APPENDICES

Tisotumab Vedotin (Tivdak) for Cervical Cancer

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The Medicaid Evidence and Review of Cost Initiative (MERCI) describes policy considerations for drugs approved by the US Food and Drug Administration (FDA) through the accelerated approval pathway. This document is the appendix of a brief titled *Tisotumab Vedotin (Tivdak) for Cervical Cancer*. 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 projected 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, as these states do not submit claim information related to dual enrollment status using this method. Cohorts for analysis were anchored in the most recent year of data available (2021), with preceding years used to maintain internal validity for diagnosis and service-use identification, based on established methods specific to the indication of interest. Other sources informing 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, the Medicaid Data Quality (DQ) Atlas was used as a reference.[1] In general, if the DQ Atlas identified a state's data as unusable for a topic, variable, or year, that state was eliminated from analysis. If a state's data were of high concern, we investigated further 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 towards under-reporting (as opposed to over-reporting). 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 which 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 1 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. Thus, 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. In the brief, 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 where matching is based only on age
- Drug uptake, if applicable

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

Illinois Claims

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

Reporting of Data

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

Prevalence Estimates

We identified members with cervical cancer based on having at least 1 inpatient claim or 2 outpatient claims with an ICD-10 (International Classification of Diseases, 10th revision) diagnosis code C53 in the past 3 years. A member was classified as having recurrent or metastatic cervical cancer if they also had at least 1 claim for a systemic treatment for cervical cancer on the same date, or after the first cervical diagnosis code excluding treatments that occurred within 60 days of any radiation therapy or a relevant surgery of female genital system. This method and the list of systemic treatments are based on other studies in existing literature.[3-5]

Matched Comparison Group

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

Comorbid Conditions

We used the Chronic Disability Payment System (CDPS) algorithm to identify prevalence of affected body systems and relevant comorbidities in the cervical cancer cohort and matched comparisons.[6] The CDPS has a hierarchical method to classify members into risk groups by body system using ICD-10 diagnosis codes in medical claims. There are multiple risk groups per body system, and a member may only belong to 1 risk group per body system. Once categorized, we aggregated risk groups into whole-system categories (e.g., cardiovascular, pulmonary).

Health Care Service Use

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

Cost Estimates

The cost estimates represent the projected annual total national costs associated with covering tisotumab vedotin-tftv for treatment of Medicaid members with recurrent or metastatic cervical cancer. There is no diagnosis code specific to the stage or progression of the disease in the claims. Accordingly, we identified recurrent and metastatic cervical cancer patients using the methods in the literature as described above for diagnosis and procedure codes, as well as the National Drug Codes (NDCs) reported in inpatient, outpatient, and pharmacy claims. Due to data quality issues in outpatient procedure codes in Illinois and New York, we excluded those 2 states from this analysis. These 2 states and the other 3 states excluded due to other data quality issues (Alabama, Mississippi, and Utah) are included in the national cost estimates, with the estimated patient populations set at the average prevalence rate in other states.

We then assumed 38% of recurrent and metastatic cervical cancer patients get a second-line treatment based on the percentage of such patients previously reported for Medicaid.[4] We were unable to use real uptake data for uptake rates because tisotumab vedotin-tftv was approved towards the end of our study period (late September 2021) and there were only few Medicaid claims for this treatment in 2021. Instead, we assumed that 20% of those who receive second-line treatment for cervical cancer will get tisotumab vedotin-tftv, based on the uptake rates reported for other second-line treatments in the literature.[3,7,8] We combined prevalence and drug uptake rates with current wholesale acquisition cost for the drug along with statutorily required rebate percentages to calculate total annual costs. All model inputs and justifications are summarized in Exhibit A1.

EXHIBIT A1

Cost modeling inputs for recurrent or metastatic cervical cancer patients

Input name	Input	Source	Sensitivity analysis bounds
Prevalence/uptake			
Prevalence of recurrent or metastatic cervical cancer (# members)[a]	6,792	Data	5,944 to 7,720
% recurrent or metastatic cervical cancer patients receiving second-line treatment	38%	Leath et al. 2023[4]	5% to 60%
Uptake (% using the drug)	20%	Musa et al. 2023[3], Leath et al. 2023[7]	5% to 45%
Drug cost			
Annual drug cost (WAC)	$466,208	IPD Analytics[9]	--
Federal rebates[b]	23.1%	SSA §1927(c)(1)(B)(i)[10]	--
Treatment duration			
Average treatment duration (months)	3.5	Musa et al. 2023[3], Leath et al. 2023[7]	1 month to 7 months

Notes. [a] Includes estimated patient populations in Alabama, Illinois, Mississippi, New York, and Utah, at the national prevalence rate. [b] Number sourced from T-MSIS data. [b] Does not include state-negotiated supplemental rebates.
Abbreviations. SSA: Social Security Administration; WAC: wholesale acquisition cost.

As our focus is direct drug costs, we did not include the costs of drug dispensing and monitoring. Due to lack of published data, we also did not include cost offsets associated with replacement of treatment-as-usual or cost implications of treatment effectiveness in terms of recovery, reduced health care service use, or mortality.

We performed sensitivity analyses using Monte Carlo simulations, considering uncertainty in the model inputs and reporting the range that contained 95% of the simulated cost values as the confidence bounds for our cost estimate. The lower bound for prevalence has a 6-month full enrollment requirement from the first cervical diagnosis code, corrects for known data quality issues in some states (i.e., overreporting in Massachusetts and New Jersey), and assumes the lowest prevalence observed in other states for the states with missing data rather than the national average rate. The upper bound corrects for known underreporting of claims in Rhode Island and uses the highest prevalence observed in other states for the states with missing data, rather than the national average.

For 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 prevalence of cervical cancer and recurrent and metastatic cervical cancer identified in the claims data, and the reported percentage of patients who receive second-line treatment. Given that the TAF do not include clinical information relevant to identifying individuals eligible for tisotumab vedotin-tftv, we had to approximate the clinical indication using an approach based on claims data. The accuracy of our analysis depends on the completeness and reliability of the claims and the information recorded in the data (e.g., diagnosis and procedure codes in the inpatient and outpatient claims) as well as enrollment and demographic information (e.g., dual enrollment, age) for each member.

Similarly, identification of patients with prior treatment would be best accomplished with clinical information. When using claims data, identification of such patients is only an approximation and is contingent on complete and accurate data on procedure codes in the inpatient and outpatient claims, the NDC codes in pharmacy and outpatient claims, and entire history of treatments for each patient.

For the 3 states for which we have no data on cervical cancer prevalence (Alabama, Mississippi, and Utah), our cost estimates assume that recurrent and metastatic cervical cancer prevalence in these states are similar to that observed in other states. For the 2 states for which we have cervical prevalence data but none on recurrent and metastatic cervical cancer, our cost estimates assume the percentages of recurrent and metastatic cervical cancer patients within the larger cervical cancer patient cohorts in these states are similar to other states. Our cost estimates do not include supplemental rebates, and the estimated total cost is broken down by state and federal share without any consideration for third-party liability or other insurance payments.

APPENDIX B

DEMOGRAPHIC INFORMATION

EXHIBIT B1

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

	Members with recurrent or metastatic cervical cancer	%	Members with any cervical cancer	%	Members without cervical cancer	%
Total	*5,944*	-	*20,121*	-	*26,183,040*	-
Race or ethnicity available	4,556	76.6	14,429	71.7	18,435,018	70.4
Race or ethnicity not reported[a]	982	16.5	4,527	22.5	6,314,387	24.1
Race or ethnicity missing[b]	406	6.8	1,165	5.8	1,433,635	5.5

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. [b] Missing in states for which race and ethnicity data is reported.

APPENDIX C

MEDICAID MEMBERS WITH AND WITHOUT CERVICAL CANCER, 2021

EXHIBIT C1

Medicaid members included in analyses, aged 18 to 64 with and without cervical cancer, 2021

State	Total Medicaid population	Members with recurrent or metastatic cervical cancer			Members with cervical cancer			Members without cervical cancer
		n	Per 10,000 members	%	n	Per 10,000 members	%	n
United States	26,203,160	5,944	2.3	0.02	20,121	7.7	0.08	26,183,039
Alabama[a]	--	--	--	--	--	--	--	--
Alaska	70,271	14	2.0	0.02	43	6.1	0.06	70,228
Arizona	675,252	139	2.1	0.02	477	7.1	0.07	674,775
Arkansas	309,816	60	1.9	0.02	175	5.6	0.06	309,641
California	5,118,789	1,047	2.0	0.02	3,468	6.8	0.07	5,115,321
Colorado	486,577	102	2.1	0.02	296	6.1	0.06	486,281
Connecticut	338,986	57	1.7	0.02	233	6.9	0.07	338,753
Delaware	86,675	16	1.8	0.02	54	6.2	0.06	86,621
District of Columbia	84,834	18	2.1	0.02	46	5.4	0.05	84,788
Florida	1,027,374	332	3.2	0.03	1,061	10.3	0.10	1,026,313
Georgia	582,359	255	4.4	0.04	552	9.5	0.09	581,807
Hawaii	127,928	28	2.2	0.02	87	6.8	0.07	127,841
Idaho	116,561	31	2.7	0.03	94	8.1	0.08	116,467
Illinois	1,030,076	--	--	--	796	7.7	0.08	1,029,280
Indiana	570,778	192	3.4	0.03	475	8.3	0.08	570,303
Iowa	228,974	53	2.3	0.02	159	6.9	0.07	228,815
Kansas	91,406	35	3.8	0.04	91	10.0	0.10	91,315
Kentucky	549,412	167	3.0	0.03	492	9.0	0.09	548,920
Louisiana	573,040	198	3.5	0.03	516	9.0	0.09	572,524

State	Total Medicaid population	Members with recurrent or metastatic cervical cancer			Members with cervical cancer			Members without cervical cancer
		n	Per 10,000 members	%	n	Per 10,000 members	%	n
Maine	115,146	28	2.4	0.02	66	5.7	0.06	115,080
Maryland	494,100	122	2.5	0.02	352	7.1	0.07	493,748
Massachusetts	619,593	70	1.1	0.01	317	5.1	0.05	619,276
Michigan	897,365	209	2.3	0.02	689	7.7	0.08	896,676
Minnesota	363,741	78	2.1	0.02	199	5.5	0.05	363,542
Mississippi[a]	--	--	--	--	--	--	--	--
Missouri	307,353	69	2.2	0.02	335	10.9	0.11	307,018
Montana	89,048	19	2.1	0.02	52	5.8	0.06	88,996
Nebraska	86,797	20	2.3	0.02	55	6.3	0.06	86,742
Nevada	252,701	83	3.3	0.03	245	9.7	0.10	252,456
New Hampshire	71,890	--	--	--	32	4.5	0.04	71,858
New Jersey	599,350	143	2.4	0.02	444	7.4	0.07	598,906
New Mexico	287,319	55	1.9	0.02	184	6.4	0.06	287,135
New York	2,223,692	--	--	--	1,607	7.2	0.07	2,222,085
North Carolina	737,232	160	2.2	0.02	422	5.7	0.06	736,810
North Dakota	32,754	--	--	--	25	7.6	0.08	32,729
Ohio	969,641	330	3.4	0.03	992	10.2	0.10	968,649
Oklahoma	298,761	115	3.8	0.04	269	9.0	0.09	298,492
Oregon	440,529	127	2.9	0.03	323	7.3	0.07	440,206
Pennsylvania	1,037,529	289	2.8	0.03	947	9.1	0.09	1,036,582
Rhode Island	108,130	17	1.6	0.02	71	6.6	0.07	108,059
South Carolina	411,411	114	2.8	0.03	280	6.8	0.07	411,131
South Dakota	25,645	13	5.1	0.05	21	8.2	0.08	25,624
Tennessee	470,758	153	3.3	0.03	390	8.3	0.08	470,368
Texas	1,334,952	527	3.9	0.04	1,422	10.7	0.11	1,333,530
Utah[a]	--	--	--	--	--	--	--	--

State	Total Medicaid population	Members with recurrent or metastatic cervical cancer			Members with cervical cancer			Members without cervical cancer
		n	Per 10,000 members	%	n	Per 10,000 members	%	n
Vermont	52,476	--	--	--	18	3.4	0.03	52,458
Virginia	581,914	127	2.2	0.02	374	6.4	0.06	581,540
Washington	617,466	153	2.5	0.02	420	6.8	0.07	617,046
West Virginia	193,942	72	3.7	0.04	179	9.2	0.09	193,763
Wisconsin	397,031	79	2.0	0.02	255	6.4	0.06	396,776
Wyoming	15,787	--	--	--	21	13.3	0.13	15,766

Notes. [a] Data not available.

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Suggested citation

Shaw B, Cil G, Burbank C, Yeddala S, Ryan J, Radley D, Stuard S. *Appendices: tisotumab vedotin-tftv (Tivdak) for cervical cancer.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2024.

Conflict of interest disclosure

No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

Funding and support

Research reported in this brief was supported by a grant from Arnold Ventures.

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