MEDICAID EVIDENCE REVIEW AND COST INITIATIVE BRIEF

Deferiprone (Ferriprox) for Transfusional Iron Overload

OVERVIEW

In 2011, the US Food and Drug Administration (FDA) granted deferiprone (branded as Ferriprox) accelerated approval as a treatment for transfusional iron overload.[1] A rare and potentially fatal condition, transfusional iron overload develops in individuals who receive repeated blood transfusions to treat certain causes of low red blood cell count, including thalassemia syndromes and sickle cell disease.[2-5] In our analysis of 81 million members enrolled in Medicaid from 2019 through 2021, we identified 429 members taking deferiprone for transfusional iron overload.

To treat iron buildup in the body caused by repeated blood transfusions, deferiprone (a chelator) binds with iron to help the body remove the excess iron.[6] Distributed through a specialty pharmacy, deferiprone was granted accelerated approval based on a blood biomarker (serum ferritin, a protein that correlates with iron levels in the body) as a surrogate clinical endpoint.[7-12] As a provision of the 2011 accelerated approval, the FDA required the completion by 2016 of a confirmatory trial to verify and describe clinical benefit of deferiprone.[1] The trial was completed[13] in 2019

MERCI Aims

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 brief provides 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).

MERCI analyses include national and state-level data where available to inform budget and policy decisions by state and federal policymakers.

and the manufacturer submitted final reports to the FDA in 2020.[14-16] In 2021, the FDA converted deferiprone to traditional approval, maintaining a black box warning for serious infections and death.[17,18] The confirmatory trial demonstrated that the efficacy of deferiprone was noninferior to a less costly, first-line, FDA-approved iron chelator with no black box warning.[19] Based on our analysis of Centers for Medicare & Medicaid Services (CMS) Transformed Medicaid Statistical Information System (T-MSIS) data, Medicaid spent $106.9 million to cover deferiprone for 429 Medicaid members from 2019 through 2021.

What Is Transfusional Iron Overload?

Transfusional iron overload (also called transfusional hemosiderosis) is a rare and potentially fatal disease that develops in individuals who receive repeated blood transfusions as part of treatment for underlying causes of a low red blood cell count.[2,24] Thalassemia syndromes and sickle cell disease are some of the conditions which result in red blood cell abnormalities leading to the cells' premature destruction, requiring repeated blood transfusions.[2-5]

For individuals requiring ongoing blood transfusions, iron levels may build up and become toxic over time.[24-27] Without a mechanism to remove this excess iron from the body, repeated blood transfusions result in the potentially fatal accumulation of iron deposits in tissues and organs.[24,26,27]

Complications of transfusional iron overload can vary from person to person.[2,27] Patients can develop diabetes, liver failure, severe heart problems, hormonal abnormalities, and joint damage

TRANSFUSIONAL IRON OVERLOAD and DEFERIPRONE

OVERVIEW

PREVALENCE

IN MEDICAID

429 beneficiaries had a claim for deferiprone between 2019 and 2021

DEFERIPRONE FACTS

DRUG PRICE PER PATIENT

$335,012 to $479,369 per year[20]

FDA ACCELERATED APPROVAL DATES

October 2011: 500-mg tablets (3 times per day)[1]
September 2015: 100-mg/mL oral solution (3 times per day)[21]
July 2019: 1,000-mg tablets (3 times per day)[22]
May 2020: 1,000-mg tablets (2 times per day)[23]

FDA TRADITIONAL APPROVAL DATE

April 2021[17,18]

MEDICAID COST ESTIMATES

PROJECTED ANNUAL COST TO MEDICAID

$86.8 million, with $52.4 million coming from federal funds and $34.4 million from state funds

Sources. Information sourced from IPD Analytics and the FDA websites, unless otherwise referenced. Estimates of costs to Medicaid are based on our analysis presented in the sections about potential Medicaid spending on deferiprone.
Abbreviations. FDA: US Food and Drug Administration.

(arthritis).[2,24,27] Heart damage (cardiomyopathy with heart failure) and liver damage (hepatitis, cirrhosis, or cancer) are typically the most severe complications and are the leading causes of death among individuals who receive repeated blood transfusions.[2,24,27]

Transfusional iron overload is a condition secondary to several rare diseases; not all individuals with the primary underlying diseases will receive recurring blood transfusions, and there are variations in how frequently individuals receive blood transfusions.[24] As a result, detailed calculations of transfusional iron overload prevalence in the US are not readily available but some estimates cap the number of affected individuals in the thousands.[28]

How Is Transfusional Iron Overload Managed?

Due to the risk of fatal organ damage, patients who receive repeated blood transfusions require ongoing monitoring to evaluate for iron overload.[2,24,29,30] Ferritin levels in the blood can be measured at regular intervals to identify and monitor iron overload.[2,24,31] In addition to monitoring blood iron levels, health care providers may also periodically evaluate for iron accumulation in the liver or the heart via magnetic resonance imaging (MRI).[29,30,32]

To address the negative long-term effects that transfusional iron overload can have on quality of life and lifespan, iron chelation therapy may be prescribed.[2,4-6] There are 3 iron chelators approved in the US for transfusional iron overload.[6] Deferoxamine, administered by injection (subcutaneously, intramuscularly, or intravenously) was approved in 1968.[33] Deferasirox, administered orally, was approved in 2005.[33,34] Deferiprone (Ferriprox), administered orally, was first approved via the accelerated pathway in 2011 and converted to traditional approval in 2021.[17,18,35] Deferasirox and deferiprone each carry a boxed warning related to serious side effects, including death, but the first-approved iron chelation treatment, deferoxamine, does not have any boxed warnings.[36]

How Much Does Transfusional Iron Overload Cost to Treat?

A recent analysis of US data from 2010 to 2019 found that transfusion-dependent beta-thalassemia (a condition that causes a chronically low red blood cell count) was associated with higher annual ($137,125) and lifetime ($7.1 million) US health care costs compared with matched controls; iron chelation therapy accounted for about half ($71,506) of these annual expenditures.[37]

DRUG INFORMATION

From 2011 through 2020, the chelating agent deferiprone had accelerated FDA approval under 3 new drug applications (NDAs) for 5 distinct formulations treating transfusional iron overload.[1,21,23,35,38-40] These formulations included 3 tablets and 2 oral solutions. The accelerated approvals were based on a reduction in ferritin, used as a surrogate endpoint.[8-12,35,38,39] The approved indication for the 5 deferiprone formulations was initially limited to treatment of transfusional iron overload in patients with thalassemia syndromes.[8-12]

In 2021, all formulations of deferiprone were converted to traditional FDA approval.[17,18] The indication for deferiprone was expanded to include patients with sickle cell disease and other severe anemias.[14-16,41-43] However, 1 of the oral solution formulations was discontinued in 2021.[38]

When each of the 5 formulations of deferiprone were approved through the accelerated approval pathway starting in 2011, the associated prescribing labels carried nearly identical safety warnings, highlighting serious and potentially fatal decreases in blood neutrophil counts (i.e. agranulocytosis), resulting in compromise of the immune system and vulnerability to severe life-threatening infections.[7,47-51]

DEFERIPRONE Ferriprox®

DRUG SUMMARY

BASIC INFORMATION

DRUG CLASS
Chelating agent

MANUFACTURER
Chiesi USA, Inc[a]

PRICE PER PATIENT[b]
$335,004 to $479,369 per year

DOSING

ROUTE Oral

FORMULATIONS
500-mg tablets (3 times per day)[1]
100-mg/mL oral solution (3 times per day)[24]
1,000-mg tablets (3 times per day)[25]
1,000-mg tablets (2 times per day)[26]

FDA APPROVAL

PATHWAY Accelerated approval

DATE
October 2011: 500-mg tablets
September 2015: 100-mg/mL oral solution
July 2019: 1,000-mg tablets
May 2020: 1,000-mg tablets

PRESCRIBING LABEL
Tablets: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021825s010lbl.pdf

Oral solution: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208030s007lbl.pdf

APPROVED INDICATION(S)

For the treatment of transfusional iron overload in adult and pediatric patients with thalassemia syndromes, sickle cell disease, or other anemias. Tablets for patients aged 8 years and older; oral solution for patients aged 3 years and older.

SAFETY

BOXED WARNINGS
Deferiprone can cause agranulocytosis (severely low neutrophil counts) that can lead to serious infections and death. Neutropenia (moderately low neutrophil counts) may precede the development of agranulocytosis.

Measure the absolute neutrophil count before starting deferiprone and monitor regularly while on therapy.

Interrupt deferiprone therapy if neutropenia develops.

Interrupt deferiprone if infection develops and monitor the absolute neutrophil count more frequently.

Advise patients taking deferiprone to report immediately any symptoms indicative of infection.

PRECAUTIONS
Liver enzyme elevations: Monitor monthly and discontinue for persistent elevations.

Zinc deficiency: Monitor during therapy and supplement for deficiency.

Embryo-fetal toxicity: Can cause fetal harm.

ADVERSE REACTIONS[c]
The most common adverse reactions in patients with thalassemia (incidence ≥ 6%) are nausea, vomiting, abdominal pain, arthralgia, ALT increased and neutropenia.

Fever, abdominal pain, bone pain, headache, vomiting, pain in extremity, sickle cell anemia with crisis, back pain, ALT increased, AST increased, joint pain, sore throat, nasopharyngitis (common cold), neutrophil count decreases, cough, and nausea.

[a] In 2020, Chiesi acquired the rights to Ferriprox (deferiprone) from ApoPharma USA Inc. [b] Costs are annualized based on an 80-kg patient and therefore assume use of 6,000 mg daily; [c] The most common reactions (incidence ≥ 6%) in patients with sickle cell disease or other anemias.
Sources. IPD Analytics, the US Food and Drug Administration (FDA), and Chiesi.
Abbreviations. ALT: alanine aminotransferase; AST: aspartate aminotransferase; FDA: US Food and Drug Administration.

FINDINGS

What Evidence Was Used by the FDA to Approve Deferiprone?

The pooled analysis used to approve the first 4 deferiprone formulations, starting in 2011, is summarized in Exhibit 1. The analysis was not registered on ClinicalTrials.gov.

When the first deferiprone oral solution was approved in 2015, the results of an open-label, bioavailability study (LA21-BE) were submitted to the FDA.[53] No new data from participants with transfusional iron overload were submitted to the FDA; results were from 42 healthy adults who were given a single dose of deferiprone oral solution.[53] A fifth formulation of deferiprone was approved in 2020[23,39]; unlike the first 4 deferiprone formulations which were to be taken 3 times per day, the newest formulation is tablets taken twice per day.

A generic version of the 500-mg deferiprone tablets was introduced by Taro Pharmaceuticals in 2020, followed by generics of the 500-mg and 1,000-mg tablets introduced by Hikma Pharmaceuticals in 2021 and 2022, respectively.[54,55] Taro Pharmaceuticals also introduced 1,000-mg tablets in 2024.[54]

Why Did the FDA Grant Accelerated Approval?

For the first 4 approved deferiprone formulations, the FDA considered results of the pooled analysis (study LA36-0310) of data selected from 12 previously completed manufacturer-funded studies.[8-11,52] From a sponsor database, an independent committee retrospectively selected individuals who had taken deferiprone and met inclusion criteria for the pooled analysis, but most of the data were from individuals with thalassemia.[52] A subgroup analysis included 236 individuals who had received deferiprone as a monotherapy; results were that serum ferritin decreased by at least 20% over a 1-year time frame in half (50%) of the subgroup.[8-11,52]

EXHIBIT 1

Summary characteristics of pooled analysis used to support accelerated FDA approval of Deferiprone

	Pooled analysis LA36-0310[52]
Official title	Analysis of data from clinical studies of Ferriprox to evaluate its efficacy in patients with iron overload for whom previous chelation therapy has been inadequate
Study design	Pooled analysis of preexisting data from 12 completed studies (LA-01, LA-02/06, LA-03, LA-04/06B, LA08-9701, LA-11, LA12-9907, LA15-0002, LA16-0102, LA28-CMP, LA30-0307, and Borgna-Pignatti [2006])
Study population description	236 participants with transfusion-dependent iron overload
Patient status requirement	For subgroup analysis, participants needed to have had previous iron chelation therapy that had failed or was considered inadequate due to poor tolerance
Primary outcome used for accelerated approval	Serum ferritin (≥ 20% decrease within 1 year of starting deferiprone)
Study funding	ApoPharma, Inc. a

Notes. [a]In 2020, Chiesi acquired the rights to Ferriprox (deferiprone) from ApoPharma Inc.
Sources. Center for Drug Evaluation and Research (CDER) NDA 021825 Medical Review(s)[52]; Deferiprone (Ferriprox) prescribing labels from 2011, 2015, 2018, and 2019.[8-11]
Abbreviation. NDA: new drug application.

EXHIBIT 2

Summary characteristics of the study requested to support full approval

	FIRST[19,56,57]
Official title	Efficacy and safety of Ferriprox for the treatment of transfusional iron overload in patients with sickle cell disease or other anemias
ClinicalTrials.gov ID	NCT02041299
Study design	Randomized, open-label, noninferiority study
Study population description	228 adults and children (aged 3 to 59 years) with sickle cell disease or a transfusion-dependent anemia. Participants had each received at least 20 blood transfusions with an expectation to continue receiving transfusions during the trial. At least 80% of participants had a diagnosis of sickle cell disease.
Study arms	2 interventional study arms
Intervention	Deferiprone 500-mg tablets or 80-mg/mL oral solution (3 times per day)
Control	Deferoxamine by subcutaneous infusion
Study duration	Up to 52 weeks (12 months) for each study participant
Study sites	34 study sites located in 8 countries, including the US
Trial funding	Chiesi[a]
Primary outcome	Liver iron concentration (assessed by MRI) from baseline to 12 months
Outcome requested by the FDA	Cardiac iron concentration and liver iron concentration
Estimated date of final report submission at the time of accelerated approval	July 2016
Status of requested study	Completed; published in February 2022[19]
Primary completion date	April 2019 (actual)

Notes. [a] In 2020, Chiesi acquired the rights to Ferriprox (deferiprone) from ApoPharma Inc.
Sources. Kwiatkowski et al.,[19] FIRST study ClinicalTrials.gov page (NCT02041299),[56] FIRST clinical study protocol version 10.1,[57] and deferiprone (Ferriprox) prescribing labels (04/2021).[41-43]
Abbreviations. FDA: US Food and Drug Administration; ID: identifier; MRI: magnetic resonance imaging.

What Studies Were Requested to Convert Deferiprone to Traditional Approval?

As a stipulation of the first accelerated approval in 2011, the FDA specified that completion of a confirmatory trial by 2016 was required to verify and describe the clinical benefit of deferiprone.[1] The FDA said this further research should include individuals with sickle cell disease, requiring that "[t]he trial will enroll a sufficient number of patients with sickle cell disease … to provide sufficient evidence to assess the efficacy and safety in the sickle cell disease population described. The trial will stratify for hematologic diagnosis for the randomization. The primary and secondary endpoints will measure changes in cardiac iron concentration and liver iron concentration."[1,21,23,40] The FIRST trial was completed in 2019[13] and the manufacturer submitted final reports to the FDA in 2020.[14-16] Similar confirmatory trial requirements were set for subsequent

accelerated approvals for the 4 additional deferiprone formulations.

What Evidence Was Used to Approve Deferiprone Via the Traditional Approval Pathway in 2021?

Results of the FIRST trial were submitted to the FDA in 2020[14-16] and used for deferiprone approval through the traditional pathway in 2021.[19] The FIRST trial was a randomized, open-label, noninferiority study comparing deferiprone to deferoxamine in individuals with a diagnosis of sickle cell disease or other transfusion-dependent anemias.[19,56,57] Participants were randomized to deferiprone 3 times per day (as either 500-mg tablets or the later discontinued 80-mg/mL oral solution) or to deferoxamine (administered via 8- to 12-hour subcutaneous infusions 5 to 7 nights per week).[57]

Why Did the FDA Grant Traditional Approval of Deferiprone?

The primary efficacy endpoint of the FIRST trial was change in liver iron concentration over 12 months.[19,56,57] Liver iron concentration was measured by MRI.[19,56,57] Noninferior reduction in liver iron concentration (compared with deferoxamine) was used to verify clinical benefit for attaining traditional FDA approval of deferiprone.[19 13-16,19] Results of the FIRST trial were published in 2022.[19]

Baseline characteristics of the 228 participants who enrolled in the FIRST trial and received at least 1 dose of a study drug are summarized in Exhibit 2. The deferiprone group included 152 participants while the deferoxamine group included 76 participants.[13,19] During the trial, 68.9% of participants in the deferiprone group and 78.9% of participants in the deferoxamine group met the study definition for compliance (i.e., medication adherence).[19]

The most prevalent primary diagnoses in the study were a heterogeneous group of participants with "sickle cell disease, sickle cell anemia, or thalassemia sickle cell" (82.9%, n = 189).[19] Participants were mostly White (77.2%).[19] Additional details regarding the demographics of FIRST trial participants are included in Appendix A.

DATA METHODS SUMMARY

Deferiprone is an iron chelator indicated for the treatment of transfusional iron overload in patients with thalassemia syndromes, sickle cell disease, or other anemias. Researchers at the Center for Evidence-based Policy (Center) used T-MSIS analytic files from CMS to identify Medicaid members who had at least 1 claim for this treatment.

We identified members aged 2 to 64 years with at least 1 pharmacy claim with a National Drug Code (NDC) for deferiprone in the years 2019, 2020, and 2021. As our focus was Medicaid expenditures, we excluded members with evidence of dual enrollment (members with both Medicaid and Medicare), as dually eligible members also have pharmacy benefits under Medicare Part D. Using these criteria, data from Alabama and Utah were excluded as these states do not report dual-enrollment status. Other state-based analysis exclusions were determined based on recommendations from the CMS Data Quality Atlas, which reports state-specific data availability and completeness. We generally did not report data elements (e.g., race or ethnicity) for states identified as "unusable" or "high concern" data quality according to Data Quality Atlas.

Our cost model estimated annual cost for the drug based on drug uptake and treatment patterns observed in the data, as well as average drug acquisition costs and statutorily required rebates. Refer to Appendix B for additional detail on how we conducted this study.

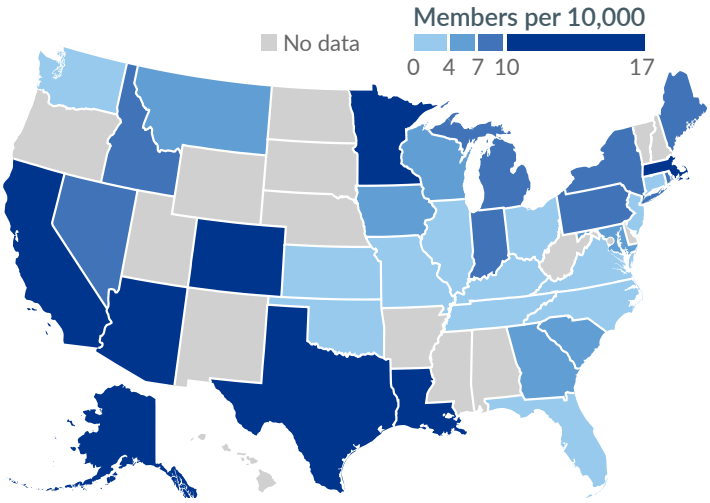
How Common Was Deferiprone Use Among Medicaid Members?

We identified 429 nondually eligible Medicaid members aged 2 to 64 years with at least 1 claim for deferiprone from 2019 through 2021 (members in Alabama and Utah were excluded because of data availability). These members had a total of 6,428 pharmacy claims for deferiprone over 3 years. Only 23 of those claims were for generic deferiprone.

Both the number of deferiprone claims and the number of Medicaid members with deferiprone claims increased over time (Exhibit 3). The number of deferiprone claims varied across states, from less than 0.5 claims per 10,000 members in Delaware, Hawaii, Nebraska, New Mexico, North Dakota, South Dakota, Vermont, West Virginia, and Wyoming, to more than 15 claims per 10,000 members in Arizona, California, Massachusetts, and Minnesota (Exhibit 4).

EXHIBIT 4

Number of deferiprone claims per 10,000 members aged 2 to 64, by state, 2021



Note. Data not available for Alabama and Utah, and suppressed (n < 11) for Arkansas, Delaware, District of Columbia, Hawaii, Mississippi, Nebraska, New Hampshire, New Mexico, North Dakota, Oregon, South Dakota, Utah, Vermont, West Virginia, and Wyoming.

EXHIBIT 3

Percentage increase of (nondually eligible) Medicaid members aged 2 to 64 years with at least 1 deferiprone claim and percentage increase of deferiprone claims, 2019 to 2021

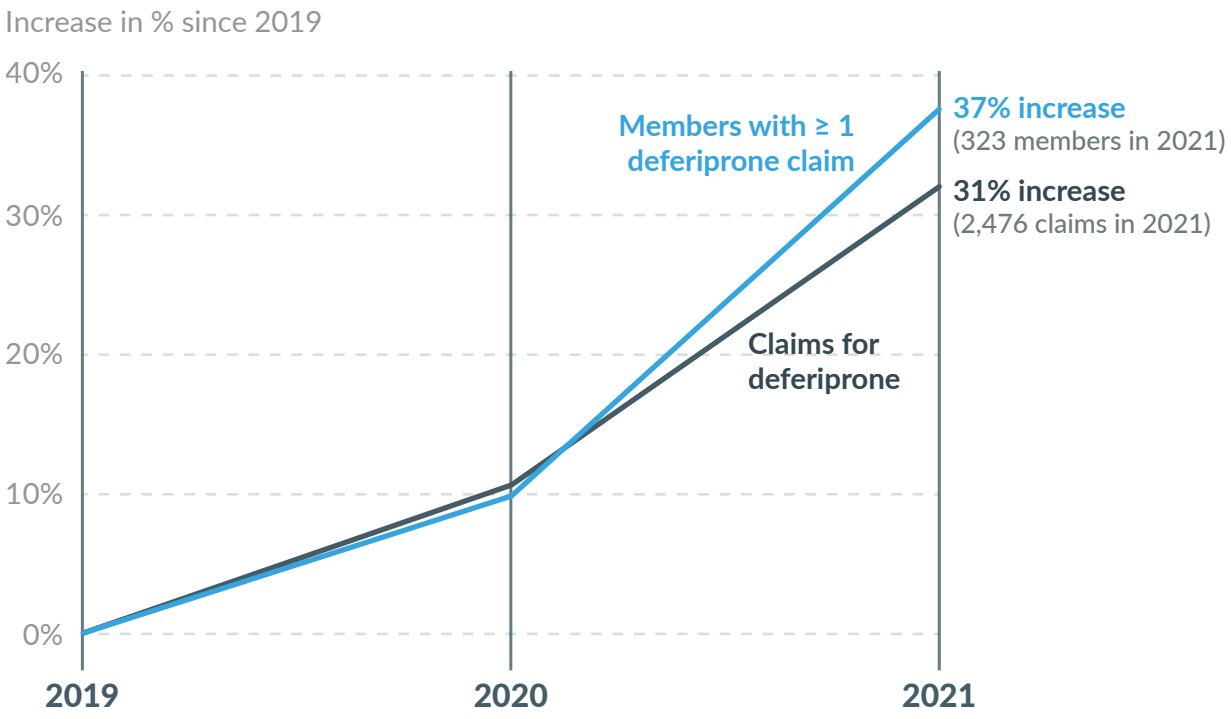


EXHIBIT 5

Characteristics of Medicaid members aged 2 to 64 with at least 1 deferiprone claim

	with at least 1 deferiprone claim in 2019 to 2021[a,b]	%[c]	with at least 1 deferiprone claim in 2021[a,d]	%[c]	with no deferiprone claim in 2021[a,d]	%[c]
Total members	*429*		*321*		*77,962,901*	
Age, in years						
2 to 11[e]	77	17.9	61	19.0	20,580,948	26.4
12 to 17	89	20.7	74	23.1	12,126,010	15.6
18 to 34	172	40.1	125	38.9	22,821,584	29.3
35 to 64	89	20.7	61	19.0	22,434,356	28.8
Sex						
Female	230	53.6	182	57.3	42,377,376	54.4
Race and ethnicity						
Black, non-Hispanic	86	35.5	62	33.5	11,345,274	20.8
Hispanic	36	14.9	24	13.2	16,338,561	29.9
White, non-Hispanic	40	16.5	33	18.1	22,762,276	41.7
Other race or ethnicity, non-Hispanic	80	33.1	64	35.2	4,114,835	7.5

Note. [a] Excludes dually eligible members and members in Alabama and Utah. [b] As reported at the time of last treatment. [c] Percentage of members with nonmissing data on demographic characteristics; 56.4% of members with at least 1 deferiprone claim and 70% of members without any deferiprone claims had nonmissing race or ethnicity data. For more detail see Appendix C. [d] Members enrolled in 2021; excludes members In Mississippi due to data quality issues. [e] Although deferiprone was approved for patients aged 3 years or older, we identified deferiprone claims for some Medicaid members aged 2 years, and included these members in our analyses.

Deferiprone use was most common among non-Hispanic Black and other non-Hispanic non-White race and ethnicities Medicaid members (35.5% and 33.1%, respectively) and majority of the users were between the ages of 18 and 34 years (40.1%; Exhibit 5).

How Do Medicaid Members With Deferiprone Claims Compare to Trial Populations?

The demographic characteristics of participants included in the FIRST confirmatory drug trial varied substantially from our Medicaid cohort in terms of age, sex, and racial and ethnic composition. The cohort of trial participants was 46.9% female, compared with 53.6% of Medicaid members with a deferiprone claim. The trial cohort was younger (62.3% of participants aged < 18 years) than the deferiprone users in the Medicaid cohort (38.7% members aged < 18 years). While in the study cohort 65.4% of participants were White and 7% were Hispanic, only 16.5% non-Hispanic White and 14.9% were Hispanic in the Medicaid cohort.

Medication adherence was also lower in the Medicaid cohort (57.6%) compared with the trial (68.9%). We calculated Medication Possession Ratio (MPR), a member-level metric describing the ratio of total days supplied to days in the measurement year, for members with deferiprone claims in 2021. Each member's measurement year began at the date of their first medication

fill and ended on the last day of 2021. A member was considered adherent if their individual MPR was at least 0.8, meaning they possessed their medication on at least 80% of the days in their measurement year. In 2021, 57.6% of members with deferiprone claims demonstrated adherence at this level; the mean MPR for the Medicaid cohort was 0.79 (79% of the days in the measurement year).

Exhibit 6 describes the prevalence of body system-level impairments (as defined by the Chronic Illness and Disability Payment System methodology) for Medicaid members aged 64 years or younger with a history of deferiprone use, compared with members without any history of deferiprone use (matched 1:3 on state, age, sex, and race and ethnicity) as identified in 2021 Medicaid claims. A larger proportion of members with a history of deferiprone use had comorbid conditions across all body systems than their matched comparisons with no deferiprone claim. More than 88% of deferiprone users had metabolic or hematological conditions, compared with 1.5% of matched controls having metabolic conditions. Among people who do not use deferiprone, psychological conditions were the most common type (13.3% of matched members); however, there was still a higher proportion of deferiprone users with these conditions (19.4%).

Members with deferiprone claims had substantially higher hospital and emergency department use than their matched comparisons (Exhibit 7). Specifically, 37.4% of Medicaid members with deferiprone claims experienced at least 1 hospitalization in 2021, compared with 4.3% of members without any deferiprone claims. Members with deferiprone claims also experienced substantially more total inpatient days (8,402 vs. 214 per 1,000 members) and had higher emergency department use across multiple measures.

EXHIBIT 6

Prevalence of affected body systems in Medicaid members with and without deferiprone claims, 2021

	Medicaid members with at least 1 deferiprone claim		Matched Medicaid members with no deferiprone claim	
System/condition	N	%	N	%
Total members[a]	*320*	-	*960*	-
Cardiovascular	125	39.1	67	7.0
CNS	49	15.3	24	2.5
Gastrointestinal	64	20.0	35	3.6
Hematological	292	91.3	-	-
Infectious disease	35	10.9	14	1.5
Metabolic	283	88.4	14	1.5
Psychological	63	19.7	127	13.2
Pulmonary	74	23.1	66	6.9
Renal	58	18.1	12	1.3

Note. [a] Members included in this calculation are those under age 65 with at least 1 inpatient or 1 outpatient claim in 2021; there was 1 member with at least 1 pharmacy claim for deferiprone but no inpatient or outpatient claims in 2021 eliminated from this analysis along with their matched members.

What Was the Impact of Deferiprone on State Medicaid Spending in 2019 to 2021?

We estimated that total Medicaid spending on deferiprone was $106.9 million nationally for 2019 through 2021. This estimate is based on converting the total number of days' supply in deferiprone claims into a dollar cost using the price of the drug at the time. We estimate $68.9 million of the total cost came from federal funds and the remaining $38 million from state funds. Refer to Appendix B for additional detail on how the costs were calculated.

EXHIBIT 7

Health service use by matched Medicaid members with and without deferiprone claims, 2021

	members with at least 1 deferiprone claim	matched members with no deferiprone claims or hemochromatosis due to repeated transfusions[b]
Total members[a]	*321*	*963*
Hospitalizations		
% with ≥ 1 hospitalization	37.4	4.3
% with ≥ 2 hospitalizations	22.4	-[c]
Total hospitalizations, per 1,000 members	1,246	53
Total inpatient days, per 1,000 members	8,402	214
Average length of stay per hospitalization, days	6.7	4.0
% with ≥ 1 hospitalization lasting ≥ 5 days	20.9	-[c]
Emergency visits		
% with ≥ 1 ED visit	50.8	23.2
% with ≥ 5 ED visits	12.5	1.5
Total ED visits, per 1,000 members	1,935	490

Note. [a] Excluding members in Mississippi due to data availability. [b] Medicaid members without deferiprone claims matched to members with deferiprone claims 3:1 on state, age, sex, race, and ethnicity; members with any claims with a diagnosis code for hemochromatosis due to repeated red blood cell transfusions (ICD-10 E83.111) were excluded from matching candidate pool. [c] Suppressed (n < 11). Abbreviation. ED: emergency department.

What Is the Potential Impact of Deferiprone on State Medicaid Spending?

Due to provisions of the Omnibus Budget Reconciliation Act of 1990 that established the Medicaid Drug Rebate Program, state Medicaid programs must cover FDA-approved drugs if the manufacturer signed a rebate agreement with US Department of Health and Human Services. Therefore, FDA approval, including accelerated approval, is a key factor in establishing the requirement for Medicaid coverage. We estimate that the future total annual cost of deferiprone for transfusional iron overload treatment in Medicaid to be $86.8 million (95% confidence bounds, $73.8 million and $96.6 million). This corresponds to a per-member per-month (PMPM) cost of $0.10 (95% confidence bounds, $0.09 and $0.11) for all Medicaid members. Based on the enrollment composition of the current members with deferiprone claims in CHIP (Children's Health Insurance Program) and Medicaid expansion, and the weighted national average of corresponding federal match rates, we estimate that $52.4 million of the total costs would come from federal funds and the remaining $34.4 million would be paid by the states. This estimate is based on the current prices of brand name and generic deferiprone, and the assumption that the uptake rate of deferiprone will increase by 38% from 2021 level and the share of generics will be 23%. Our cost estimate will represent the lower bound for future costs if the upward trend in the uptake of this treatment continues. Refer to the Methods Appendix (Appendix B) for additional detail on model inputs and assumptions.

CONSIDERATIONS

Deferiprone, granted accelerated approval by the FDA in 2011 and traditional approval in 2021, is a drug therapy for transfusional iron overload, a rare and potentially fatal disease.[1] In our analysis of 81 million members enrolled in Medicaid between 2019 and 2021, we identified 429 beneficiaries taking deferiprone for transfusional iron overload.

The evidence used for the accelerated approval of deferiprone had unusual limitations, as it relied on results of research not registered on ClinicalTrials.gov as well as the pooled analysis of retrospectively selected clinical data. In addition, the FIRST confirmatory trial, focused on a population with sickle cell disease, was completed nearly 8 years after FDA accelerated approval. It was also a noninferiority study, meaning that it was not designed to assess whether deferiprone had greater efficacy than the established therapy, but merely similar efficacy to the established therapy.

Notably, the FIRST confirmatory trial demographics did not reflect those of individuals with sickle cell disease in Medicaid. Of the estimated 50,000 individuals with sickle cell disease enrolled in Medicaid, 87% identify as non-Hispanic Black while the FIRST confirmatory trial reported only 16% of its study population was Black. Another area of concern is the young pediatric population. Only 12 participants aged 3 to 6 years were included in the confirmatory trial, but the drug was still given a traditional approval indication for those aged 3 and older.

The weaknesses of the FIRST trial evidence are particularly concerning. In contrast to the established therapy (deferoxamine), deferiprone carries a black box warning for serious infections and death and is priced by its manufacturer at a cost of $300,000 to $400,000 per patient per year. When selecting transfusional iron overload treatment, patients and health care providers must weigh the benefit and convenience of taking deferiprone orally versus the less convenient administration of deferoxamine (subcutaneously, intramuscularly, or intravenously). They must also consider the accessibility of weekly blood draws for deferiprone safety monitoring and the risk of serious infections and death.

In future years, state and federal policymakers should plan for annual deferiprone expenditures of $86.8 million, with $52.4 million from federal funds and $34.4 million from state funds. Moreover, mismatch of demographics between the confirmatory trial and the target Medicaid population warrants ongoing monitoring of the drug's serious risks, particularly for children aged 3 to 6 years.

PROJECT TEAM

RHONDA ANDERSON, RPH
Director of Pharmacy

MARCUS BACHHUBER, MD, MSHP
Clinical Epidemiologist

CAITLIN BURBANK, PT, PHD
Research Associate III

GÜLCAN ÇIL, PHD
Senior Statistician

GALEN GAMBLE, BA
Project Coordinator

DAVID RADLEY, PHD, MPH
Research Director, Data and Analytics

JENNIFER RYAN, ND, MS, CCRP
Research Associate II

BETH SHAW, MSC
Research Director, Evidence Synthesis

SUSAN STUARD, MBA
Director, State Technical Assistance

SNEHA YEDDALA, PHARM D, MS
Research Associate I

REFERENCES

1. US Food and Drug Administration. Ferriprox (deferiprone) tablets accelerated approval letter dated 10.14.2011 (NDA 021825). 2011; https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021825Orig1s000ltr.pdf. Accessed February 14, 2024.

2. Hamilton JP. Secondary iron overload (professional version). Merck Publishing; 2022; https://www.merckmanuals.com/professional/hematology-and-oncology/iron-overload/secondary-iron-overload. Accessed March 14, 2024.

3. American Society of Hematology. Sickle cell disease and thalassemia. 2008; https://www.hematology.org/about/history/50-years/sickle-cell-disease-thalassemia. Accessed March 15, 2024.

4. Centers for Disease Control and Prevention. Thalassemia: complications and treatment. 2023; https://www.cdc.gov/ncbddd/thalassemia/treatment.html. Accessed March 14, 2024.

5. Centers for Disease Control and Prevention. What is sickle cell disease? 2023; https://www.cdc.gov/ncbddd/sicklecell/facts.html. Accessed March 14, 2024.

6. Entezari S, Haghi SM, Norouzkhani N, et al. Iron chelators in treatment of iron overload. *J Toxicol.* 2022;2022:4911205. doi: 10.1155/2022/4911205.

7. Chiesi USA, Inc. Chiesi total care Ferriprox (deferiprone) specialty pharmacy starter kit (version 2.0). US Food and Drug Administration; 2022; https://resources.chiesiusa.com/Ferriprox/Ferriprox_HCP_Starter_Kit.pdf. Accessed February 28, 2024.

8. US Food and Drug Administration. Ferriprox (deferiprone) tablets prescribing information (revised 10/2011, NDA 021825). 2011; https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021825lbl.pdf. Accessed February 14, 2024.

9. US Food and Drug Administration. Ferriprox (deferiprone) oral solution prescribing information (revised 9/2015, NDA 208030). 2015; https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208030lbl.pdf. Accessed February 14, 2024.

10. US Food and Drug Administration. Ferriprox (deferiprone) oral solution prescribing information (revised 4/2018, NDA 208030). 2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208030s002lbl.pdf. Accessed February 20, 2024.

11. US Food and Drug Administration. Ferriprox (deferiprone) tablets prescribing information (revised 7/2019, NDA 021825). 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021825s004lbl.pdf. Accessed February 20, 2024.

12. US Food and Drug Administration. Ferriprox (deferiprone) tablets (twice-a-day) prescribing information (revised 5/2020, NDA 212269). 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212266s000lbl.pdf. Accessed February 20, 2024.

13. ClinicalTrials.gov. NCT02041299. Efficacy and safety of Ferriprox in patients with sickle cell disease or other anemias (FIRST): results posted. 2021; https://clinicaltrials.gov/study/NCT02041299?tab=results. Accessed March 11, 2024.

14. US Food and Drug Administration. Ferriprox (deferiprone) tablets supplement approval letter dated 04.30.2021 (NDA 021825). 2021; https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/021825Orig1s008ltr.pdf. Accessed February 22, 2024.

15. US Food and Drug Administration. Ferriprox (deferiprone) oral solution supplement approval letter dated 04.30.2021 (NDA 208030). 2021; https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/208030Orig1s005ltr.pdf. Accessed February 22, 2024.

16. US Food and Drug Administration. Ferriprox (deferiprone) tablets (twice-a-day) supplement approval letter dated 04.30.2021 (NDA 212269). 2021; https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/212269Orig1s001ltr.pdf. Accessed February 22, 2024.

17. US Food and Drug Administration. Verified clinical benefit: non-malignant hematological, neurological, and other disorder indications accelerated approvals. 2021; https://www.fda.gov/drugs/accelerated-approval-program/verified-clinical-benefit-non-malignant-hematological-neurological-and-other-disorder-indications. Accessed February 22, 2024.

18. US Food and Drug Administration. FDA accelerated approvals report - CDER drug and biologic accelerated approvals based on a surrogate endpoint (updated December 31 2023). 2023; https://www.fda.gov/media/151146/download?attachment. Accessed February 26, 2024.

19. Kwiatkowski JL, Hamdy M, El-Beshlawy A, et al. Deferiprone vs deferoxamine for transfusional iron overload in SCD and other anemias: a randomized, open-label noninferiority study. *Blood Adv.* 2022;6(4):1243-1254. doi: 10.1182/bloodadvances.2021004938.

20. IPD Analytics. Hematology: iron overload: iron chelators. 2024; https://www.ipdanalytics.com/. Accessed February 29, 2024.

21. US Food and Drug Administration. Ferriprox (deferiprone) oral solution accelerated approval letter dated 09.09.2015 (NDA 208030). 2015; https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/208030Orig1s000ltr.pdf. Accessed February 15, 2024.

22. US Food and Drug Administration. Ferriprox (deferiprone) tablets supplement approval letter dated 07.25.2019 (NDA 021825). 2019; https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/021825Orig1s004ltr.pdf. Accessed February 20, 2024.

23. US Food and Drug Administration. Ferriprox (deferiprone) tablets (twice-a-day) accelerated approval letter dated 05.19.2020 (NDA 212269). 2020; https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/212269Orig1s000replacementltr.pdf. Accessed February 20, 2024.

24. Shander A, Cappellini MD, Goodnough LT. Iron overload and toxicity: the hidden risk of multiple blood transfusions. *Vox Sang.* 2009;97(3):185-197. doi: 10.1111/j.1423-0410.2009.01207.x.

25. Slusarczyk P, Mleczko-Sanecka K. The multiple facets of iron recycling. *Genes (Basel).* 2021;12(9):1364. doi: 10.3390/genes12091364.

26. Sawicki KT, De Jesus A, Ardehali H. Iron metabolism in cardiovascular disease: physiology, mechanisms, and therapeutic targets. *Circ Res.* 2023;132(3):379-396. doi: 10.1161/CIRCRESAHA.122.321667.

27. Porter JB. Pathophysiology of transfusional iron overload: contrasting patterns in thalassemia major and sickle cell disease. *Hemoglobin.* 2009;33 Suppl 1:S37-45. doi: 10.3109/03630260903346627.

28. Brittenham GM. Chapter 36: disorders of iron homeostasis: iron deficiency and overload. In: Hoffman R, Benz EJ, Silberstein LE, et al., eds. *Hematology (Seventh Edition)*: Elsevier; 2018:478-490.

29. Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. *Blood Adv.* 2020;4(2):327-355. doi: 10.1182/bloodadvances.2019001143.

30. Remacha A, Sanz C, Contreras E, et al. Guidelines on haemovigilance of post-transfusional iron overload. *Blood Transfus.* 2013;11(1):128-139. doi: 10.2450/2012.0114-11.

31. Knovich MA, Storey JA, Coffman LG, Torti SV, Torti FM. Ferritin for the clinician. *Blood Rev.* 2009;23(3):95-104. doi: 10.1016/j.blre.2008.08.001.

32. Quinn CT, St Pierre TG. MRI measurements of iron load in transfusion-dependent patients: implementation, challenges, and pitfalls. *Pediatr Blood Cancer.* 2016;63(5):773-780. doi: 10.1002/pbc.25882.

33. US Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Deferoxamine mesylate (NDA 016267). https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016267. Accessed March 14, 2024.

34. US Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Deferasirox (NDA 021882). https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021882. Accessed March 14, 2024.

35. US Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Ferriprox tablets (NDA 021825). https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021825. Accessed March 11, 2024.

36. Office of the Federal Register. Code of Federal Regulations Title 21, Part 201, Subpart B, Section 201.56. 2023; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=201.57. Accessed April 3, 2024.

37. Udeze C, Evans KA, Yang Y, et al. Economic and clinical burden of managing transfusion-dependent beta-thalassemia in the United States. *J Med Econ.* 2023;26(1):924-932. doi: 10.1080/13696998.2023.2235928.

38. US Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Ferriprox oral solution (NDA 208030). https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208030. Accessed February 29, 2024.

39. US Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Ferriprox tablets (NDA 212269). https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=212269. Accessed March 11, 2024.

40. US Food and Drug Administration. Ferriprox (deferiprone) oral solution accelerated approval letter dated 04.20.2018 (NDA 208030). 2018; https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/208030Orig1s002ltr.pdf. Accessed February 20, 2024.

41. US Food and Drug Administration. Ferriprox (deferiprone) tablets prescribing information (revised 4/2021, NDA 021825). 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021825s008lbl.pdf. Accessed February 22, 2024.

42. US Food and Drug Administration. Ferriprox (deferiprone) tablets (twice-a-day) prescribing information (revised 4/2021, NDA 212269). 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212269s001lbl.pdf. Accessed February 22, 2024.

43. US Food and Drug Administration. Ferriprox (deferiprone) oral solution prescribing information (revised 4/2021, NDA 208030). 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208030s005lbl.pdf. Accessed February 22, 2024.

44. US Food and Drug Administration. Search orphan drug designations and approvals. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accessed April 1, 2024.

45. Chiesi USA, Inc. Ferriprox (deferiprone) tablets prescribing information (revised 11/2021, NDA 021825 and NDA 212269). US Food and Drug Administration; 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021825s010lbl.pdf. Accessed March 21, 2024.

46. Chiesi USA, Inc. Ferriprox (deferiprone) oral solution prescribing information (revised 11/2021, NDA 208030). US Food and Drug Administration; 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208030s007lbl.pdf. Accessed March 21, 2024.

47. Chiesi USA, Inc. Ferriprox (deferiprone) tablets prescribing information (revised 11/2021, 021825). US Food and Drug Administration; 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021825s010lbl.pdf. Accessed February 27, 2024.

48. Chiesi USA, Inc. Ferriprox (deferiprone) oral solution prescribing information (revised 11/2021, NDA 208030). US Food and Drug Administration; 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208030s007lbl.pdf. Accessed February 27, 2024.

49. Chiesi USA, Inc. Ferriprox (deferiprone) information for patients. US Food and Drug Administration; 2023; https://ferriprox.com/. Accessed February 28, 2024.

50. Chiesi USA, Inc. Ferriprox (deferiprone) tablets (twice-a-day) prescribing information (revised 11/2021, NDA 212269). US Food and Drug Administration; 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212269s003lbl.pdf. Accessed March 1, 2024.

51. Tricta F, Uetrecht J, Galanello R, et al. Deferiprone-induced agranulocytosis: 20 years of clinical observations. *Am J Hematol.* 2016;91(10):1026-1031. doi: 10.1002/ajh.24479.

52. Center for Drug Evaluation and Research. NDA 021825: medical review(s). US Food and Drug Administration; 2011; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021825Orig1s000MedR.pdf. Accessed April 2, 2024.

53. Center for Drug Evaluation and Research. NDA 208030: medical review(s). US Food and Drug Administration; 2015; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208030Orig1s000MedR.pdf. Accessed March 28, 2024.

54. IPD Analytics. Coding and reimbursement tool. 2024; https://www.ipdanalytics.com/. Accessed February 9, 2024.

55. Taro Pharmaceutical Industries Ltd. Taro launches specialty generic deferiprone tablets, 500mg in the US. 2020; https://taro.gcs-web.com/node/10991/pdf. Accessed November 3, 2024.

56. ClinicalTrials.gov. NCT02041299. Efficacy and safety of Ferriprox in patients with sickle cell disease or other anemias (FIRST). 2021; https://clinicaltrials.gov/study/NCT02041299?tab=table. Accessed March 11, 2024.

57. ApoPharma Inc. Clinical study protocol (Ferriprox in patients with iron overload in sickle cell disease trial - FIRST) LA38-0411, US only version 10.1. 2017; https://classic.clinicaltrials.gov/ProvidedDocs/99/NCT02041299/Prot_000.pdf. Accessed March 11, 2024.

APPENDIX A

DETAILED PARTICIPANT DEMOGRAPHIC INFORMATION OF THE *FIRST* CONFIRMATORY TRIAL

See attachment for these tables.

EXHIBIT A1

Demographic information of the participants in the efficacy and safety of deferiprone (Ferriprox) in patients with sickle cell disease or other anemias (FIRST) trial

EXHIBIT A2

Primary diagsosis of the participants in the efficacy and safety of deferiprone (Ferriprox) in patients with sickle cell disease or other anemias (FIRST) trial

APPENDIX B

METHODS

See attachment for a full description of the methods used to prepare this brief.

EXHIBIT B1

Annual wholesale acquisition cost (WAC) for deferiprone

EXHIBIT B2

Share of deferiprone claims for each formulation by age and sex of patients, 2021

EXHIBIT B3

Other modeling inputs for deferiprone cost estimates

APPENDIX C

DEMOGRAPHIC INFORMATION

See attachment for a table describing the availability of demographic information of Medicaid members included in our study.

APPENDIX D

DEFERIPRONE CLAIMS, 2019 TO 2021

See attachment for this table.

Suggested citation

Ryan J, Cil G, Burbank C, Shaw B, Yeddala S, Radley D, Stuard S. *Deferiprone (Ferriprox) for transfusional iron overload*. 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.

About the Center for Evidence-based Policy

The Center for Evidence-based Policy (Center) is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring that diverse and relevant perspectives are considered and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon.

centerforevidencebasedpolicy.org

Center for Evidence-based Policy

3030 South Moody Avenue, Suite 250
Portland, OR 97201

Phone: (503) 494-2182
Fax: (503) 494-3807

centerforevidencebasedpolicy.org