



Nusinersen and Risdiplam – Drugs for the Treatment of Spinal Muscular Atrophy

December 15, 2022
DURB Meeting



Background

- The aim of the DURB review is to examine the utilization of nusinersen (Spinraza®) and risdiplam (Evrysdi®) across the entire New York State (NYS) Medicaid population, including the fee-for-service (FFS) program and managed care organizations (MCOs)
- Recommendations for the management of nusinersen and risdiplam will be provided based on a review of the literature and results from the utilization data analyses



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Background: Spinal Muscular Atrophy (SMA)

- Progressive disease characterized by loss of motor neurons leading to muscle weakness and atrophy
- Most common form: mutations in *survival motor neuron 1* (*SMN1*) gene on chromosome 5q
- *SMN1* mutations lead to reduced production of functional SMN proteins
- Reduced production can be partially offset by *SMN2* genes
 - Larger number of *SMN2* copies → greater availability of functional SMN protein
- Presentation of SMA varies with regard to age of onset and level of motor function

NIH. SMA Fact Sheet. <https://www.ninds.nih.gov/spinal-muscular-atrophy-fact-sheet>

Muscular Dystrophy Association (MDA). SMA. <https://www.mda.org/disease/spinal-muscular-atrophy/>.



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Types of SMA

SMA Type	SMN2 Copies	Age at Onset of Symptoms	Typical Presentation	Disease Progression	Life Expectancy
0 – prenatal	1	Before birth, late during third trimester	Decreased fetal movements; at birth, severe weakness and hypotonia, facial paralysis, cardiac defects	Rapid; failure to thrive	<6 months
1 – infantile	1-3	0-3 months	Weakness, difficulty sucking, swallowing, and breathing; atrophy and fasciculations in tongue and limb muscles	Rapid; death ensues due to respiratory complications	<2 years, median ~1 year
2 – chronic childhood, intermediate	2-3	6-18 months	Muscle weakness that is predominantly proximal, lower limbs affected more than upper limbs	Slower than type 1; patients can sit up without support but are unable to walk	>2 years; 75-93% of patients survive beyond age 20
3 – juvenile	3-4	>18 months	Weakness of proximal limb muscles without involvement of bulbar muscles.	Gradual with disability in adulthood; able to walk initially, but increasingly limited mobility over time	Adulthood, longer than those with type 2 disease
4 – adult-onset	≥4	Second or third decade, usually >35 years	Mild	Able to attain motor milestones and maintain mobility throughout life	Adulthood, longest of all SMA types

SMA=spinal muscular atrophy; SMN2=survival motor neuron 2 gene

Muscular Dystrophy Association (MDA). Types of SMA. <https://www.mda.org/disease/spinal-muscular-atrophy/types>.

Brown, Jr. RH. Amyotrophic lateral sclerosis and other motor neuron diseases. In: *Harrison's Principles of Internal Medicine*. 21st ed.

CureSMA. Types of SMA. <https://www.curesma.org/types-of-sma/>

NIH. National Human Genome Research Institute. <https://www.genome.gov/Genetic-Disorders/Spinal-Muscular-Atrophy>



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Treatment: SMN-targeting Therapies

- Three agents approved by the Food and Drug Administration (FDA):
 - Nusinersen (Spinraza®) – December 2016
 - Onasemnogene abeparvovec-xioi (Zolgensma®) – May 2019
 - Risdiplam (Evrysdi®) – August 2020
- Nusinersen and risdiplam: messenger ribonucleic acid (mRNA) splicing modulators
- Onasemnogene abeparvovec-xioi: gene transfer therapy*

*Excluded from this review; policy recently implemented

Chiriboga CA. *Paediatr Drugs* 2022. Published online ahead of print.



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Nusinersen and Risdiplam

Characteristics	Spinraza® (nusinersen)	Evrysdi® (risdiplam)
FDA-approved indications	Treatment of SMA in pediatric and adult patients.	Treatment of SMA in pediatric and adult patients.
Compendia-supported uses	No additional uses.	No additional uses.
Manufacturer	Biogen	Genentech
Dosing regimen	<p>12 mg (5 mL) per dose.</p> <ul style="list-style-type: none"> Initiate with 4 loading doses; administer first 3 doses in 14-day intervals, administer fourth 30 days after the third dose. Maintenance doses: once every 4 months thereafter. 	<p>Dosage is age- and weight-based and should be administered once daily:</p> <ul style="list-style-type: none"> <2 months: 0.15 mg/kg/day 2 months to <2 years: 0.2 mg/kg/day ≥2 years and weight <20 kg: 0.25 mg/kg/day ≥2 years and weight ≥20 kg: 5 mg/day
Administration	<p>Administer intrathecally.</p> <ul style="list-style-type: none"> Prior to administration, 5 mL of cerebrospinal fluid should be removed. Nusinersen should then be injected as a bolus over 1 to 3 minutes using a spinal anesthesia needle. 	<p>Administer orally after a meal at the same time each day (once daily)</p> <ul style="list-style-type: none"> Risdiplam powder should be constituted to an oral solution by a pharmacist or other healthcare provider prior to dispensing; oral syringes should be dispensed for use when administering the drug.
Availability and storage	<p>12 mg/5 mL injection solution in single-dose glass vial.</p> <ul style="list-style-type: none"> Store in a refrigerator between 2 and 8°C (36 to 46°F) in original carton, protected from light. Nusinersen can be stored in its original carton at or below 30°C (86°F) for up to 14 days. 	<p>60 mg powder for constitution in amber glass bottle (final concentration: 0.75 mg/mL). Also supplied with bottle adapter and 4 reusable oral syringes.</p> <ul style="list-style-type: none"> Store dry powder at 20 to 25°C (68 to 77°F) in its original carton. Store constituted oral solution in the amber glass bottle in a refrigerator at 2 to 8°C (36 to 46°F) for up to 64 days.

Spinraza® (nusinersen) [package insert]. Cambridge, MA: Biogen; 2020.

Evrysdi® (risdiplam) [package insert]. South San Francisco, CA: Genentech, Inc.; 2022.



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Nusinersen and Risdiplam

Characteristics	Spinraza® (nusinersen)	Evrysdi® (risdiplam)
Warnings/ precautions	<ul style="list-style-type: none"> Potential for thrombocytopenia and coagulation abnormalities. Potential for renal toxicity, including fatal glomerulonephritis. 	<ul style="list-style-type: none"> None reported by the manufacturer.
Adverse events	<p>Reactions occurring in $\geq 5\%$ of patients receiving nusinersen in clinical trials evaluating infantile-onset SMA:</p> <ul style="list-style-type: none"> Lower respiratory infection, constipation, teething, urinary tract infection, upper respiratory tract congestion, ear infection, flatulence, decreased weight <p>Reactions occurring in $\geq 5\%$ of patients receiving nusinersen in clinical trials evaluating later-onset SMA:</p> <ul style="list-style-type: none"> Pyrexia, headache, vomiting, back pain, epistaxis, fall, respiratory tract congestion, seasonal allergy <p>Post-marketing: serious infections, hypersensitivity reactions, potential for immunogenicity or anti-drug antibody formation.</p>	<p>Reactions occurring in $\geq 10\%$ of patients receiving risdiplam in clinical trials evaluating infantile-onset SMA:</p> <ul style="list-style-type: none"> Upper respiratory tract infection, lower respiratory tract infection, constipation, vomiting, cough <p>Reactions occurring in $\geq 5\%$ of patients receiving risdiplam in clinical trials evaluating later-onset SMA:</p> <ul style="list-style-type: none"> Fever, diarrhea, rash, mouth and aphthous ulcers, arthralgia, urinary tract infection <p>Reactions observed in a clinical trial of patients with pre-symptomatic SMA were consistent with those observed in clinical trials of patients with symptomatic SMA.</p>
Specific populations	<ul style="list-style-type: none"> Pregnant women: inadequate data Lactation: no data on presence of nusinersen in breast milk, effects of the drug on breastfed infants, or effects on milk production. Geriatric patients (≥ 65 years of age): safety is unknown. 	<ul style="list-style-type: none"> Body weight and age have significant effects on the pharmacokinetics of risdiplam. Hepatic impairment: mild to moderate (Child-Pugh class A and B) – absorption of risdiplam lower, but not considered clinically important. Severe hepatic impairment (Child-Pugh class C) – not evaluated.
Monitoring parameters	<p>At baseline and prior to each dose:</p> <ul style="list-style-type: none"> Conduct quantitative spot urine testing using first morning void. Obtain a platelet count. Perform coagulation laboratory testing. 	<ul style="list-style-type: none"> No monitoring parameters are specified by the manufacturer.

Spinraza® (nusinersen) [package insert]. Cambridge, MA: Biogen; 2020.

Evrysdi® (risdiplam) [package insert]. South San Francisco, CA: Genentech, Inc.; 2022.



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Motor Function Scales

Instrument	Description	Total score range ^a
CHOP-INTEND	16 items; evaluates movement of different muscle groups through active or reflexive movement and spontaneous or goal-directed tasks	0 to 64
GMFM	88 items; evaluates gross motor activities across 5 dimensions: 1) lying and rolling; 2) sitting; 3) crawling and kneeling; 4) standing; and 5) walking, running, and jumping	Each item rated on a 3-point ordinal scale; scores expressed as raw totals and percentages for each dimension
HFMS	20 scored activities graded on a 3-point scale; evaluates development in children with limited mobility	0 to 40
HF MSE	33 items graded on a 3-point scale; evaluates advanced motor skills often in ambulatory patients	0 to 66
HINE-2	HINE consists of 37 items; evaluates neurologic function, development (HINE-2), behavior	0 to 26
MFM32	32 items; evaluates motor abilities in 3 dimensions: 1) standing position and transfers; 2) axial and proximal motor function; 3) distal motor function	0 to 96; often expressed as a percentage of the maximum score of 96
RULM	20 items; addresses functional abilities across ambulatory and nonambulatory patients	0 to 37
6MWT	Measure of exercise capacity and motor function; measures maximum distance a patient can walk in 6 minutes over a 25-meter linear course	Not specified

6MWT=6-minute walk test; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; GMFM=Gross Motor Function Measure; HFMS=Hammersmith Functional Motor Scale; HF MSE=Hammersmith Functional Motor Scale-Expanded; HINE-2=section 2 of the Hammersmith Infant Neurological Examination; MFM32=Motor Function Measure 32; RULM=Revised Upper Limb Module; SMA=spinal muscular atrophy

^aHigher scores indicate better motor function.

Wu JW. *Am J Phys Med Rehabil.* 2022;101(6):590-608.



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Guidelines and Consensus Statements

- Multiple guidelines and consensus statements have been published on treatment of SMA
- Most were authored by organizations outside of the US
- Overall recommendations highlight the need for:
 - Established and experienced practitioners/treatment centers
 - Early initiation of therapy in newly diagnosed patients, particularly infants
 - Genetic confirmation of diagnosis and number of *SMN2* copies
 - Monitoring of motor function at baseline and regularly thereafter with validated scales

Pitarch Castellano I. *Neurologia (Engl Ed)*. 2022;37(3):216-228.

Finkel RS. *Neuromuscul Disord*. 2018;28(3):197-207.

Brazilian Medical Association. *Rev Assoc Med Bras (1992)*. 2018;64(6):484-491.

Canadian Agency for Drugs and Technologies in Health (CADTH). ©. <https://www.cadth.ca/sites/default/files/DRR/2022/SR0713-Spinraza-Reassessment.pdf>. <https://www.cadth.ca/sites/default/files/DRR/2021/SR0661%20Evrysdi%20Recommendation%20Final.pdf>.

National Institute for Health and Care Excellence (NICE). <https://www.nice.org.uk/guidance/ta588/resources/nusinersen-for-treating-spinal-muscular-atrophy-pdf-82607209989829>. <https://www.nice.org.uk/guidance/ta755/resources/risdiplam-for-treating-spinal-muscular-atrophy-pdf-82611377117125>.



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Efficacy of Nusinersen: Phase 3 Trials

Characteristics	ENDEAR	CHERISH
Design, duration	<ul style="list-style-type: none"> Multicenter, randomized, double-blind, sham-controlled Event-driven; median duration 187 to 280 days 	<ul style="list-style-type: none"> Multicenter, randomized, double-blind, sham-controlled Treatment for 9 months; follow-up for 6 months
Population	<p>122 children with infantile-onset SMA</p> <ul style="list-style-type: none"> Genetic documentation of homozygous deletion or mutation in the <i>SMN1</i> gene and 2 copies of the <i>SMN2</i> gene Onset of clinical symptoms of SMA at age ≤6 months Unable to sit independently Age ≤7 months at screening GA 37 to 42 weeks Body weight at or exceeding third percentile for age <p>Excluded patients with peripheral oxygen saturation <96% without ventilation support; history of gene therapy or antisense oligonucleotide therapy; disorder/condition(s) interfering with lumbar puncture</p>	<p>126 children with later-onset SMA</p> <ul style="list-style-type: none"> Genetic documentation of homozygous deletion or mutation in the <i>SMN1</i> gene Onset of clinical symptoms of SMA at age >6 months. Age 2 to 12 years at screening Able to sit independently but never was able to walk independently HFMSE score ≥10 and ≤54 <p>Excluded patients with respiratory insufficiency; history of gene therapy or antisense oligonucleotide therapy; disorder/condition(s) interfering with lumbar puncture</p>
Interventions	<p>Nusinersen (n=81) or sham procedure (n=41)</p> <ul style="list-style-type: none"> Adjusted doses, on days 1, 15, 29, 64, 183 and 302 	<p>Nusinersen (n=84) or sham procedure (n=42)</p> <ul style="list-style-type: none"> 12 mg dose administered on days 1, 29, 85, and 274
Primary endpoints	<ul style="list-style-type: none"> Motor-milestone response, defined according to HINE-2 Event-free survival, defined as time to death or use of permanent assisted ventilation 	<ul style="list-style-type: none"> LS mean change from baseline in total HFMSE score at month 15
Baseline characteristics	<ul style="list-style-type: none"> All infants were symptomatic, hypotonic, and weak with median disease duration of 13.1 weeks 	<ul style="list-style-type: none"> All children were able to sit without support; none were able to walk independently
Outcomes	<ul style="list-style-type: none"> Motor-milestone response (nusinersen vs. control): 51% vs. 0% Event-free survival (HR, 95% CI): 0.53 (0.32 to 0.89) 	<ul style="list-style-type: none"> Nusinersen vs. control: 3.9 vs. -1.0 Mean difference (95% CI): 4.9 (3.1 to 6.7)

CI=confidence interval; CNS=central nervous system; GA=gestational age; HFMSE=Hammersmith Functional Motor Scale-Expanded; HINE-2=section 2 of the Hammersmith Infant Neurological Examination; HR=hazard ratio; LS=least-squares; SMA=spinal muscular atrophy; SMN=survival motor neuron



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Efficacy of Risdiplam: Phase 2 / 3 Trials

Characteristics	FIREFISH part 2	SUNFISH part 2
Design, duration	<ul style="list-style-type: none"> Multicenter, open-label, historical-control 12 months 	<ul style="list-style-type: none"> Multicenter, randomized, double-blind, placebo-controlled 12 months
Population	<p>41 children with infantile-onset SMA</p> <ul style="list-style-type: none"> Genetic documentation of homozygous deletion or mutation in the <i>SMN1</i> gene and 2 copies of <i>SMN2</i> Onset of clinical symptoms of SMA at age ≥ 28 days and ≤ 3 months Age ≥ 28 days and ≤ 7 months at screening GA 37 to 42 weeks Body weight at or exceeding third percentile for age <p>Excluded patients requiring invasive ventilation or tracheostomy; history or concomitant use of gene therapy, antisense oligonucleotide therapy, or <i>SMN2</i> splicing modifier; hematologic/blood chemistry abnormalities</p>	<p>180 children with later-onset SMA</p> <ul style="list-style-type: none"> Genetic documentation of homozygous deletion or mutation in <i>SMN1</i> Clinical symptoms consistent with SMA type 2 or 3 Age 2 to 25 years at screening Non-ambulant patients: RULM score ≥ 2 and able to sit independently for ≥ 5 seconds <p>Excluded patients requiring invasive ventilation or tracheostomy; history or concomitant use of gene therapy, antisense oligonucleotide therapy, or <i>SMN2</i> splicing modifier; hematologic/blood chemistry abnormalities</p>
Interventions	<p>Risdiplam (n=41) or no treatment in historical control</p> <ul style="list-style-type: none"> Age-adjusted doses administered PO or through feeding tube once daily 	<p>Risdiplam (n=120) or placebo (n=60)</p> <ul style="list-style-type: none"> Age-adjusted doses administered PO or through feeding tube once daily
Primary endpoint	<ul style="list-style-type: none"> Ability to sit without support for ≥ 5 seconds after 12 months of treatment 	<ul style="list-style-type: none"> Change from baseline in MFM32 total score at 12 months
Baseline characteristics	<ul style="list-style-type: none"> All infants were symptomatic with median disease duration of 3.4 months 	<ul style="list-style-type: none"> All children had either SMA type 2 or non-ambulant SMA type 3 with mean MFM32 score of 46.11
Outcomes	<ul style="list-style-type: none"> Risdiplam vs. control: 29% vs. 5%, $p < 0.001$ 	<ul style="list-style-type: none"> Risdiplam vs. control: 1.36 vs. -0.19 Mean difference (95% CI): 1.55 (0.30 to 2.81)

CI=confidence interval; GA=gestational age; MFM32=32-item Motor Function Measure; PO=by mouth; R=randomized; RULM=Revised Upper Limb Module; SMA=spinal muscular atrophy; SMN=survival motor neuron



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Comparator State Medicaid Coverage: Nusinersen

- N=9: CA, CO, FL, IL, MA, MI, Penn, TX, WA
 - 8 of 9 programs cover nusinersen
 - 7 programs require prior authorization (PA)
- Similar criteria for initiation and continuation of therapy

Initiation	Continuation
<ul style="list-style-type: none"> • Involvement of a specialist (n=7) • Patient demographic data (n=3) • Genetic laboratory confirmation (n=7) • Pulmonary status (n=6) • Results of ≥ 1 neuromotor assessment (n=7) • Stability in other baseline laboratory measures (n=4) • No other SMN-targeting drug use (n=6) • Appropriate dosing (n=6) • Other/additional (n=5) 	<ul style="list-style-type: none"> • Documentation of positive response to therapy (n=7) • Confirmation of pulmonary status (n=6) • Documentation of other laboratory measurements (n=3) • No other SMN-targeting therapies used (n=2) • Adherence to dosing regimen (n=2) • Other/additional (n=4)

SMN=survival motor neuron



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Comparator State Medicaid Coverage: Risdiplam

- N=9: CA, CO, FL, IL, MA, MI, Penn, TX, WA
 - All 9 programs cover risdiplam
 - 8 programs require PA; criteria identified for 6 programs

Initiation	Continuation
<ul style="list-style-type: none"> • Involvement of a specialist (n=6) • Patient demographics (n=5) • Genetic laboratory confirmation of diagnosis (n=6) • Pulmonary status (n=4) • Results of ≥ 1 neuromotor assessment (n=6) • Negative pregnancy test, need for contraception (n=2) • No hepatic impairment (n=1) • No other SMN-targeting drug use (n=6) • Appropriate dosing (n=4) 	<ul style="list-style-type: none"> • Documentation of positive response to therapy (n=6) • Confirmation of pulmonary status (n=3) • Confirmation of negative pregnancy (n=1) • No hepatic impairment (n=1) • No other SMN-targeting therapies used (n=2) • Adherence to dosing regimen (n=2) • Other/additional (n=4)

SMN=survival motor neuron



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NYS Medicaid MCOs Coverage

Nusinersen

- Covered by 14 of 16 plans
 - All require PA
- Criteria identified for 11 plans:
 - Diagnosis requirement (n=11)
 - Quantity limits (n=11)
 - Duration limits (n=8)
 - Age limits (n=2)
 - Prescriber specialization (n=7)
 - Contraindication or intolerance to risdiplam (n=3)

Risdiplam

- Covered by 11 of 16 plans
 - All require PA
- Criteria identified for 9 plans:
 - Diagnosis requirement (n=9)
 - Quantity limits (n=8)
 - Duration limits (n=9)
 - Age limits (n=5)
 - Prescriber specialization (n=6)

NYSDOH. Managed Care Plans. <https://mmcdruginformation.nysdoh.suny.edu/>.



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Drug Utilization Data: Overview of Analyses

- Procedure and pharmacy claims for nusinersen and risdiplam for members in FFS and managed care (MC) with service dates between April 1, 2017 and March 31, 2022 were identified
- Data source: Medicaid Data Warehouse (MDW)
- Utilization was further assessed by state fiscal year (SFY):
 - SFY18: April 1, 2017 – March 31, 2018
 - SFY19: April 1, 2018 – March 31, 2019
 - SFY20: April 1, 2019 – March 31, 2020
 - SFY21: April 1, 2020 – March 31, 2021
 - SFY22: April 1, 2021 – March 31, 2022



Drug Utilization Data: Overview of Analyses, Continued

- Medicaid Confidential Data Cell Size Policy (OHIP-0001)
 - Requires that no cell containing a value of 1 to 30 be reported; such values must be reported as ≤ 30 in all public-facing documents
- The following limitations should also be considered:
 - While time periods analyzed take into account inherent delays in claim/encounter submissions, data may not be fully complete
 - Per a memo issued September 23, 2022, by the MDW Customer Care Center, the MDW Encounters Intake System (EIS) is rejecting Pharmacy/National Council for Prescription Drug Programs (NCPDP)
 - Encounters for a subset of national drug codes (NDC) are missing from its reference data
 - Encounters containing NDCs added to the approved formulary since December 2021 are being rejected and this could potentially result in incorrect data analytics/reporting



Summary Utilization

- In the overall period, SFY18 – SFY22 (April 1, 2017 – March 31, 2022):
 - Nusinersen or risdiplam: 147 members with 1,626 claims

Data source: MDW, April 1, 2017 - March 31, 2022

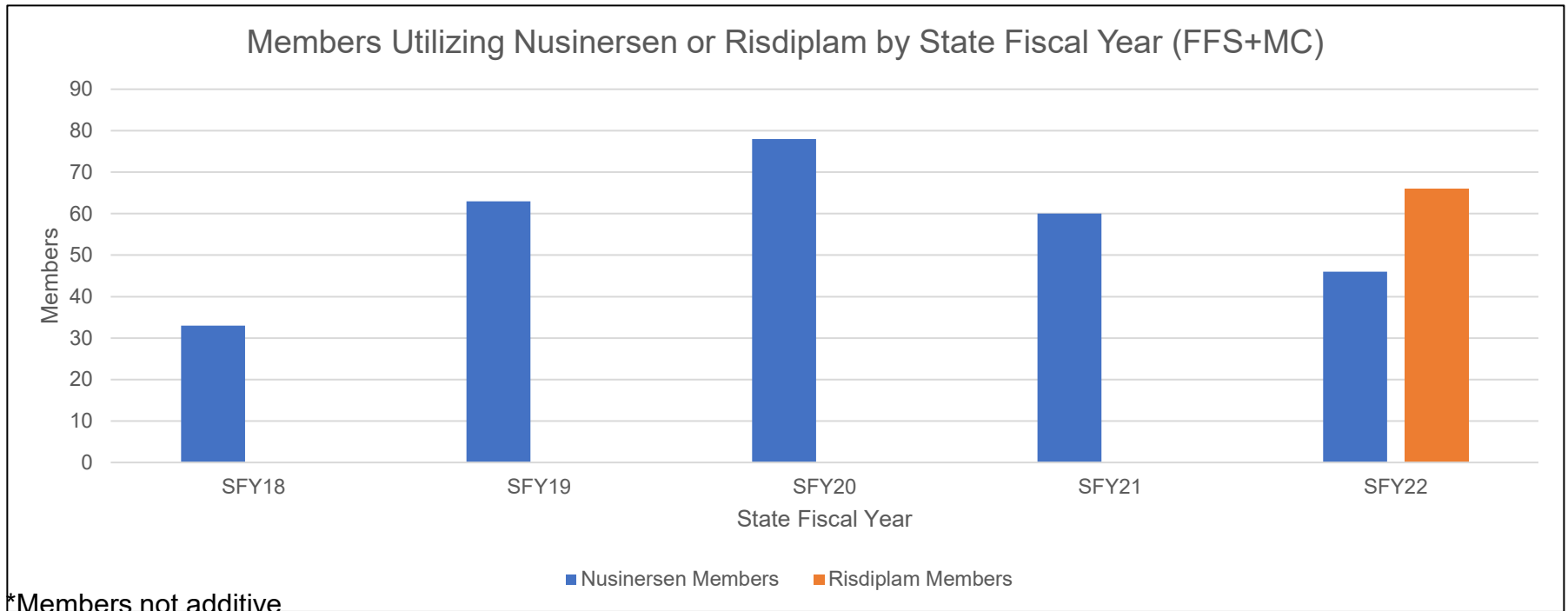


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Utilization by Drug and SFY



- Nusinersen was approved in December 2016 and risdiplam was approved in August 2020
- Utilization in the FFS+MC population appeared to shift from nusinersen to risdiplam in SFY21 and SFY22
- There were also members with claims for both drugs in the same SFY

Data source: MDW, April 1, 2017 - March 31, 2022

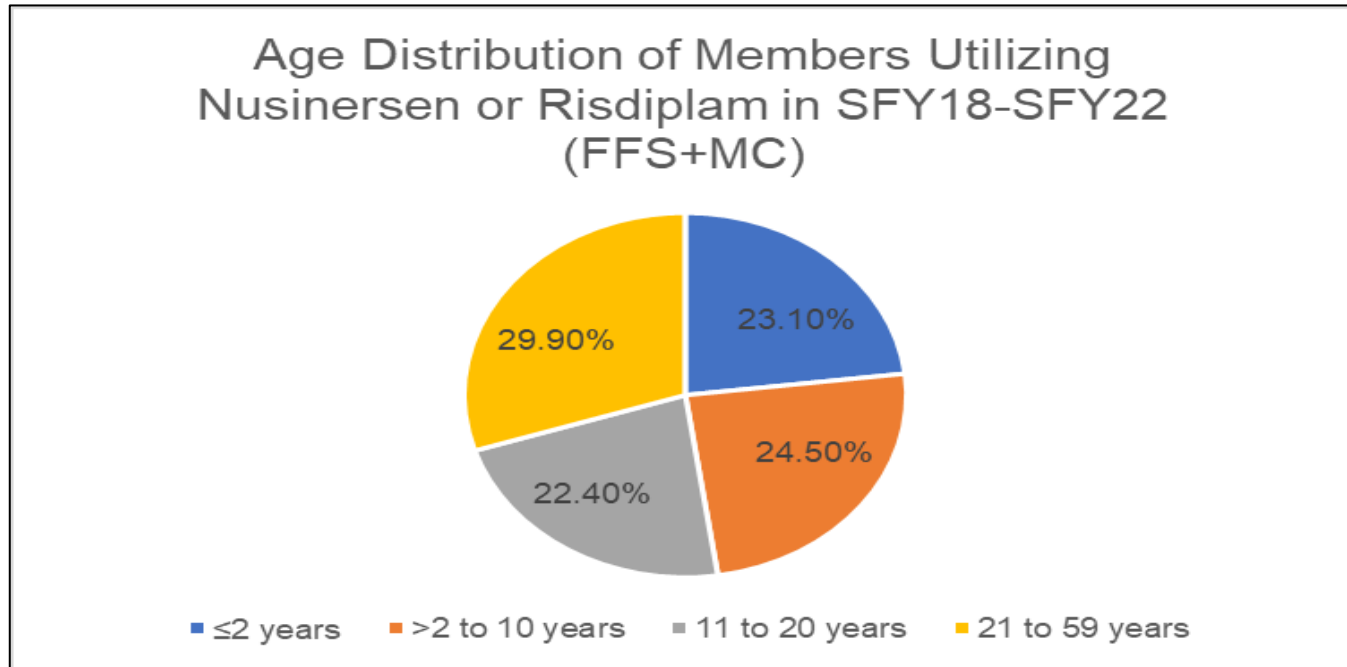


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Utilization by Age and Sex



- Ages of members utilizing nusinersen or risdiplam ranged from 0 to 59 years
 - >20% of members were ≤2 years of age at their first claim
 - Nearly 60% of members (n=88) were <18 years of age at their first claim
- Of the 147 members, 54.4% (n=80) were male and 45.6% (n=67) were female

Data source: MDW, April 1, 2017 - March 31, 2022



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Diagnoses

- Diagnoses of members utilizing nusinersen or risdiplam were assessed using international classification of diseases, tenth revision (ICD-10) codes
- ICD-10 codes of interest were identified from practitioner, clinic, or hospital claims between April 1, 2016 (1-year lookback) and March 31, 2022
- Over 98% of members had a diagnosis of SMA

Data source: MDW, April 1, 2016 - March 31, 2022



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Conclusions

- SMA is a progressive neurodegenerative disease that leads to muscle weakness and atrophy
- The most common form of SMA is caused by defects in both copies of the *SMN1* gene on chromosome 5q
- SMA presentation varies with regard to age of onset and level of motor function
- Treatment options are limited with only 3 FDA-approved agents: nusinersen, risdiplam, and onasemnogene abeparvovec-xioi
 - Nusinersen was approved in 2016 for treatment of SMA of all types in pediatric and adult patients
 - Risdiplam was approved in 2020 for treatment of SMA of all types in pediatric and adult patients

NIH. SMA Fact Sheet. <https://www.ninds.nih.gov/spinal-muscular-atrophy-fact-sheet>

Muscular Dystrophy Association (MDA). SMA. <https://www.mda.org/disease/spinal-muscular-atrophy/>.

Chiriboga CA. *Paediatr Drugs* 2022. Published online ahead of print.



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Conclusions, Continued

- Available guidelines and consensus statements underscore the need for established and experienced practitioners/treatment centers, early initiation of therapy, genetic confirmation of diagnosis and number of *SMN2* copies, and monitoring of motor function at baseline and regularly thereafter
- Published clinical trials are limited to drug development studies; patients with advanced disease were excluded from these trials

NIH. SMA Fact Sheet. <https://www.ninds.nih.gov/spinal-muscular-atrophy-fact-sheet>

Muscular Dystrophy Association (MDA). SMA. <https://www.mda.org/disease/spinal-muscular-atrophy/>.

Chiriboga CA. *Paediatr Drugs* 2022. Published online ahead of print.



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Conclusions, Continued

- Based on a retrospective analysis of procedure claims and pharmacy claims from the MDW:
 - 147 members in the FFS+MC population utilized nusinersen or risdiplam between April 1, 2017 and March 31, 2022
 - Ages of members ranged from 0 to 59 years
 - Age <18 years: 59.9%
 - Age ≤2 years: 23.1%
 - Over 98% of members had a diagnosis code for SMA during the analysis period

Data source: MDW, April 1, 2017 - March 31, 2022



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UB Recommendations

- The following should be considered:
 - Development of a practitioner-administered drug (PAD) policy for nusinersen with criteria consistent with those of other therapies for SMA and recommendations from the FDA-approved labeling
 - Implementation of clinical criteria for risdiplam consistent with those of other therapies for SMA and recommendations from the FDA-approved labeling



APPENDIX

Definitions of Permanent Ventilation from Phase 3 Trials

Reference	Related Terms and Descriptions	Notes
Nusinersen (Spinraza®)		
ENDEAR Finkel et al, 2018	Permanent-assisted ventilation: Tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible event	Permanent-assisted ventilation included in primary efficacy endpoint of event-free survival
CHERISH Mercuri et al, 2018	Respiratory insufficiency: invasive or non-invasive ventilation for >6 hours during a 24-hour period	Permanent ventilation not addressed in published trial; respiratory insufficiency at screening was an exclusion criterion
Risdiplam (Evrysdi®)		
FIREFISH part 2 Darras et al, 2021	Permanent ventilation: Tracheostomy or ventilation for ≥16 hours per day continuously for >3 weeks or continuous intubation for >3 weeks in the absence of, or after resolution of, an acute reversible event	Permanent ventilation included in a secondary efficacy endpoint of event-free survival
SUNFISH part 2 Mercuri et al, 2022	Invasive ventilation or tracheostomy (no term specified)	Permanent ventilation not addressed in published trial; invasive ventilation or tracheostomy were exclusion criteria

Definitions of Permanent Ventilation from Phase 3 Trials

Reference	Related Terms and Descriptions	Notes
Onasemnogene abeparvovec-xioi (Zolgensma®)		
STR1VE Day et al, 2021	Permanent ventilation: Tracheostomy or ≥16 hours of daily non-invasive ventilation support for ≥14 days in the absence of acute reversible illness or perioperative ventilation	Permanent ventilation included in the coprimary endpoint of survival at 14 months of age
SPR1NT Strauss et al, 2022	Permanent ventilation: Tracheostomy or ≥16 hours of daily respiratory assistance for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation	Permanent ventilation included as an exploratory endpoint of survival at 14 months of age

Finkel RS. *N Engl J Med.* 2017;377(18):1723-1732. Mercuri E. *N Engl J Med.* 2018;378(7):625-635.
 Darras BT. *N Engl J Med.* 2021;385(5):427-435. Mercuri E. *Lancet Neurol.* 2022;21(1):42-52.
 Day JW. *Lancet Neurol.* 2021;20(4):284-293. Strauss KA. *Nat Med.* 2022;28(7):1390-1397.



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Drug Utilization Review: Ocrelizumab (Ocrevus®)

Drug Utilization Review Board Meeting
December 15, 2022



Purpose

- The primary objective is to examine the utilization of ocrelizumab (Ocrevus®) across the entire New York State (NYS) Medicaid population, including the fee-for-service (FFS) and managed care (MC) programs.
- Recommendations for the management of ocrelizumab will be provided based on a review of the literature and utilization analyses.



Background

- Ocrelizumab (Ocrevus®) is a CD20-directed antibody approved by the FDA for treatment of:
 - Primary progressive multiple sclerosis (PPMS)
 - Relapsing forms of MS in adults including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease
- Ocrelizumab is covered by the NYS Medicaid FFS program.

Ocrevus® [package insert]. South San Francisco, CA: Genentech, Inc.; 2022.



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Dosage and Administration

- Starting dose: 300 mg IV infusion, followed 2 weeks later by a second 300 mg IV infusion.
- Subsequent doses: 600 mg IV infusion every 6 months.
- Patients must be closely monitored during and for at least 1-hour after the infusion due to the risk of infusion reactions.
- Must be administered by an experienced healthcare professional with access to medical support in the event of a serious adverse reaction.

Ocrevus® [package insert]. South San Francisco, CA: Genentech, Inc.; 2022.



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Treatment Requirements Prior to First Dose

- HBV and quantitative serum immunoglobulin screening are required prior to the first dose.
- Infusion should be delayed if the patient has an active infection.
- Live and live-attenuated vaccines should be administered at least 4 weeks prior to initiation of ocrelizumab as they are not recommended during treatment.
- Non-live vaccines should be administered at least 2 weeks prior to initiation of ocrelizumab.

Ocrevus® [package insert]. South San Francisco, CA: Genentech, Inc.; 2022.



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Contraindications

- Active hepatitis B virus
- History of a life-threatening infusion reaction to ocrelizumab

Ocrevus® [package insert]. South San Francisco, CA: Genentech, Inc.; 2022.



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Warnings/Precautions

- Infusion reactions (pruritis, rash, urticaria, erythema, bronchospasm): ocrelizumab should be permanently discontinued if a life-threatening or disabling reaction occurs.
- Infections: treatment should be delayed in patients with an active infection until it is resolved.
- PML: ocrelizumab should not be administered at the first sign/symptom indicative of PML.

PML=progressive multifocal leukoencephalopathy.

Ocrevus® [package insert]. South San Francisco, CA: Genentech, Inc.; 2022.



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Warnings/Precautions

- Reduction in immunoglobulins: immunoglobulins should be monitored prior to, during, and following treatment discontinuation (until B-cell repletion), especially if recurrent serious infections are suspected
 - Treatment discontinuation should be considered in patients with serious opportunistic or recurrent serious infections and if hypogammaglobulinemia is prolonged and requires treatment with IVIG.
- Malignancies: increased risk of malignancies, especially breast cancer, may exist.
- Post-marketing reports of immune-mediated colitis; patients should be monitored for new or persistent diarrhea or GI symptoms.

Ocrevus® [package insert]. South San Francisco, CA: Genentech, Inc.; 2022.



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Guideline/Consensus Statement Recommendations

Guideline	Guideline recommendations
AAN (2018)	<ul style="list-style-type: none"> • Treatment initiation: current evidence supports higher efficacy in reduction of relapses and MRI activity with fingolimod and other agents administered by IV infusion (alemtuzumab and natalizumab) vs other approved self-injectable agents (e.g., interferon-beta therapy) in patients with high disease activity (Level B recommendation). • Breakthrough disease activity despite treatment (continued relapses, MRI activity): based on current evidence, alemtuzumab, fingolimod, natalizumab, and ocrelizumab have a higher efficacy compared to previously approved self-injectable DMTs.* • Ocrelizumab is the only DMT to alter disease progression in ambulatory patients with PPMS. Patients should be offered this agent unless the potential risks outweigh the benefits of treatment (Level B recommendation). • Notes the potential for risk of PML with ocrelizumab, natalizumab, fingolimod, rituximab, and dimethyl fumarate.

*Level of evidence not provided for breakthrough disease activity recommendation.

AAN=American Academy of Neurology; DMT=disease-modifying treatment; PML=progressive multifocal leukoencephalopathy; PPMS=primary progressive multiple sclerosis.

Rae-Grant A et al. <https://www.aan.com/Guidelines/home/GuidelineDetail/898>.



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Guideline/Consensus Statement Recommendations

Guideline	Guideline recommendations
ECTRIMS/EAN (2018)	<ul style="list-style-type: none"> • Active RRMS: interferon beta-1a, interferon beta-1b, peginterferon beta-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, daclizumab, natalizumab, ocrelizumab, fingolimod, or alemtuzumab may be considered (consensus statement). • Patients with disease activity despite treatment with an interferon or glatiramer acetate: switching to another agent should be considered (strong recommendation); patient characteristics, safety, and disease activity/severity should be considered (consensus statement). • Treatment with ocrelizumab should be considered for patients with PPMS (weak recommendation). • Treatment with ocrelizumab or cladribine should be considered for patients with active SPMS (weak recommendation).

ECTRIMS/EAN=European Committee of Treatment and Research in Multiple Sclerosis/European Academy of Neurology; PPMS=primary progressive multiple sclerosis; RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis.

Montalban X et al. *Multiple Sclerosis Journal*. 2018;24(2):96-120.



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Guideline/Consensus Statement Recommendations

Guideline	Guideline recommendations
NICE (2018) - RRMS	<ul style="list-style-type: none"> • Recommends ocrelizumab in adults with active disease (with clinical or imaging features) only if alemtuzumab is contraindicated or unsuitable. • Ocrelizumab reduced the number of relapses and slowed disability vs interferon beta-1a in clinical trials; there are no other trials directly comparing ocrelizumab to other DMTs. • Indirect comparisons to interferon beta-1b, glatiramer acetate, dimethyl fumarate, fingolimod, and teriflunomide showed that ocrelizumab reduced the number of relapses; indirect comparisons to alemtuzumab and natalizumab also showed that ocrelizumab is as effective. • Analyses from trials suggest that ocrelizumab may slow disease progression, but notes that this effect is uncertain in patients with highly active/rapidly evolving severe disease. • Ocrelizumab is more costly than alemtuzumab (in the UK).
NICE (2019) - PPMS	<ul style="list-style-type: none"> • Recommends ocrelizumab as a treatment option in patients with imaging features indicative of inflammatory activity. • States that 1 trial showed that ocrelizumab can slow the worsening of disability but notes the uncertainty of the size and duration of this effect. • Ocrelizumab is the only agent approved by the FDA for treatment of PPMS.

DMT=disease-modifying treatment; FDA=Food and Drug Administration; NICE=National Institute for Health and Care Excellence; PPMS=primary progressive multiple sclerosis; RRMS=relapsing-remitting multiple sclerosis; UK=United Kingdom.

NICE. <https://www.nice.org.uk/guidance/ta533>.

NICE. <https://www.nice.org.uk/guidance/ta585>.



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Comparator State Medicaid Programs

State	Coverage
CO	<ul style="list-style-type: none"> • Requires a PA: must be administered by a HCP and prescribed by or in consultation with a neurologist. • Maximum dose (maintenance): 600 mg every 6 months. • PPMS: member is ≥ 18 years of age AND is not taking any other DMTs. • RRMS: member is ≥ 18 years of age, has a diagnosis of RRMS, has experienced a relapse within prior year or 2 relapses within prior 2 years, and does not have active HBV or anti-JC virus antibodies at baseline. <ul style="list-style-type: none"> – Requires one of the following: 1) trial and failure (e.g., intolerable side effects, drug-drug interaction, contraindication, or lack of efficacy with either presence of new spinal/cerebellar/brainstem lesions or change in brain atrophy OR signs/symptoms on clinical exam consistent with functional limitations that last ≥ 1 month) with any 2 high-efficacy DMTs (such as ofatumumab, natalizumab, fingolimod, rituximab, or alemtuzumab) OR 2) member has a diagnosis of highly active RRMS (based on measures of relapsing activity and MRI markers of disease activity) AND has had trial and failure with any 1 high-efficacy DMT.
MA	<ul style="list-style-type: none"> • Requires a PA: needs an appropriate diagnosis and must be prescribed by a neurologist (or must provide consult notes from a neurology office); maximum dose is 600 mg every 6 months.

CO=Colorado; DMT=disease modifying treatment; FDA=Food and Drug Administration; HBV=hepatitis B virus; HCP=healthcare professional; JC=John Cunningham or human polyomavirus 2; MA=Massachusetts; MRI=magnetic resonance imaging; PA=prior authorization; PDL=Preferred Drug List; PPMS=primary progressive multiple sclerosis; RRMS=relapsing-remitting multiple sclerosis.

See end of slide presentation for references.



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Comparator State Medicaid Programs

State	Coverage
WA	<ul style="list-style-type: none"> • Non-preferred in the PDL; requires intolerance due to a serious adverse event, contraindication, or inadequate response to at least 2 preferred agents. • RRMS: requires a diagnosis of RRMS; ≥18 years of age; inadequate response to ≥2 agents with the same indication and/or medications which are considered the standard of care; not currently taking other DMTs; received a negative HBV test; does not exceed FDA or Compendia-supported limitations; if treated with DMTs with long-lasting effects (e.g., natalizumab, alemtuzumab), an appropriate wash-out period has elapsed; and for patients with an EDSS score of ≥6.5, there is imaging evidence of active disease, documentation of at least 1 relapsing event in the last 2 years, and documentation the HCP discussed the risks and benefits of treatment. • PPMS: requires a diagnosis of PPMS; ≥18 years of age; documentation of oligoclonal IgG bands in cerebrospinal fluid; T2 lesions on brain or spinal imaging; ambulatory stage of disease (EDSS<7); not currently taking other DMTs; received a negative HBV test; and does not exceed FDA or Compendia-supported limitations. • Quantity limit: 300 mg on days 1 and 15, then 600 mg every 6 months.

DMT=disease modifying treatments; EDSS=Expanded Disability Status Scale; FDA=Food and Drug Administration; HBV=hepatitis B virus; HCP=healthcare professional; IgG=immunoglobulin G; JC=John Cunningham or human polyomavirus 2; MRI=magnetic resonance imaging; PA=prior authorization; PDL=Preferred Drug List; PPMS=primary progressive multiple sclerosis; RRMS=relapsing-remitting multiple sclerosis; WA=Washington.

- Not listed in PDL or requiring a prior authorization: California, Florida, Michigan, and Texas.
- Listed as non-preferred in the PDL: Illinois, Pennsylvania.

See end of slide presentation for references.



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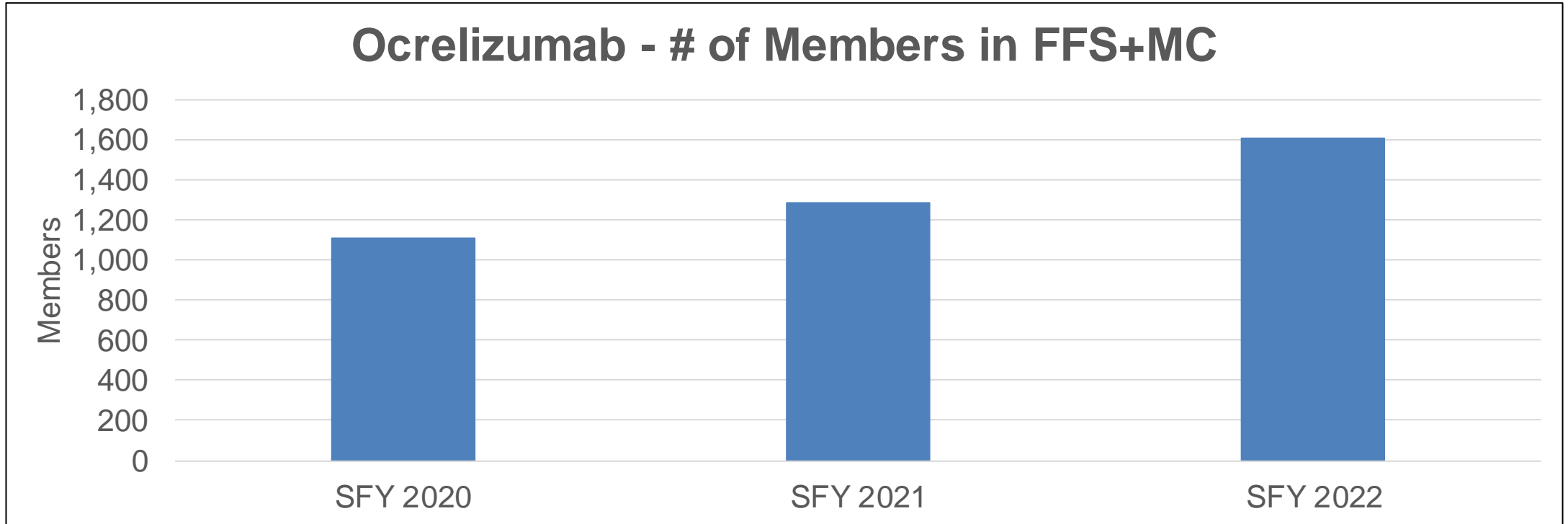


Utilization Analysis - Methodology

- Data source: Medicaid Data Warehouse (MDW).
- Timeframe: April 1, 2019 – March 31, 2022.
- Sample: Members enrolled in the NYS Medicaid Program (FFS+MC) with either a medical or pharmacy claim for ocrelizumab.
- Limitations:
 - While time periods analyzed take into account inherent delays in claim/encounter submissions, data may not be fully complete.
 - Per a memo issued September 23, 2022 by the MDW Customer Care Center, the MDW Encounters Intake System (EIS) is rejecting Pharmacy/National Council for Prescription Drug Programs (NCPDP) Encounters for a subset of national drug codes (NDCs) missing from its reference data. Encounters containing NDCs added to the approved formulary since December 2021 are being rejected and this could potentially result in incorrect data analytics/reporting.
 - The Medicaid Confidential Data Cell Size Policy (OHIP-0001) requires that no cell containing a value of 1 to 30 be reported and no cell can be reported that allows a value of 1 to 30 to be derived from other reported cells or information.



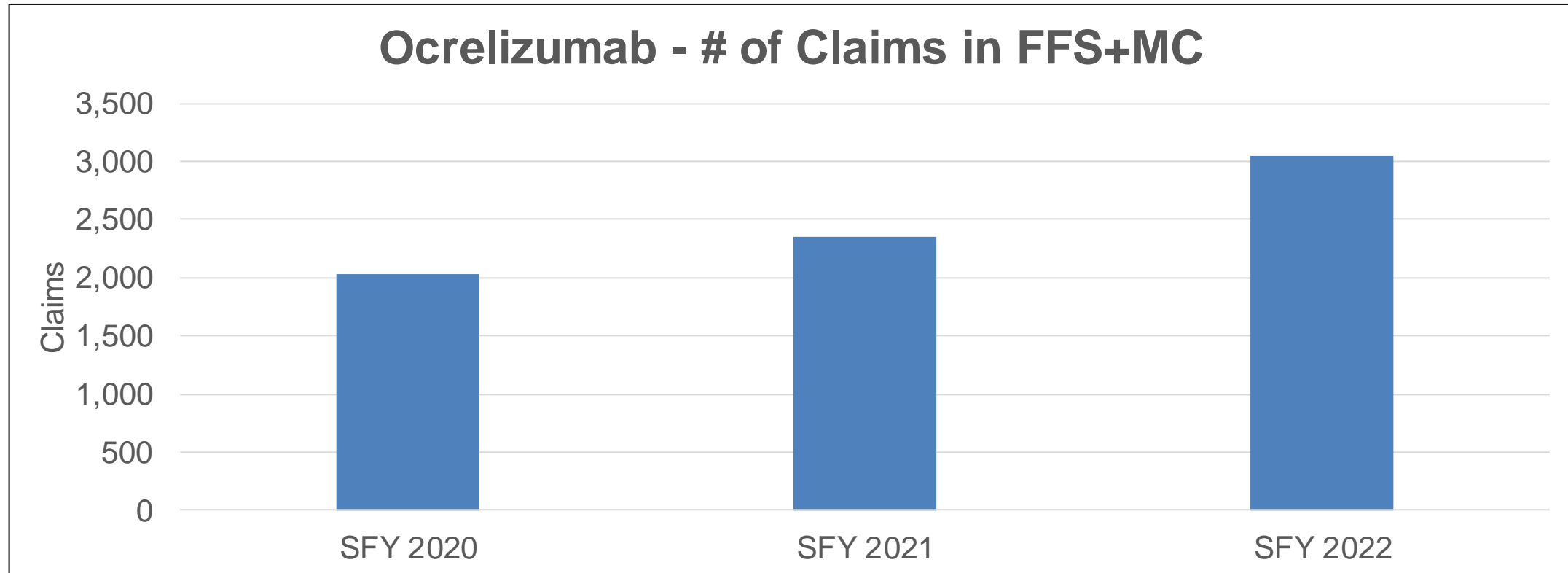
Utilization in FFS+MC



Data source: MDW; date range: 4/1/19 – 3/31/22; extract date: 9/20/22.
FFS=fee-for-service; MC=managed care; SFY=state fiscal year.

- There was a 45.4% increase in the number of members who utilized ocrelizumab between SFY 2020 and SFY 2022.

Utilization in FFS+MC



Data source: MDW; date range: 4/1/19 – 3/31/22; extract date: 9/20/22.
FFS=fee-for-service; MC=managed care; SFY=state fiscal year.

- There was a 50.2% increase in the number of claims between SFY 2020 and SFY 2022.

Results

- Approximately 500 members started ocrelizumab for the first time in SFY 2022 and an estimated 20% had evidence of step therapy within 365 days (e.g., trying a drug from the FFS Preferred Drug Program MS therapeutic class prior to ocrelizumab).
- Ocrelizumab should be administered as 300 mg IV on days 1 and 15, then 600 mg IV every 6 months.
 - 9.0% (n=89) of members received ocrelizumab before the recommended duration of 2 weeks (initial claims) or <6 months (non-initial claims), representing 6.9% of service dates that were earlier than recommended.

Conclusions

- Ocrelizumab is approved by the FDA for the treatment of RRMS and PPMS in adult patients; it is currently the only approved product for PPMS.
- Guidelines assert that choice of a DMT depends on type of MS, stage of treatment (treatment naïve vs experienced) and disease activity.
- There was a 45.4% increase in the number of members who utilized ocrelizumab between SFY 2020 and SFY 2022; there was also a 50.2% increase in the number of claims during the same timeframe.
- Approximately 500 members started ocrelizumab for the first time in SFY 2022.
 - An estimated 20% had evidence of step therapy within 365 days (e.g., trying a drug from the FFS PDP MS therapeutic class prior to ocrelizumab).

UB Recommendations to DOH

1. Step therapy with an agent subject to the fee-for-service Preferred Drug Program multiple sclerosis therapeutic class prior to ocrelizumab (Ocrevus®) (excludes patients with primary progressive multiple sclerosis who are ambulatory and have documentation of inflammatory activity).
2. Frequency/quantity/duration limits: 300 mg on days 1 and 15, then 600 mg every 6 months.



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New York State Medicaid Drug Utilization Review Program



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Betibeglogene Autotemcel (Zynteglo®, beti-cel)

December 15, 2022
DURB Meeting



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Purpose

- The aim of the DURB review is to provide recommendations for the management of betibeglogene autotemcel (beti-cel) in the New York State Medicaid program.



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Background

- Adult hemoglobin (HbA) consists of 2 alpha-globin chains and 2 beta-globin chains ($\alpha_2\beta_2$), and each $\alpha_2\beta_2$ globin chain makes up the HbA that can bind one molecule of oxygen.
- Thalassemias are autosomal recessive inherited defects that affect the production of hemoglobin (Hb).
- Beta-thalassemias are monogenic (single gene) disorders caused by a beta-globin gene (HBB) mutation.
- The HBB mutation results in either a reduced production (β^+) or no production (B^0) of functional beta-globin in HbA, leading to ineffective erythropoiesis, hemolysis, and anemia.
- Beta-thalassemias are categorized as beta-thalassemia major (Cooley's anemia or Mediterranean anemia), beta-thalassemia intermedia, and beta-thalassemia minor (trait).
- The categorizations have since been modified to include transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT).

Background

- In 2008, the World Health Organization reported that approximately 40,000 infants are born annually with beta-thalassemia, and an estimated 25,000 infants will have transfusion-dependent beta-thalassemia.
- The current standard of care for transfusion-dependent beta-thalassemia is regular packed red blood cell (pRBC) transfusions.
- Regular RBC transfusions often lead to iron accumulation that requires iron chelation therapy.
- Transfusion-induced iron overload can cause organ damage (e.g., enlarged heart and liver) and is a major cause of morbidity and mortality.
- The only curative treatment for transfusion-dependent beta-thalassemia is allogeneic hematopoietic stem-cell transplantation (allo-HSCT).
 - For patients who received an allo-HSCT, the best results have occurred in patients <14 years of age and with a human leukocyte antigen (HLA)-identical sibling donor.
- For patients with transfusion-dependent beta-thalassemia who would be candidates for allo-HSCT but do not have an HLA-identical sibling donor, beti-cel is an option.

Zynteglo® (betibeglogene autotemcel [beti-cel]) Suspension for Intravenous Infusion

Manufacturer	bluebird bio, Inc.
Indication	Treatment of adult and pediatric patients with beta-thalassemia who require regular red blood cell transfusions.
FDA-Approval Date	August 17, 2022
Administration	<ul style="list-style-type: none"> • For autologous use only. • Administered via an intravenous infusion by a trained practitioner at a Zynteglo® Qualified Treatment Center.
Mechanism of Action	<ul style="list-style-type: none"> • Ex vivo gene therapy that requires the removal of the patient's hematopoietic stem cell, followed by myeloablative conditioning with a busulfan-containing regimen and the infusion of autologous CD34+ stem cells genetically modified with the BB305 lentiviral vector (BB305 LVV) that contains functional copies of an engineered beta-globin with a threonine to glutamine substitution at position 87 (β^A-T87Q globin). • The expression of β^A-T87Q-globin in the erythroid lineage results in the correction of the alpha-globin and beta-globin imbalance, thereby increasing the production of functional hemoglobin.
Dose	<ul style="list-style-type: none"> • Intended for one-time administration. • The target beti-cel dose is $\geq 12 \times 10^6$ CD34+ cells/kg. • The minimum recommended beti-cel dose is 5.0×10^6 CD34+ cells/kg.



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Use of Beti-cel in Special Populations

- Pregnancy: The drug has not been studied in pregnant persons.
- Lactation: There is no information regarding the presence of beti-cel in human breast milk.
- Females and males of reproductive potential:
 - A negative pregnancy test must be confirmed before the start of hematopoietic stem cell mobilization and re-confirmed before myeloablative conditioning procedures, and re-confirmed before beti-cel administration.
 - An effective method of contraception from the start of mobilization through at least 6 months after the administration of beti-cel is advised.
- Geriatrics: In clinical trials, individuals >50 years of age were excluded.
- Pediatrics: The safety and efficacy in pediatric patients <4 years of age have not been established.
- Patients seropositive for human immunodeficiency virus (HIV): Beti-cel has not been studied in patients with HIV. Per the manufacturer, apheresis material from a patient with an HIV-positive test will not be accepted.
- Renal impairment: The drug has not been studied in patients with renal impairment.
- Liver impairment: The drug has not been studied in patients with hepatic impairment.

Phase 1/ 2 Clinical Trials (n=22)

- Two open-label, phase 1/2 clinical trials with identical designs were conducted in patients with transfusion-dependent beta-thalassemia.
 - In the clinical trials, TDT-beta thalassemia was defined as a history of at least 100 mL/kg/year of packed red blood cells (pRBCs) or ≥ 8 transfusions of pRBCs per year for the prior 2 consecutive years.
- Patients with TDT beta-thalassemia ≤ 35 years of age, regardless of genotype were enrolled.
 - HGB-204 (NCT01745120): Patients had to be ≥ 12 years of age.
 - HGB-205 (NCT02151526): Patients had to be ≥ 5 years of age.
- The primary endpoint was the number of participants who achieved transfusion independence (TI).
 - TI was defined as a weighted average Hb ≥ 9 g/dL without any pRBC transfusions for a continuous period of ≥ 12 months post-infusion.

Phase 1/ 2 Clinical Trials (n=22)

- For the 13 patients who were non B⁰/B⁰ genotype:
 - 12 patients stopped receiving RBC transfusions.
 - The median duration of TI was 26 months (range, 15 to 42 months).
 - 1 patient did not achieve TI, the primary endpoint of the study.
- For the 8 patients who were B⁰/B⁰ genotype and 1 patient who was homozygous for the IVS-I-110 mutation:
 - For 6 patients (B⁰/B⁰ genotype or homozygous for the IVS-I-110 mutation), their median annualized transfusion volume decreased by 73%.
 - 3 patients (B⁰/B⁰ genotype) discontinued RBC transfusions for 14 to 20 months.

Phase 3 Clinical Trial (n=23)

- Open-label, phase 3 clinical trial for TI beta-thalassemia in patients with non- B⁰/B⁰ genotype (HGB-207 [NCT02906202])
- Patients with B⁰/B⁰ genotype and patients homozygous for the IVS-I-110 mutation were excluded from this study. IVS-I-110 mutation was considered equivalent to a B⁰ mutation.
- 23 patients received beti-cel. The final age distribution was:
 - 8 patients <12 years of age,
 - 6 patients 12 to <18 years of age, and
 - 9 patients ≥18 years of age.
 - Note: Patients <12 years of age were enrolled if approved by the relevant regulatory authority.
- 22 patients were evaluated, and 1 patient was excluded from the analysis.
- 20 of the 22 (90.9%) patients evaluated achieved TI. The median duration of TI was 20.4 months (range, 15.7 to 21.6 months).
 - 12 years to 50 years of age cohort: 14 of the 15 patients evaluated achieved TI and
 - <12 years of age cohort: 6 of the 7 patients achieved TI.

Summary

- Zynteglo® (betibeglogene autotemcel, beti-cel) is the first cell-based gene therapy approved by the FDA for the treatment of adult and pediatric patients with beta-thalassemia who require regular RBC transfusions.
- The aim of beti-cel therapy is to achieve long-term TI for patients with TDT beta- thalassemia.
- For the 2 identically designed phase 1/2 clinical trials, 68.2% (15/22) of patients achieved TI.
 - 6/9 patients with B⁰/B⁰ genotype or homozygous for the IVS-I-110 mutation did not achieve TI.
- For the phase 3 clinical trial, 90.9% (20/22) of patients evaluated achieved TI.
 - Patients with B⁰/B⁰ genotype and patients homozygous for the IVS-I-110 mutation were excluded from this study.
- The Long-term Follow-up of Subjects with Transfusion-Dependent β -Thalassemia Treated with Ex Vivo Gene Therapy (LTF-303 [NCT02633943]) clinical trial has been initiated and will follow patients for an additional 13 years to monitor for safety and efficacy.

Recommendations for Zynteglo® (betibeglogene autotemcel) Clinical Coverage Policy

The following coverage parameters should be considered:

1. The patient is ≤ 50 years of age.
 - If the patient is < 5 years of age, the patient weight must be ≥ 6 kg and it is anticipated the minimum number of cells required to initiate the manufacturing process can be collected.
2. The patient has a diagnosis of transfusion-dependent beta-thalassemia.
 - Transfusion-dependent beta-thalassemia is defined as a history of ≥ 100 mL/kg/year of packed red blood cells or ≥ 8 packed red blood cell transfusions per year for the prior 2 years.
3. The individual is a candidate for allogeneic hematopoietic cell transplantation but is ineligible due to the absence of a donor.



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Update: New York State Medicaid Prescriber Education Program (NYSMPEP)

New York State Medicaid
Drug Utilization Review Board (DURB)
December 15, 2022



Legislation

NYS Public Health Law § 279

The department shall develop in collaboration with an academic institution a program designed to provide prescribers with an evidence-based, non-commercial source of the latest objective information about pharmaceuticals. Information shall be presented to prescribers by specially-trained pharmacists, nurses or other health professionals to assist the prescriber in making appropriate therapeutic recommendations.

NYS Public Health Law Chapter 45, Article 2-A, Title 2, Section 279



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Program Mission

To assist prescribers in making therapeutic recommendations in accordance with best practices through the delivery of accredited evidence-based educational activities.



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Program Objectives

- Provide the latest evidence about pharmacotherapy
- Utilize best practices in education throughout the development and delivery of information



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Program Evolution

2008
NYSMPEP
formed

2020
Diabetes
enduring
activity launch
(pilot)

2008-2021
In-person academic detailing:
- Antibiotic stewardship
- Chronic non-cancer pain
- Diabetes
- Hyperlipidemia
- Hypertension
- Respiratory syncytial virus
- Smoking cessation

2022
Antibiotic
stewardship
enduring
activity
launch

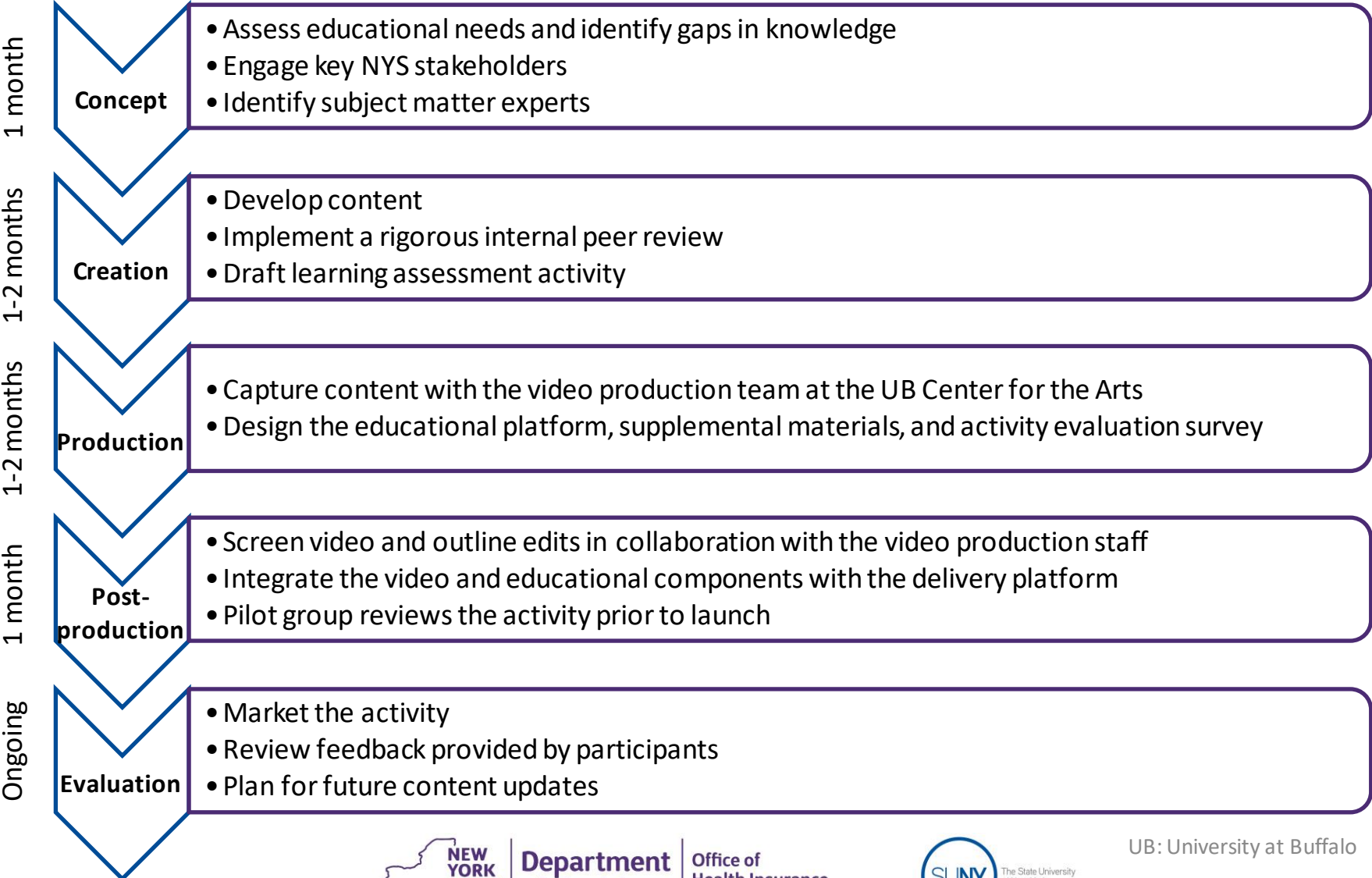


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Educational Material Development Process



Marketing

- Digital marketing
 - Email marketing campaigns
 - Integrated Health Alerting and Notification System (IHANS)
- Inbound marketing
 - Redesigned website
- Exploratory



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Website

- New layout, navigation, and visual appeal
- Mobile device responsive
- Added features:
 - Option to join mailing list to develop engagement
 - Contact us and suggestion forms for enhanced communication

nysep.nysdoh.suny.edu



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NYSMPEP Educational Programs ▾

Other Learning Opportunities

About NYSMPEP ▾



New York State Medicaid Prescriber Education Program

An Evidence-Based, Non-Commercial Source
of Pharmacotherapy Information

Photo Credit: Meredith Forrest Kulwicki, University at Buffalo



About

The New York State Medicaid Prescriber Education Program (NYSMPEP) offers prescribers information on best practices in pharmacotherapy



Educational Programs

Continuing education on topics central to your practice. Prescribers enroll free of charge!



Additional Learning

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About NYSMPEP

What is NYSMPEP?

The New York State Medicaid Prescriber Education Program (NYSMPEP) is a partnership between the New York State Department of Health (NYSDOH) and the State University of New York (SUNY). NYSMPEP, formed in response to [legislation](#) in April 2008, educates prescribers on evidence-based, non-commercial pharmacotherapy information.

What is the Goal of the Program?

The goal of the program is to optimize the quality of care for NYS Medicaid members by providing prescribers the most current information on best practices in pharmaceuticals and therapeutics.

How Does the NYSMPEP Program Work?

NYSMPEP educational materials are prepared and delivered by skilled content experts. Our enduring programs are recorded continuing education sessions that are available to complete any day and time for Accreditation Council for Continuing Medical Education (ACCME) PRA Category 1 credit. Educational materials incorporate disease management information including best practices for selected disease states and conditions.

For a list of currently available and upcoming educational content, visit the [Educational Programs](#) page.

Who is the NYSMPEP Team?

An interdisciplinary network that works collaboratively to identify content experts to meet the timely educational needs of Medicaid prescribers across New York State. Information created and disseminated through the program is peer-reviewed to ensure quality.

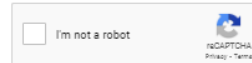
To download our print brochure [click here](#)



Suggest a CE topic

Preferred delivery method(s) *

- Live webinar
- On-demand video recording
- Audio program
- Home study monograph
- Other (please specify below)



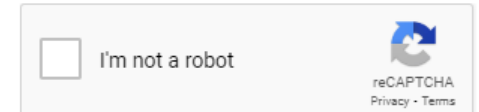
Sign up to be notified of new CE programs

* indicates required

Suggest a CE topic

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Sign up to be notified of new CE programs

* indicates required

Featured Home Study Activity

- Outpatient Antibiotic Stewardship as a Tool to Curb Antibiotic Resistance
 - 1.0 contact hours of accredited continuing education for prescribers and pharmacists
 - Program objectives:
 1. Explain factors contributing to increasing antibiotic resistance and why antibiotic resistance is important
 2. Recognize resources that promote optimal antibiotic use in routine practice
 3. Identify evidence-based infection prevention and control measures
 4. Describe patient counseling tips and techniques to generate informative conversations with patients/caregivers about antibiotics and their appropriate use



Collaborative Approach

- Subject matter expert/researcher
 - Recruited a specialist for the development and delivery of the antibiotic stewardship home study activity
- Multidisciplinary review
 - During the development phase written material was reviewed by representatives from the NYS Department of Health Bureau of Healthcare Associated Infections (BHAi) and Healthcare Epidemiology and Infection Control (HEIC) Program
- Accreditation partners
 - Prescribers: UB Office of Continuing Medical Education
 - Pharmacists: UB Office of Continuing Pharmacy Education



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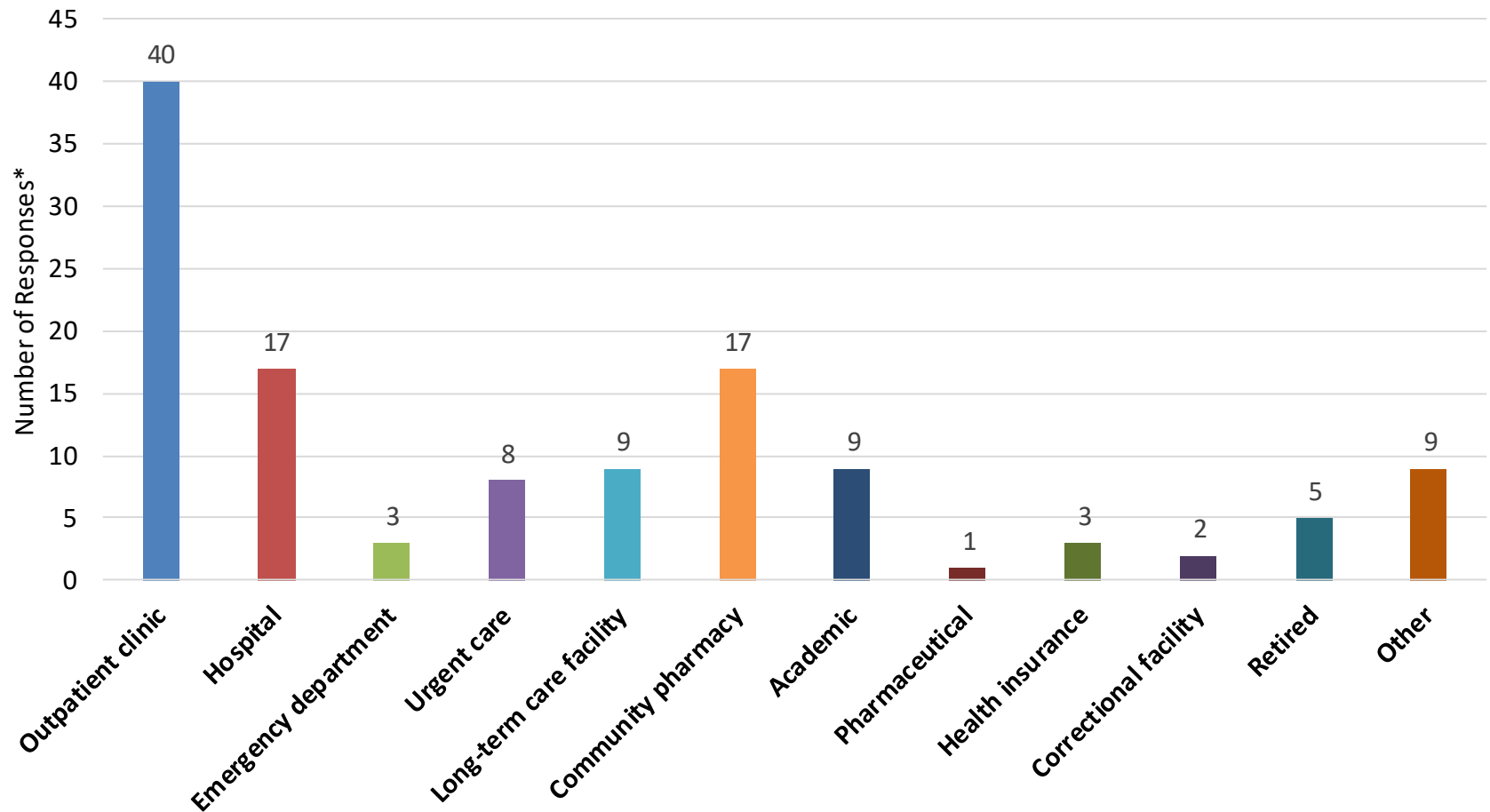


Enduring Online Format

- Flexibility
- Reach potential
- Participant satisfaction
- Improved knowledge
- Antibiotic stewardship participation as of October 20, 2022:
 - 386 individuals registered
 - 204 participants issued a certificate of completion
- Enrollees across a variety of professions and practice settings



Antibiotic Stewardship Home Study Participant Practice Settings



*Survey respondents were permitted to select more than one practice setting



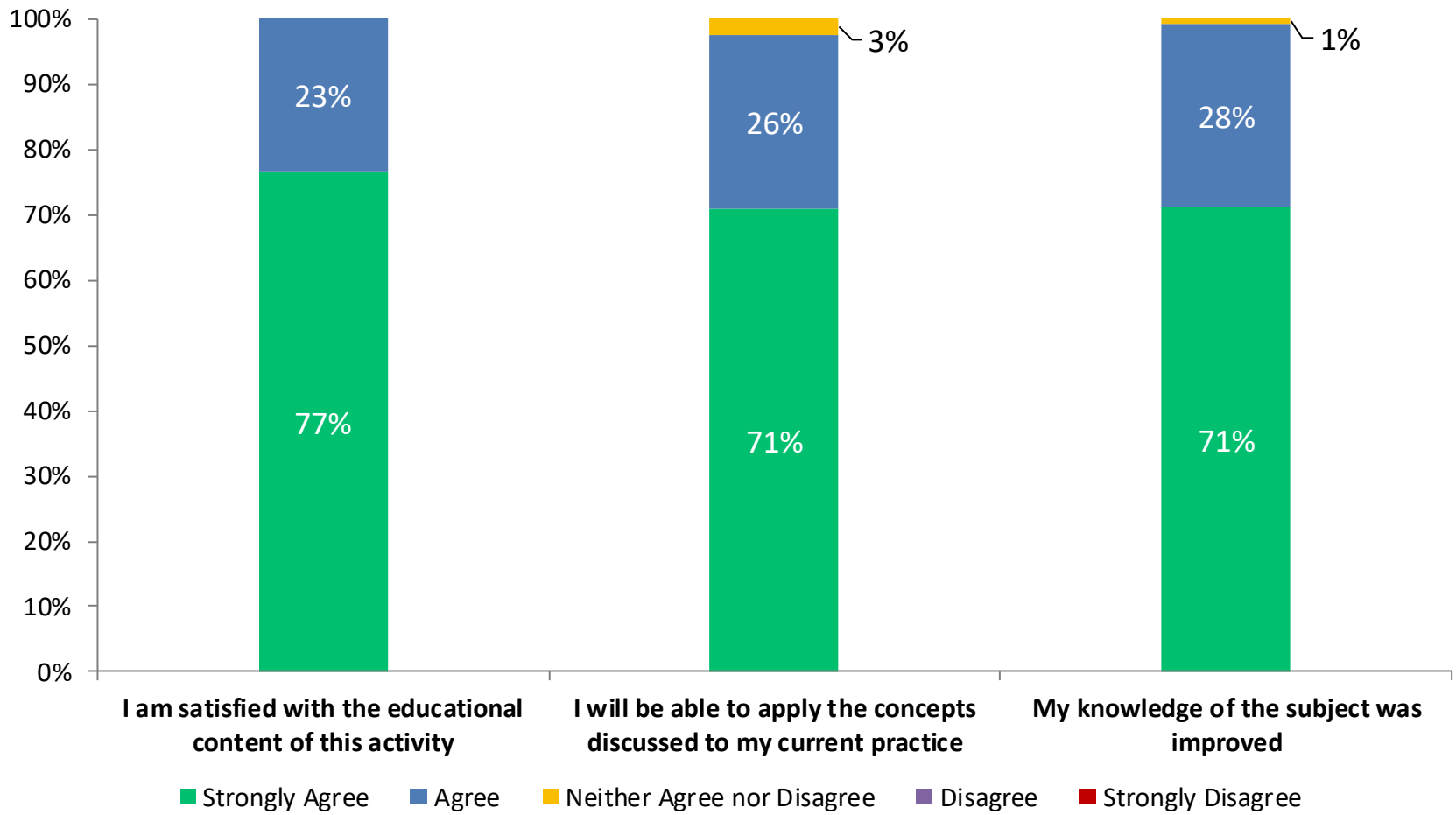
Department of Health

Office of Health Insurance Programs



Antibiotic Stewardship Home Study Participant Survey Responses

n=116



Department of Health

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Looking Ahead

- Develop an expanded library of programming:
 - Hyperlipidemia
 - Diabetes
- Examine participant feedback for information about requested topics, learning preferences, and/or delivery methods



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Conclusion

- NYSMPEP serves as a resource for NYS Medicaid prescribers
- Contact: pep@nysdoh.suny.edu
- Learn more: nypep.nysdoh.suny.edu



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Hepatitis C Direct-Acting Antiviral (DAA) Agents Pharmacy Program Update

December 15, 2022

DURB Meeting

Purpose

- Discuss the NYS Medicaid Drug Utilization Review Board (DURB) actions related to the hepatitis C direct-acting antiviral (DAA) agents.
- Evaluate the utilization of the hepatitis C DAA agents in the Medicaid program.

Background

- The hepatitis C virus (HCV) is a bloodborne virus that is primarily transmitted by parenteral exposures to infectious blood or body fluids that contain blood.
- Exposure can occur as the result of:
 - Injection drug use (IDU): In the United States (US) IDU is estimated to account for 60% of the acute hepatitis cases and is the most common mode of HCV transmission,
 - Receipt of donated blood, blood products, and organs (blood screening became available in 1992 in the US),
 - Receipt of clotting factor concentrates before 1987,
 - Long-term hemodialysis,
 - Needlestick injuries in health care settings, or
 - Birth to an HCV-infected mother.

HCV US Statistics

- During 2013-2016, an estimated 2.4 million United States (US) adults were living with chronic HCV infection.
- In 2019 the Centers for Disease Control and Prevention (CDC) reported:
 - Acute infections were estimated at 57,500 cases (95% Bootstrap Confidence Interval: 45,500–196,000).
 - From 2012 to 2019, the number of acute HCV cases per year increased by 133%.
 - The most rapid increase in the incidence of acute HCV infections was in people 20 to 39 years of age who inject drugs.
 - A total of 123,312 new chronic hepatitis C cases were reported during 2019.

Management of HCV DAA Agents

NYS Standardized Clinical HCV Criteria Development: 2014

- A workgroup comprised of representatives from all NYS Medicaid Managed Care Organizations (MCOs), NYS Department of Health Office of Health Insurance Programs (OHIP), the NYS AIDS Institute, and practitioners who are involved in the treatment of chronic HCV infection was convened to develop evidence-based, standardized, clinical criteria for DAA agents utilized for the treatment of chronic HCV infection.
- The clinical criteria were based on guidance released by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA).

HCV DURB History

- **September 2014 DURB meeting/ Implemented October 2014:** DAA clinical criteria were approved that included disease prognosis and severity criteria as outlined below:
 - Patients had to have evidence of stage 3 or 4 hepatic fibrosis defined as:
 - Liver biopsy confirming a METAVIR score F3 or F4
 - Fibroscan® score ≥ 9.5 kPa
 - FibroSure® ≥ 5.8
 - APRI ≥ 1.5
 - Radiological imaging consistent with cirrhosis (e.g., evidence of portal hypertension) **OR**
 - Evidence of extra-hepatic manifestation of HCV, such as type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (e.g., vasculitis) or kidney disease (e.g., proteinuria, nephrotic syndrome or membranoproliferative glomerulonephritis). Documentation of the presence of extra-hepatic manifestation based on lab results or imaging results (e.g., CBC, erythrocyte sedimentation rate (ESR)/ C-reactive protein (CRP), urinalysis, BUN/ creatinine and angiography) must be submitted **OR**
 - Liver transplant **OR**
 - HIV-1 co-infection **OR**
 - Chronic hepatitis B co-infection **OR**
 - Other coexistent liver disease (e.g., nonalcoholic steatohepatitis/nonalcoholic fatty liver disease) **OR**
 - Type 2 diabetes mellitus (insulin resistant) **OR**
 - Porphyria cutanea tarda **OR**
 - Debilitating fatigue impacting quality of life (e.g., secondary to extra-hepatic manifestations and/or liver disease)

HCV DURB History

- **February 2015 DURB/ Implemented April 2015:** Viekira® Pak received preferred status on the Preferred Drug List (PDL) and as a result, Viekira® Pak was excluded from the HCV clinical criteria addressing disease prognosis and severity.
- **April 2016 DURB/ Implemented May 2016:** The clinical criteria were updated to remove the disease prognosis and severity clinical criteria for preferred and non-preferred DAA agents.
- **October 2017 DURB/ Implemented December 2017:** Epclusa®, Mavyret®, ribavirin, and Vosevi® received preferred status on the PDL.
- **March 2018 Governor's Initiative/ Implemented August 2018:** DAA prescriber experience and training clinical criteria were removed.
- **July 2020 DURB/ Implemented October 2020:** Removal of prior authorization for HCV DAA agents prescribed to persons not previously treated for HCV.

Current HCV DAA Agents Clinical Criteria for Members Requiring Retreatment

1. Patient demographics
2. Confirmation of chronic hepatitis C diagnosis
 - HCV genotypic testing
 - Baseline HCV RNA PCR (viral load) testing
 - Cirrhosis status
 - Hepatic laboratory testing completed at baseline
 - Screening for hepatitis B infection
 - Negative pregnancy test (for patients receiving ribavirin)
3. HCV treatment history
4. Treatment readiness
5. Retreatment/ Reinfection

Note: The [Hepatitis C Worksheet](#), outlining the clinical criteria, is available for providers.

Retrospective DAA Drug Utilization Review

Methods

- Retrospective evaluation of pharmacy and medical claims was conducted utilizing the Medicaid Data Warehouse (MDW).
- Note: When the claims or members count is in the range of 1 to 30, the value must be reported as ≤ 30 per *the Medicaid Confidential Data Cell Size Policy*.

Treatment of Chronic HCV

Timeframe: 6/1/2011 – 7/31/2022

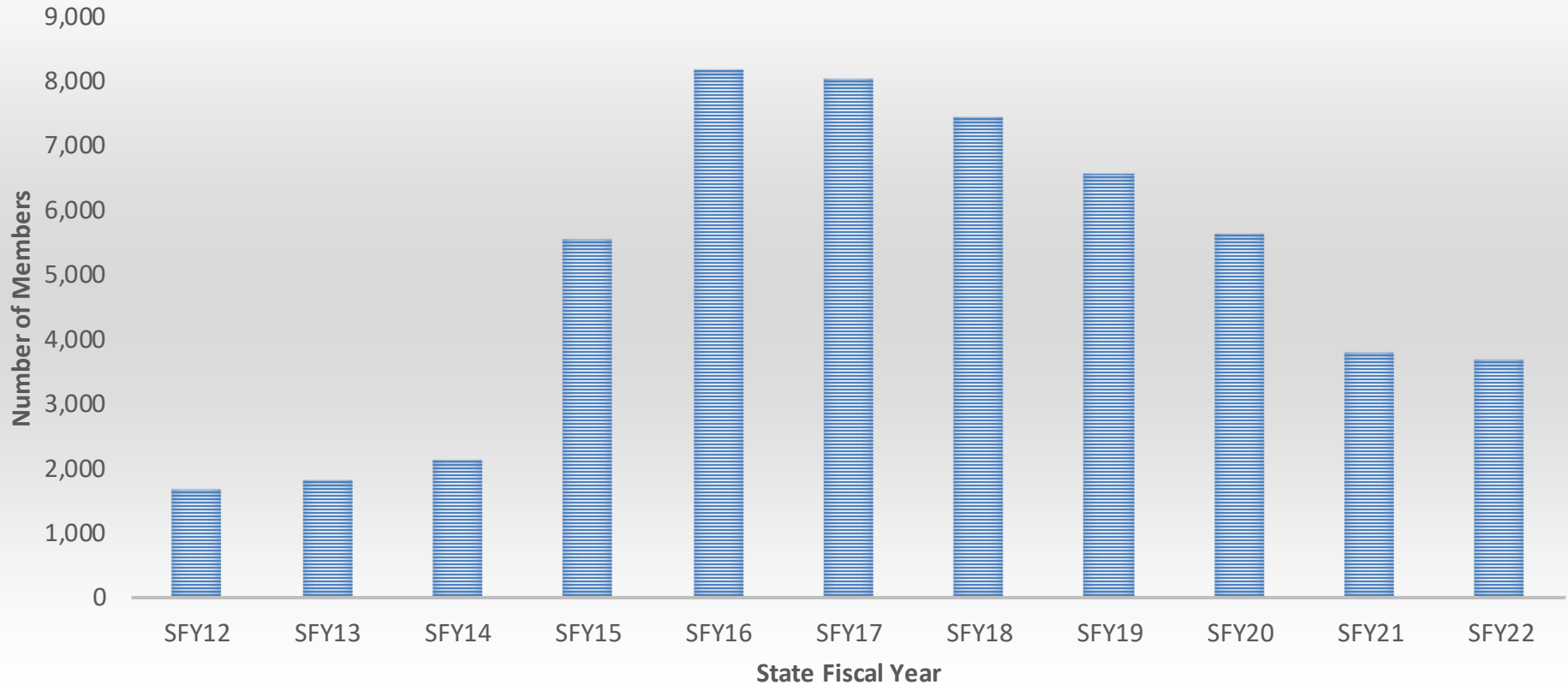
Variable	FFS+MC	FFS*	MC*
Number of Unique Members	44,638	5,094	41,506
Percentage of Members	100.0%	11.4%	93.0%
Number of Claims	140,832	12,175	128,657
Percentage of Claims	100.0%	8.6%	91.4%

FFS= fee-for-service, MC= managed care

*Not additive

- Telaprevir (Incivek®) and boceprevir (Victrelis®), NS3/4A protease inhibitors (PI), were approved 2nd quarter 2011.
- Telaprevir and boceprevir have been discontinued.
 - Telaprevir in 10/2014 and
 - Boceprevir in 12/2015.

NUMBER OF MEMBERS UTILIZING A HCV DAA AGENTS BY SFY (FFS+MC)



Viekira® Pak was excluded from disease prognosis and severity criteria.

April 2015

Disease prognosis and severity criteria were removed for preferred and nonpreferred HCV DAA agents.

May 2016

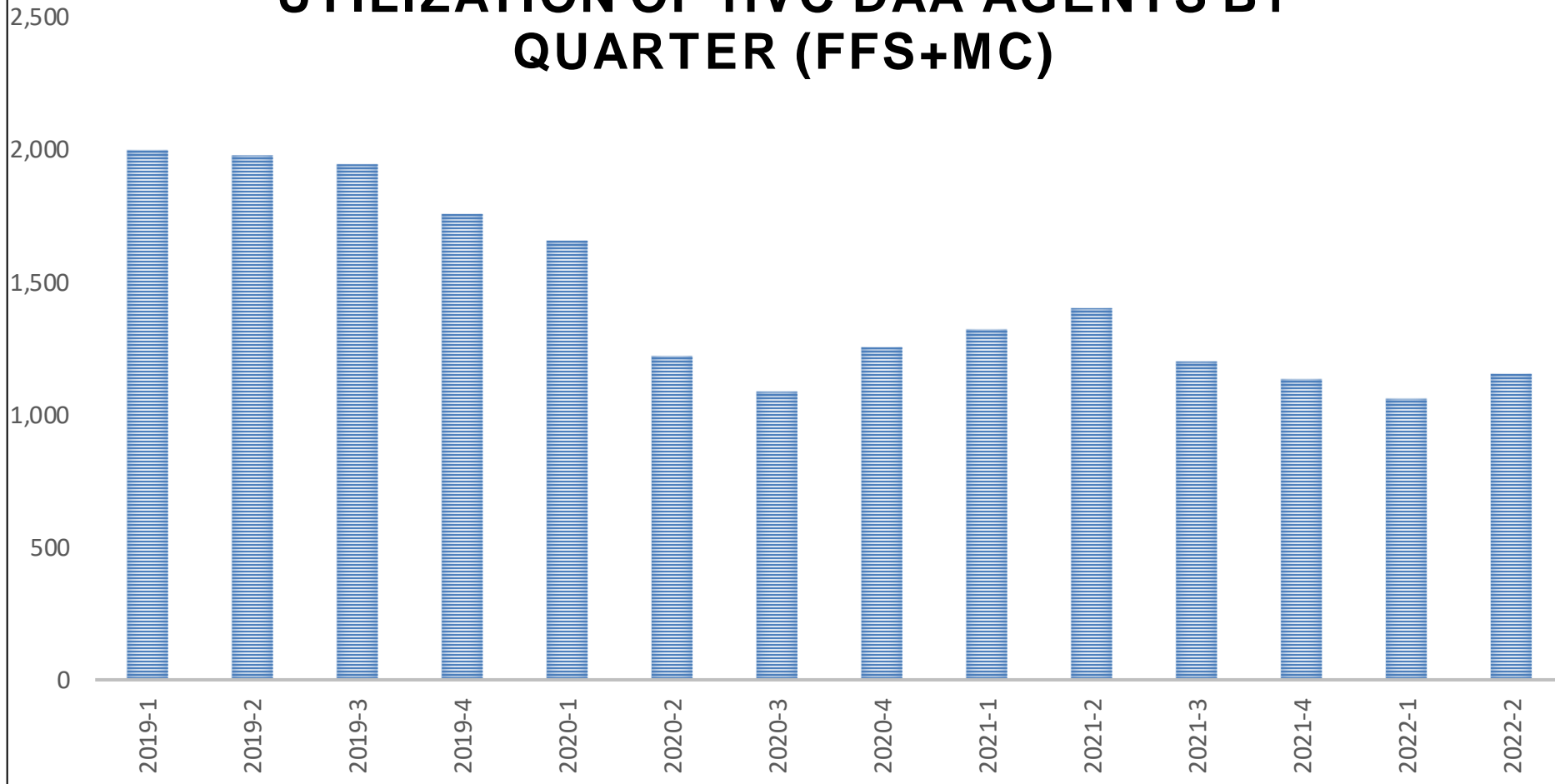
DAA prescriber experience training criteria were removed.

August 2018

Removal of PA for HCV DAA agents for persons not previously treated for HCV.

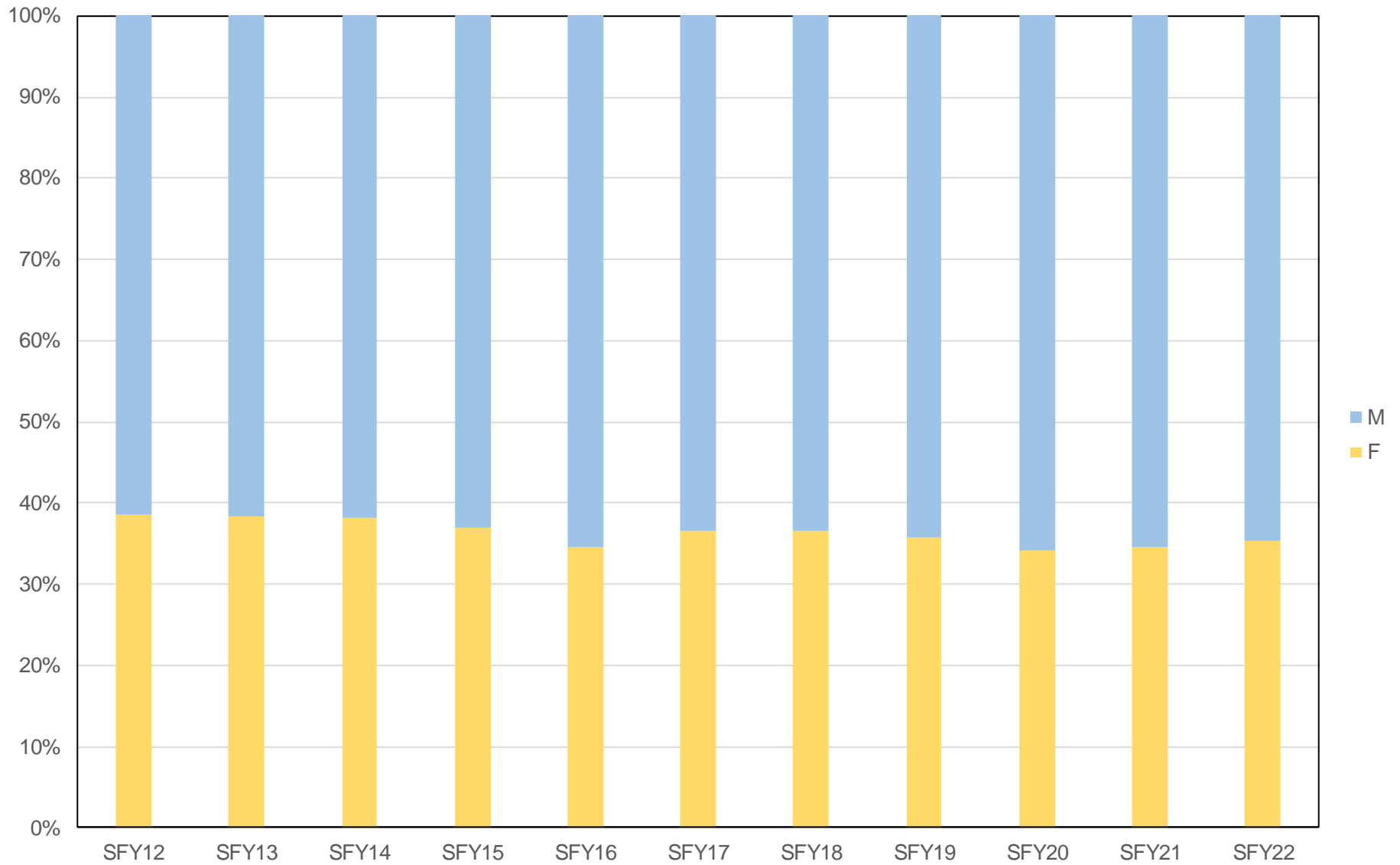
October 2020

IMPACT OF THE PANDEMIC ON MEMBERS UTILIZATION OF HVC DAA AGENTS BY QUARTER (FFS+MC)

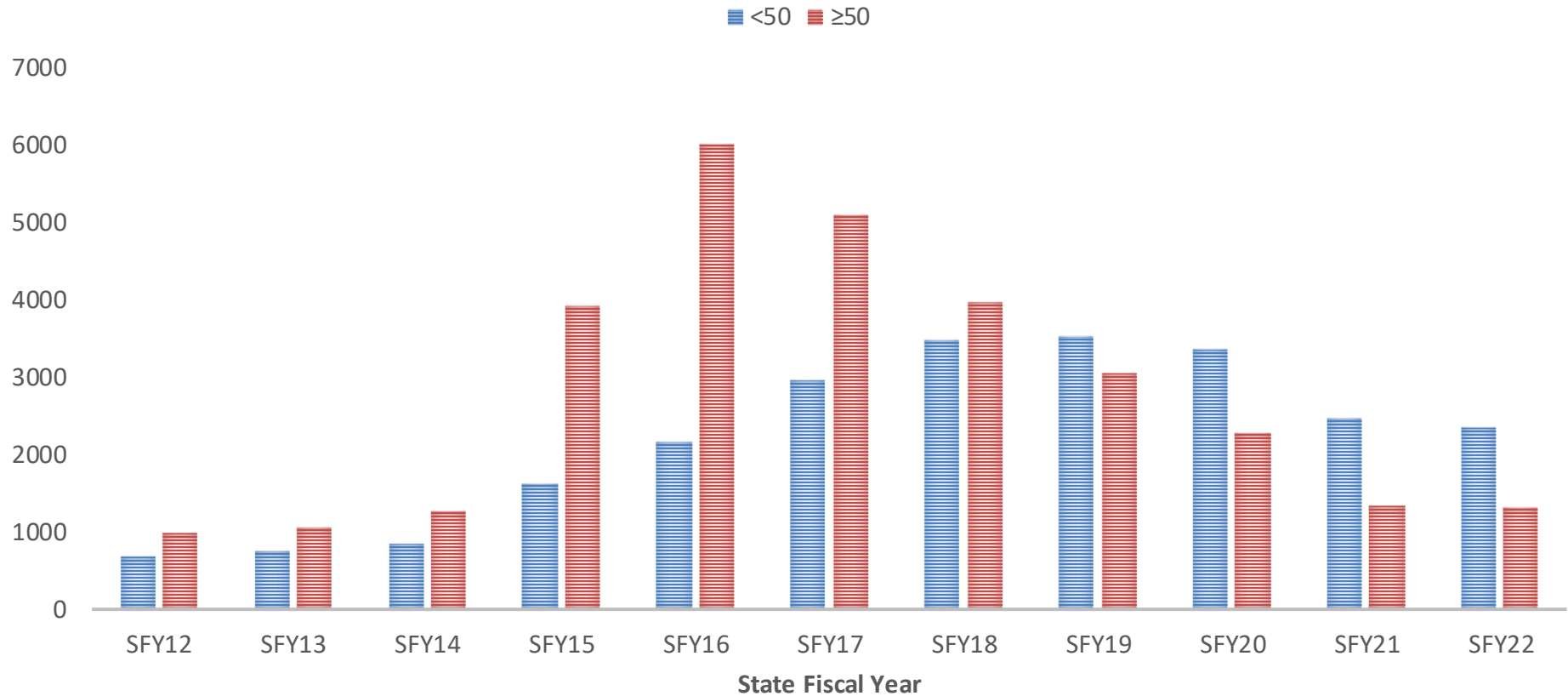


- March 1, 2020: First Coronavirus Disease 2019 (COVID-19) case in New York City (NYC).
- March 22, 2020: NYS on Pause Program begins.
- June 8, 2020: NYC begins Phase 1 reopening.
- July 19, 2020: NYC begins Phase 4 reopening.

GENDER OF MEMBERS UTILIZING HCV DAA AGENTS (FFS+MC)

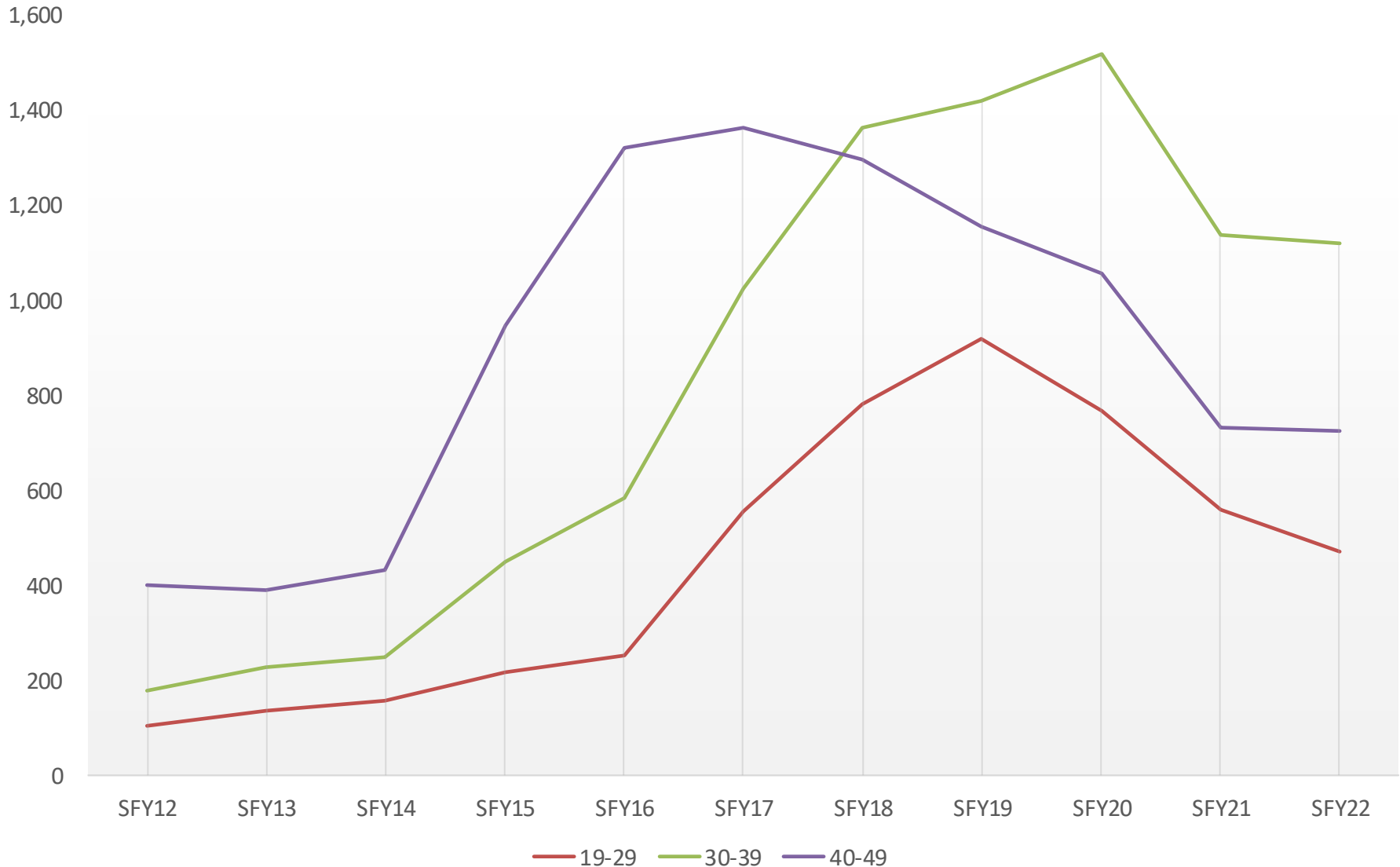


UTILIZATION OF HCV DAA AGENTS BY AGE (FFS+MC)



- Enacted January 1, 2014, Section 2171 of the NYS Public Health Law requires an HCV screening test be offered to individuals born between 1945 and 1965 when receiving health services in a hospital, freestanding diagnostic and treatment center or from a physician, physician assistant, or nurse practitioner providing primary care.
- The CDC updated their 2012 recommendations for hepatitis C screening among adults in April 2020. The 2020 update recommended screening patients ≥ 18 years of age.

UTILIZATION OF HCV DAA AGENTS IN MEMBERS LESS THAN 50 YEARS OF AGE (FFS+MC)



HCV DAA Therapy Restarted within 365 Days (FFS+MC)

- A restart of therapy was defined as an ≥ 8 -week (56 days) gap between HCV DAA claims.
- Results for SFY 2021 and SFY 2022:
 - 3.9% of members receiving HCV DAA therapy were restarted within 365 days.
 - Of the patients who restarted HCV DAA therapy within 365 days, 48.1% were treated within < 56 days.
 - $> 70\%$ of members restarting therapy within 56 days received the same DAA agent.

Summary

Utilization of DAA Agents	<ul style="list-style-type: none"> • Since June 2011, 44,638 unique members have been treated for chronic HCV disease.
Utilization of DAA agents by SFY	<ul style="list-style-type: none"> • Utilization peaked in SFY 2016 with 8,179 members receiving treatment. • Utilization in SFY 2021 could have potentially been impacted by the COVID-19 Pandemic.
Demographics	<ul style="list-style-type: none"> • Most of the members receiving HCV DAA treatment were males. • For members ≥ 50 years of age, HCV DAA utilization has declined annually since SFY 2019. • For members <50 years of age, HCV DAA utilization has increased annually from SFY 2012 through SFY 2019.
Members restarting treatment within 1 year	<ul style="list-style-type: none"> • In SFY 2021 and SFY 2022, 3.9% of members restarted treatment with an HCV DAA agent within 365 days. • Of the members restarting HCV DAA treatment within <56 days, most members ($>70.0\%$) received the same DAA agents.
Clinical Criteria	<ul style="list-style-type: none"> • No changes to the current clinical criteria are recommended. • Continue to monitor the use of HCV DAA agents and report results to the DURB annually.

COVID= coronavirus disease, DURB= Drug Utilization Review Board, DAA= direct-acting antiviral, HCV= hepatitis C virus, SFY= state fiscal year

Questions