APPENDICES

Hydroxyprogesterone Caproate (Makena) for Reducing the Risk of Preterm Birth

TABLE OF CONTENTS

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 *Hydroxyprogesterone Caproate (Makena) for Reducing the Risk of Preterm Birth*. The brief and the associated appendix provide information on: the estimated prevalence of target diagnoses (the accelerated approval drug's indication[s]) among Medicaid members; the clinical trial population used to support FDA approval, and how similar it is to Medicaid members overall; and 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, 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 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 within 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. 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.

Identification of Hydroxyprogesterone Caproate Claims

We identified members using hydroxyprogesterone caproate (HPC) based on the National Drug Codes (NDCs) and procedure codes in pharmacy and outpatient claims (Exhibit A). We searched for any claim with these codes in records for 2019 through 2021 for all nondually enrolled members who were enrolled to Medicaid at any point in these 3 years. We only included members who were identified as female and were aged 16 to 49 years in our final analysis cohort. Because the procedure codes in outpatient claims in Illinois and New York were identified as having unusable data quality by the DQ Atlas in all 3 years of analysis, we excluded these states from our analysis.[1]

We required outpatient claims to have both the relevant procedure codes and an NDC code for an HPC. Nearly 15% of the outpatient claims with a procedure code listed in Exhibit A had a missing NDC code. We excluded these claims as it is possible for some of these procedure codes to be used for coding of other treatments. This exclusion may have resulted in underestimation of prevalence and cost of HPC use. We considered this possibility of undercounting of HPC claims while calculating the upper bound for our cost estimates.

Procedure codes and National Drug Codes (NDCs) identifying HPC claims

- Procedure codes (considered an HPC claim when any of the NDCs listed is also included)
  - Healthcare Common Procedure Coding System (HCPCS): J1725, J1726, J1729, J2675 with modifier "TH," J3490 with modifier "TH," Q9985, Q9986
  - Current Procedural Terminology (CPT): 96372
- NDCs
  - Makena: 64011024301, 64011024302, 64011024702, 64011030103
  - Generic: 00517176701, 00517179101, 38779210203, 38779210204, 38779210205, 38779210208, 38779210209, 49452363902, 49452363903, 49452363906, 51552102802, 51552102805, 51552102807, 51927273300, 55150030901, 55150031001, 62559054015, 62991203401, 62991203402, 62991203403, 62991203404, 63370010550, 66993003883, 66993003901, 67457088605, 67457096701, 69238179701, 71052020005, 71225010401, 71225010501

Comorbid Conditions

We used the Chronic Disability Payment System (CDPS) algorithm to identify prevalence of affected body systems and relevant comorbidities in the cohort of women with HPC claims.[3] The CDPS uses a hierarchical method to classify members into risk groups by body system using ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th Revision) diagnosis codes in medical claims. There are multiple risk groups per body system; a member may only be assigned to 1 risk group. Once categorized, we aggregated risk groups into whole-system categories (e.g., cardiovascular, pulmonary). Additional comorbidities of interest were determined using relevant

peer-reviewed literature describing conditions pertinent to the health of pregnant women and in consultation with medical experts.[4-6] Comorbidities were identified in medical claims using ICD-10 diagnosis codes, where an instance of a code from the determined value set was indicative of presence of a condition.

We identified pregnancy status of members with HPC claims based on diagnosis and procedure codes in their outpatient and inpatient claims using the method published by CMS.[7]

Cost Estimates

The cost estimates represent the estimated total national Medicaid spending on HPC, broken down by Makena and generic HPC. We estimated costs by first calculating total quantity using the total number of days-supply in pharmacy claims for each formulation and by assuming each outpatient claim represented a weekly injection. We then converted total quantity into a dollar cost using the average per-mL price of $803 for Makena and $20 per weekly injection for generic HPCs. These are the prices mentioned in the news articles.[8-10] This Makena price also was listed in at least 1 state's Wholesale Acquisition Cost report for the subcutaneous injection, which represents 97% of all Makena claims.[11] We applied the statutorily required 23.1% rebate to these prices.[12]

The 5 states excluded from the analyses due to data availability or data quality issues (as discussed above: Alabama, Illinois, Mississippi, New York, and Utah) are included in the national cost estimates, using the estimated HPC usage rate and use patterns (e.g., proportion of Makena to generic, average quantity per user) 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 or consider cost implications of treatment effectiveness in terms of reduced health care service use or mortality.

We performed sensitivity analyses using Monte Carlo simulations, taking into consideration uncertainty in the model inputs, and reporting the range which contained 95% of the simulated cost values as the confidence bounds for our cost estimate. The lower bound considers lower price for both Makena and generic HPC ($690 and $10, respectively) and corrects for known data quality issues in some states (i.e., overreporting of outpatient claims in Massachusetts and New Jersey), and assumes the lowest usage observed in other states for the states with missing data, rather than the national average rate. The upper bound, on the other hand, considers higher prices ($1,500 for Makena and $40 for generic HPC) and higher usage inputs assuming the outpatient claims with the relevant procedure codes but missing NDCs are HPC claims. It also corrects for known underreporting in pharmacy claims (i.e., low claims volume in North Carolina and high rate of missing NDC codes in pharmacy claims in Arkansas and Florida) and uses the highest usage observed in other states for the those with missing data, rather than the national average.

Our estimate of the state versus federal breakdown of the costs is based on the enrollment composition of members with HPC claims in CHIP and Medicaid expansion. We calculated the weighted national average federal matching rates for each year based on the state federal match rates, weighted by the percentage of members with HPC claims in each corresponding enrollment category in each state each year. For the states with unusable data quality for identifying CHIP enrollment, we used the average percentage of CHIP enrollment in other states. Similarly, for expansion states with unusable data quality for identifying Medicaid adult expansion enrollment, we used the average of adult expansion enrollment share in other expansion states.

Limitations

Our cost estimates are based on the HPC claims we identified using the code set given in Exhibit A. The accuracy of our analysis depends on the completeness of the code set used and the accuracy and reliability of the procedure codes and NDCs recorded in the data, as well as enrollment and demographic information (e.g., dual enrollment, age) provided for each member.

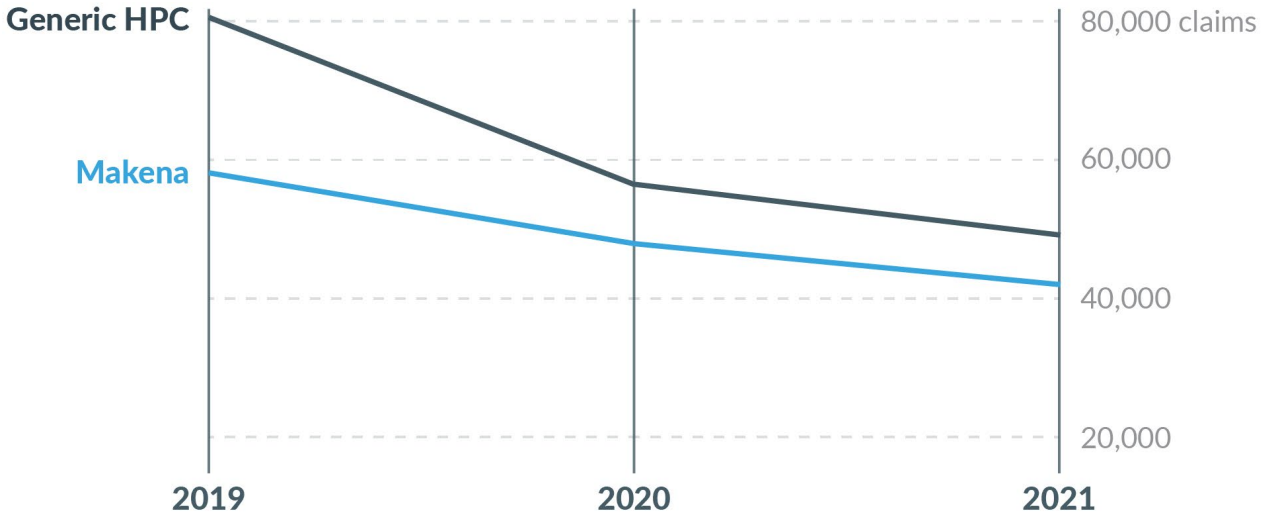
For the 5 states excluded due to data availability or data quality issues (Alabama, Illinois, Mississippi, New York, and Utah), our cost estimates assume that HPC use rate and patterns in these states are similar to what is observed in other states. Our cost estimates do not include supplemental rebates, 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

HYDROXYPROGESTERONE CAPROATE CLAIMS

EXHIBIT B

Number of HPC claims among female Medicaid members aged 16 to 49 years over time by type, 2019-2021



Abbreviation. HPC: hydroxyprogesterone caproate.

APPENDIX C

DEMOGRAPHIC INFORMATION

EXHIBIT C

Availability of demographic information for Medicaid members included in analyses, 2019-2021

	Members with at least 1 HPC claim	%	Members with at least 1 Makena claim	%	Members with at least 1 generic claim	%
Total	*66,260*	-	*36,550*	-	*34,683*	-
Race or ethnicity available	48,488	73.2	26,688	73.0	25,226	72.7
Race or ethnicity not reported[a]	15,736	23.7	8,602	23.5	8,531	24.6
Race or ethnicity missing[b]	2,036	3.1	1,260	3.4	926	2.7

Notes. Only Medicaid members aged 18 to 64 years were included in our analyses. [a] We did not report race and ethnicity from states that had unusable or high-concern data quality for race and ethnicity information, including Arizona, Connecticut, District of Columbia, Iowa, Louisiana, Massachusetts, New York, Oregon, Rhode Island, South Carolina, Tennessee, and Wyoming in all years; Arkansas, Colorado, Kansas, Maryland, and Missouri in 2019 and 2020; and Montana and West Virginia in 2019. [b] Missing in states for which race and ethnicity data is reported.

APPENDIX D

MEDICAID MEMBERS WITH AND WITHOUT CLAIMS FOR HPC, 2019-2021

EXHIBIT D

Female Medicaid members aged 16 to 49 years with at least 1 claim for HPC, 2019-2021

	2021			2020			2019		
State	HPC use rate (per 10,000 members)[c]	share of Makena, % of all HPC users	share of generic HPC, % of all HPC users	HPC use rate (per 10,000 members)[c]	share of Makena, % of all HPC users	share of generic HPC, % of all HPC users	HPC use rate (per 10,000 members)[c]	share of Makena, % of all HPC users	share of generic HPC, % of all HPC users
United States	10	57	48	13	57	48	18	50	57
Alabama[a]	--	--	--	--	--	--	--	--	--
Alaska	3	58	--	7	57	50	12	64	46
Arizona	5	95	7	9	90	13	13	75	32
Arkansas	1	55	45	3	83	26	--	--	--
California	6	56	51	6	57	49	8	55	51
Colorado	3	78	23	4	67	37	9	65	41
Connecticut	12	58	53	15	44	77	22	47	73
Delaware	11	96	--	23	93	9	27	96	11
District of Columbia[b]	12	--	--	14	--	93	22	28	84
Florida	10	80	22	16	84	19	22	77	27
Georgia	10	30	72	21	29	75	28	23	80
Hawaii[b]	2	--	95	3	--	91	3	--	73
Idaho[b]	5	--	94	6	--	83	20	18	88
Illinois[a]	--	--	--	--	--	--	--	--	--
Indiana	12	83	23	19	78	29	24	72	35
Iowa	8	52	52	12	48	55	21	42	72
Kansas	14	27	77	29	33	70	32	42	62
Kentucky	6	44	57	10	54	48	15	34	67

State	2021 HPC use rate (per 10,000 members)[c]	2021 share of Makena, % of all HPC users	2021 share of generic HPC, % of all HPC users	2020 HPC use rate (per 10,000 members)[c]	2020 share of Makena, % of all HPC users	2020 share of generic HPC, % of all HPC users	2019 HPC use rate (per 10,000 members)[c]	2019 share of Makena, % of all HPC users	2019 share of generic HPC, % of all HPC users
Louisiana	22	39	65	27	50	56	31	49	61
Maine	6	62	46	9	61	53	18	59	56
Maryland	14	53	54	19	51	56	24	51	58
Massachusetts	6	27	78	9	26	82	15	30	76
Michigan	7	15	90	10	17	89	14	16	90
Minnesota	8	20	88	11	19	87	15	27	88
Mississippi[a]	--	--	--	--	--	--	--	--	--
Missouri[b]	10	99	--	20	98	3	35	85	22
Montana[b]	2	--	74	4	--	84	11	42	77
Nebraska	10	87	14	18	89	14	33	78	32
Nevada	6	31	69	8	41	62	11	46	59
New Hampshire[b]	3	89	--	8	68	43	17	63	47
New Jersey	6	24	77	9	34	68	13	30	75
New Mexico	7	20	84	6	33	73	7	53	80
New York[a]	--	--	--	--	--	--	--	--	--
North Carolina	8	69	37	4	67	35	1	42	63
North Dakota	10	50	60	14	57	57	23	46	64
Ohio	18	25	80	22	30	77	28	32	76
Oklahoma	13	66	35	21	65	38	35	56	47
Oregon	3	14	89	6	23	79	10	21	84
Pennsylvania	13	56	46	16	51	54	25	36	67
Rhode Island	10	24	91	10	38	89	12	42	74
South Carolina	10	38	66	16	41	63	25	43	64
South Dakota[b]	10	--	93	21	--	86	24	--	89
Tennessee	15	72	33	19	73	32	17	73	33

State	2021 HPC use rate (per 10,000 members)[c]	2021 share of Makena, % of all HPC users	2021 share of generic HPC, % of all HPC users	2020 HPC use rate (per 10,000 members)[c]	2020 share of Makena, % of all HPC users	2020 share of generic HPC, % of all HPC users	2019 HPC use rate (per 10,000 members)[c]	2019 share of Makena, % of all HPC users	2019 share of generic HPC, % of all HPC users
Texas	24	87	18	31	81	26	57	56	50
Utah[a]	--	--	--	--	--	--	--	--	--
Vermont[b]	3	--	--	6	--	--	12	98	--
Virginia	8	86	20	11	83	19	13	75	29
Washington	6	18	87	8	19	86	13	24	82
West Virginia[b]	11	96	--	32	99	--	29	97	3
Wisconsin	9	14	90	13	19	87	21	39	74
Wyoming[b]	9	--	--	15	--	67	23	55	61

Notes. [a] Data not available; [b] Suppressed (N < 11); [c] Per 10,000 female members aged 16 to 49 years.
Abbreviation. HPC: hydroxyprogesterone caproate.

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