnosis, genetic testing, baseline assessment of motor function, specialist consulted, patient not ventilator-dependent.
  - Criteria for nusinersen continuation:
    - Response to therapy/lack of deterioration, adherence.

Nusinersen Coverage: Commercial Health Insurance

- 5 largest US healthcare insurance companies by membership:
  - All have nusinersen coverage criteria.
  - Criteria for nusinersen initiation:
    - Confirmation of SMA diagnosis, genetic testing, baseline assessment of motor function, specialist consulted, patient not ventilator-dependent.
    - 4 companies: varying age edits, all precluding adult use.
  - Criteria for nusinersen continuation:
    - Response to therapy/lack of deterioration, adherence.

Nusinersen Coverage: Other Countries

- Nusinersen guidance and coverage policies from 6 non-US government agencies were reviewed:
  - Australia, Brazil, Canada, European Union, Scotland, United Kingdom (UK).
- Most restrict coverage:
  - Diagnosis requirement, prescribing limited to specialists.
- Some countries have implemented pricing agreements as a condition of coverage.

In formulating a recommendation concerning a target rebate amount for a drug, the drug utilization review board may consider:

(iv) The seriousness and prevalence of the disease or condition that is treated by the drug;

SMA: Seriousness and Prevalence

- The type of SMA is based on the patient's age of onset and the highest physical milestones reached.
- Patients with more copies of the SMN2 gene generally have a less severe form of SMA.

SMA Type	SMN2 Copies	Disease Presentation	Life Expectancy
0	1	Severe weakness and hypotonia, rapid progression, failure to thrive	<6 months
1	1-3	Difficulty swallowing, breathing	<2 years
2	2-3	Unable to walk	Typically >20 years
3	3-4	Achieve ability to walk, but increasingly limited mobility over time	Adulthood
4	≥4	Able to attain motor milestones and maintain mobility throughout life	Adulthood

SMA: Seriousness and Prevalence

- SMA affects 10,000 – 25,000 people in the US.
  - Prevalence: 1 to 2 per 100,000 persons.
  - Incidence: 10 per 100,000 live births.
- Incidence in NYS:
  - 20 – 30 per 235,000 births per year.
- Childhood onset more common than adult:
  - Type 1: >50% of all new SMA cases
  - Type 2: 30% of overall cases
  - Type 3: 10% of overall cases

In formulating a recommendation concerning a target rebate amount for a drug, the drug utilization review board may consider:

(v) The extent of utilization of the drug;

Nusinersen Utilization Analysis: Purpose

- The purpose of this analysis is to provide an overview of nusinersen utilization in the NYS Medicaid Program.
  - The analysis includes both fee-for-service (FFS) and Medicaid managed care (MC) plans.

Methods

- A retrospective analysis of nusinersen utilization was conducted.
- The data source was the Medicaid Data Warehouse (MDW).
- The timeframe of the analysis was April 1, 2017 through September 30, 2019.

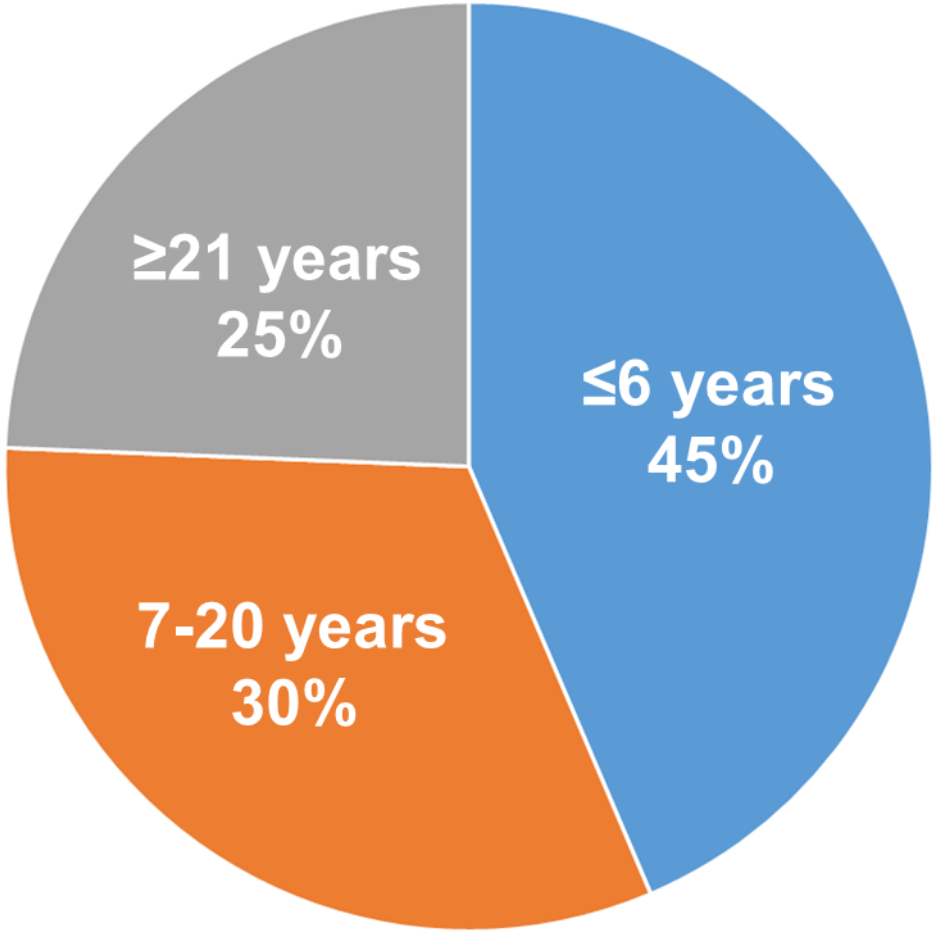
Results

- <100 unique NYS Medicaid members (FFS+MC) had a claim for nusinersen resulting in 336 claims during the timeframe of the analysis.

- Patients ranged in age from <1 year to 58 years of age.

Members Utilizing Nusinersen by Age

Timeframe: April 1, 2017 through September 30, 2019



<100 members (FFS+MC)

Data source: MDW
Extract date: February 2020

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Nusinersen Utilization

	FFS + MC	FFS	MC
SFY	# Claims	# Claims	# Claims
SFY 2018	87	13	74
SFY 2019	164	51	113
SFY 2020 (6 months only)	85	29	56
Total	336	93	243

FFS= fee-for-service, MC= managed care, SFY= state fiscal year

Data source: MDW
Extract date: February 2020

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In formulating a recommendation concerning a target rebate amount for a drug, the drug utilization review board may consider:

(vi) The effectiveness of the drug in treating the conditions for which it is prescribed, or in improving a patient's health, quality of life, or overall health outcomes;

Effectiveness: Place in Therapy

- SMA Care Group: 2018 guideline on diagnosis and management of SMA
  - Acknowledges nusinersen as an FDA-approved agent for SMA, but does not provide detail as to its place in therapy.

- CureSMA: 2018 algorithm for treatment of infants diagnosed with SMA via newborn screening
  - In NYS, testing for SMA is currently included in newborn screening.
  - 2 or 3 copies of SMN2 → Probable SMA types 1 or 2:
    - Start treatment with SMN-up-regulating therapies immediately.
  - 4 or more copies of SMN2 → Probable SMA types 3 or 4:
    - Wait to treat; monitor and then treat at onset of symptoms.

Clinical Trials: Finkel 2017
Phase 3 ENDEAR Trial in Infantile-Onset SMA

- Randomized, sham-controlled, double blind, multicenter trial
  - In infants age ≤7 months at screening with SMA symptom onset age ≤6 months.
- Treatment groups (randomized 2:1)
  - Nusinersen group:
    - 12 mg intrathecal dose equivalent (volume adjusted by age) on days 1, 15, 29, 64, 183 and 302 (n=80).
  - Control group:
    - Sham procedures on same schedule (n=41).
- Primary outcomes:
  - Motor-milestone response per Hammersmith Infant Neurologic Examination Part 2 (HINE-2), with interim analysis (response = improvement in ≥1 category[-ies] and more categories with improvement than worsening); event-free survival (time to death or permanent assisted ventilation [PAV]).

Clinical Trials: Finkel 2017, Interim Analysis

- 13 month duration planned.
- Prespecified interim analysis
  - Conducted when ~80 infants had been enrolled for ≥6 months.

HINE-2 Motor-Milestone Response Achieved		
Nusinersen: 21/51 (41%)	Control: 0/27 (0%)	P<0.001

- Results prompted early trial termination; end-of-trial visits were conducted for final analysis.

Clinical Trials: Finkel 2017, Final Analysis

- Final analysis
  - Included 121 infants (nusinersen: n=80; control: n=41) who had undergone assigned procedure at least once.

Event-Free Survival (no death or use of PAV)	
Nusinersen: 49/80 (61%)	Control: 13/41 (32%)
HR (95% CI): 0.53 (0.32–0.89)	P=0.005
Median Time to Death or PAV	
Nusinersen: not reached	Control: 22.6 weeks

- Likelihood of event-free survival was higher in infants treated with nusinersen who had disease duration ≤13.1 weeks at screening.

HR=hazard ratio;
CI=confidence interval

Clinical Trials: Mercuri 2018
Phase 3 CHERISH Trial in Later-Onset SMA

- Randomized, sham-controlled, double blind, multicenter trial
  - In children age 2-12 years with SMA symptom onset age >6 months.
- Treatment groups (randomized 2:1).
  - Nusinersen group:
    - 12 mg intrathecally on days 1, 29, 85, and 274, with 6 months of follow-up (n=84).
  - Control group:
    - Sham procedures on same schedule (n=42).
- Primary outcomes:
  - Hammersmith Functional Motor Scale Expanded (HFMSE) score (least-squares mean change from baseline at 15 months), with interim analysis.

Clinical Trials: Mercuri 2018, Interim Analysis

- 15 month duration planned.
- Prespecified interim analysis:
  - Conducted when all patients were enrolled ≥6 months and ≥39 completed 15-month assessment.

HFMSE Score: Least-Squares Mean Difference vs. Baseline (95% CI)	
Nusinersen: 4.0 (2.9 to 5.1)	Control: –1.9 (–3.8 to 0)
Difference: 5.9 (3.7 to 8.1)	P<0.001

- Results prompted early trial termination; patients who had not yet had a 15-month assessment were evaluated at a final visit.

Clinical Trials: Mercuri 2018, Final Analysis

- Final analysis
  - 66/84 patients in the nusinersen group and 34/42 in the control group completed the 15-month assessment.

HFMSE Score: Least-Squares Mean Difference vs. Baseline (95% CI)	
Nusinersen: 3.9 (3.0 to 4.9)	Control: –1.0 (–2.5 to 0.5)
Difference: 4.9 (3.1 to 6.7)	
Patients with HFMSE Score Change of ≥3 Points (95% CI)	
Nusinersen: 57% (46 to 68)	Control: 26% (12 to 40)
Difference: 30.5% (12.7 to 48.3)	Odds ratio: 6 (2 to 15)
P<0.001	

In formulating a recommendation concerning a target rebate amount for a drug, the drug utilization review board may consider:

(vii) The likelihood that use of the drug will reduce the need for other medical care, including hospitalization;

Post-Marketing Outcomes: Hagenacker 2020, Nusinersen in Adults

- Post-marketing observational cohort study on safety and effectiveness of nusinersen treatment in adults with SMA.
- Primary outcome: change in HFMSE score at 6, 10, and 14 months.
  - Clinically meaningful improvement = HFMSE score increase ≥3 points.
- 124 patients included in the 6-month analysis.
  - SMA type 1: n=2 (2%); SMA type 2: n=45 (36%); SMA type 3: n=77 (62%).
- No serious adverse events reported.
  - Most frequent adverse events at 14 months included headache (35%), back pain (22%), and nausea (11%).

Analysis	Patients	Mean HFMSE Score Change	95% CI	Patients with Clinically Meaningful Change
6 months	n=124	1.73	1.05-2.41	35/124 (28%)
10 months	n=92	2.58	1.76-3.39	33/92 (36%)
14 months	n=57	3.12	2.06-4.19	23/57 (40%)

Post-Marketing Outcomes: Weaver 2020, Quality of Life (QoL) Study

- Prospective, randomized, longitudinal, crossover survey study.
- Assessed QoL and family experience for children with SMA, with and without nusinersen.
- Patients and parents were randomized to complete 4 survey instruments in a crossover fashion.
- Participants included 58 pediatric patients with SMA (age 0.25-20 years) and parents at US specialty clinics.
  - SMA type I (n=26) — 12/26 (50%) received nusinersen
  - SMA type II (n=23) — 8/23 (35%) received nusinersen
  - SMA type III (n=9) — 1/9 (11%) received nusinersen
- Impact of nusinersen use:
  - No significant differences in scores on any of the 4 surveys.
  - However, many patients had just begun nusinersen treatment; further study needed.

Expanded Access Program (EAP) Outcomes: Ali 2019, Study of Hospital Utilization

- Retrospective cohort study in one UK hospital, assessing hospital utilization over 24-month study period.
- Patients:
  - 11 children with SMA type 1 receiving nusinersen via Expanded Access Program.
  - Median age at initiation of nusinersen: 8.1 (range 0-85.7) months
- Total number of hospital admissions since nusinersen initiation: 107.
  - Median admissions per child: 11 (range 1-25).
  - Most common reasons for admission: lower respiratory tract infection (n=42), nusinersen administration (n=38).
- Median hospital days since diagnosis per child: 118 (range 7-235).
  - Patients were hospitalized for a median of 20% (range 2-72%) of their lives.
- Overall, a total of 762 days was spent in a high-dependency unit and 248 days in pediatric intensive care unit during the 2-year study period. This equated to an estimated additional cost of £2.2M (approximately $2.7M USD at April 2020 exchange rate).

In formulating a recommendation concerning a target rebate amount for a drug, the drug utilization review board may consider:

- **(viii) The average wholesale price, wholesale acquisition cost, retail price of the drug, and the cost of the drug to the Medicaid program minus rebates received by the state;**
  - WAC was $25,500/mL as of February 2020 per eMedNY.
  - Product is only available in 12 mg/5 mL single-use vial. Based on WAC/mL, the WAC for the 5 mL single-use vial would be $127,500.

- **(ix) In the case of generic drugs, the number of pharmaceutical manufacturers that produce the drug;**
  - Spinraza® is a single-source product; currently there is no equivalent (AB-rated) generic drug.

In formulating a recommendation concerning a target rebate amount for a drug, the drug utilization review board may consider:

- **(x) Whether there are pharmaceutical equivalents to the drug; and**
  - Spinraza® is a single-source product and there are no pharmaceutical equivalents to the product.

- **xi) Information supplied by the manufacturer, if any, explaining the relationship between the pricing of the drug and the cost of development of the drug and/or the therapeutic benefit of the drug, or that is otherwise pertinent to the manufacturer's pricing decision; any such information provided shall be considered confidential and shall not be disclosed by the drug utilization review board in a form that identifies a specific manufacturer or prices charged for drugs by such manufacturer.**
  - Information supplied by the manufacturer will be provided to the DURB.

Summary

- Total WAC for initial year of nusinersen therapy: $765,000; total WAC for maintenance year of therapy: $382,500.
- Coverage policies for other states' Medicaid programs, commercial health insurance, and other countries were reviewed; most specified criteria and/or restrictions for nusinersen coverage.
- SMA affects 10,000 – 25,000 people in the US; incidence in NYS: 20–30 per 235,000 births per year. NYS includes SMA testing in newborn screening.
- Patients with severe forms of SMA may struggle to swallow or breathe, and have life expectancy of <2 years. Patients with less severe disease can survive into adulthood, but may experience mobility limitations. Severe SMA is more common, with Type 1 accounting for >50% of all new SMA cases.

Summary

- From April 2017 through September 2019, <100 unique NYS Medicaid members (FFS+MC) had a claim for nusinersen, resulting in 336 claims during the timeframe of the analysis.
- Two phase 3 clinical trials for nusinersen were terminated early after interim analyses found that treatment produced favorable results.
- Post-marketing studies also showed benefits of nusinersen in adults with SMA.

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