Pharmacy Policy Bulletin

Title: Chelation Agents

Policy #: Rx.01.22

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, gender or quantity restrictions. Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

**Intent:**
The intent of this policy is to communicate the medical necessity criteria for penicillamine (Cuprimine), trientine (Syprine), deferasirox (Exjade®/Jadenu®), and deferiprone (Ferriprox®) as provided under the member’s pharmacy benefit.

**Description:**
Wilson’s disease is a rare, inherited disorder of copper metabolism characterized by deposition of copper in the liver, brain, and other tissue. The estimated prevalence of Wilson's disease in the United States is approximately 1 per 30,000 individuals. Clinical manifestations of the disease range from asymptomatic to fulminant hepatic failure, chronic liver disease, including cirrhosis, neurologic and psychiatric manifestations. Untreated, Wilson’s disease may result in need for liver transplant or be fatal. The mainstay of therapy for Wilson’s disease is treatment with chelating agents, such as penicillamine.

Cystinuria is an autosomal recessive defect in the reabsorption of cystine. The estimated prevalence of heterozygous cystinuria is 1 per 20-200 individuals, and homozygous cystinuria is 1 per 15,000 individuals in the United States. Cystinuria manifests as cystine urolithiasis, which recurs throughout the lifetime of affected individuals. Treatment involves dietary and medical prevention of recurrent stone formation. For those without stones, initial treatment approach is conservative (adequate hydration, dietary restrictions, urinary alkalization). For those failing to achieve target urinary cystine concentrations, penicillamine or captopril may be added.
Penicillamine (Cuprimine) is indicated for the treatment of Wilson's disease, cystinuria, and in patients with severe, active rheumatoid arthritis who have failed to respond to conventional therapy.

Penicillamine chelates copper in patients with Wilson's disease resulting in a complex that is excreted in the urine. In cystinuria, penicillamine combines with cystine to form a complex more soluble than cystine which is readily secreted. This results in decreased urinary cystine concentrations and prevention of cystine calculi. The exact mechanism of action of penicillamine in rheumatoid arthritis is unknown, but may involve improvement in lymphocyte function.

Trientine (Syprine) is indicated in the treatment of patients with Wilson's disease who are intolerant of penicillamine. Syprine should be used when continued treatment with penicillamine is no longer possible because of intolerable or life endangering side effects.

Individuals, who are transfusion-dependent, receive excess iron with each transfusion. In non-transfusion-dependent thalassemia (NTDT), elevated iron levels are related to suppression of hepcidin levels, increased intestinal iron absorption, and increased release of recycled iron from the reticuloendothelial system. The excess iron accumulates in various tissues, including cardiac, liver, pulmonary, and endocrine glands, due to lack of an active mechanism to excrete iron. The goal of iron chelation therapy in iron overload is to reduce iron levels, prevent complications, and reduce morbidity.

Deferasirox (Exjade®/Jadenu®) is indicated for the treatment of transfusional hemosiderosis (chronic iron overload due to blood transfusions) in individuals who are 2 years of age or older and for the treatment of chronic iron overload in patients 10 years of age and older with NTDT syndromes and with a liver iron concentration (LIC) of at least 5 mg Fe per gram of dry weight (Fe/ g dw) and a serum ferritin greater than 300 mcg/L.

Deferiprone (Ferriprox®) is an iron chelator indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

Deferasirox (Exjade®/Jadenu®) is an orally active chelator that is selective for iron (as Fe3+). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although deferasirox has very low affinity for zinc and copper, there are variable decreases in the serum concentration of these trace metals after the administration of deferasirox. The clinical significance of these decreases is uncertain.

Deferiprone (Ferriprox®) is a chelating agent with an affinity for ferric ion (iron III). Deferiprone binds with ferric ions to form neutral 3:1 (deferiprone:iron) complexes that are stable over a wide range of pH values.

**Policy:**

Penicillamine (Cuprimine) is approved when BOTH of the following are met:

A. Diagnosis of ONE of the following:
   1. Wilson's disease
   2. Cystinuria
   3. Patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy

B. Inadequate response or inability to tolerate penicillamine (Depen)
Trientine (Syprine) is approved when BOTH of the following are met:

A. Wilson's disease
B. Inadequate response or inability to tolerate penicillamine (Depen)

**INITIAL CRITERIA**

Deferasirox (Exjade®/Jadenu®) is approved when documentation of ANY of the following is provided:

1. Diagnosis of chronic iron overload due to blood transfusions with BOTH of the following:
   a. individual is 2 years of age or older; and
   b. serum ferritin levels are consistently greater than 1000 mcg/L (as demonstrated with at least two lab values within two months prior to treatment)

2. Diagnosis of chronic iron overload in Non-Transfusion-Dependent Thalassemia Syndromes with BOTH of the following:
   a. Individual is 10 years of age or older; and
   b. Serum ferritin levels are consistently greater than 300 mcg/L and liver iron concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw) (as demonstrated with at least two lab values within 2 months prior to treatment)

Initial authorization length: 3 months

**CONTINUATION CRITERIA**

Deferasirox (Exjade®/Jadenu®) is re-approved when ANY the following inclusion criteria are met:

1. Documentation of a decreased serum ferritin level compared with the baseline level for transfusion dependent anemia; or
2. Documentation of a decreased serum ferritin level compared with the baseline level or reduction in LIC (liver iron concentration) for Non-transfusion dependent thalassemia syndrome

Authorization length for continuation of therapy: 6 month increments if a benefit is demonstrated

Deferiprone (Ferriprox) is approved when documentation is provided of ALL of the following:

1. Diagnosis of transfusional iron overload due to thalassemia syndromes; and
2. Current chelation therapy is inadequate

**Black Box Warning: Deferasirox (Exjade/ Jadenu)**

Renal failure: Deferasirox can cause acute renal failure and death, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders. Measure serum creatinine and determine creatinine clearance (CrCl) in duplicate prior to initiation of therapy and monitor renal function at least monthly thereafter. For patients with baseline renal impairment or
increased risk of acute renal failure, monitor creatinine weekly for the first month, then at least monthly thereafter. Consider dose reduction, interruption, or discontinuation based on increases in serum creatinine.

Hepatic failure: Deferasirox can cause hepatic injury including hepatic failure and death. Measure serum transaminases and bilirubin in all patients prior to initiating treatment, every 2 weeks during the first month, and at least monthly thereafter. Avoid use of deferasirox in patients with severe (Child-Pugh class C) hepatic impairment and reduce the dose in patients with moderate (Child-Pugh class B) hepatic impairment.

GI hemorrhage: Deferasirox can cause GI hemorrhages, which may be fatal, especially in elderly patients who have advanced hematologic malignancies and/or low platelet counts. Monitor patients and discontinue deferasirox for suspected GI ulceration or hemorrhage.

**Deferiprone (Ferriprox)**

Agranulocytosis/Neutropenia: Deferiprone can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis. Measure the absolute neutrophil count (ANC) before starting deferiprone therapy and monitor the ANC weekly during therapy. Interrupt deferiprone therapy if neutropenia develops. If infection develops, interrupt deferiprone and monitor the ANC more frequently. Advise patients taking deferiprone to report immediately any symptoms indicative of infection.

**Penicillamine (Cuprimine)**

Physicians planning to use penicillamine should thoroughly familiarize themselves with its toxicity, special dosage considerations, and therapeutic benefits. Penicillamine should never be used casually. Each patient should remain constantly under the close supervision of the physician. Patients should be warned to report promptly any symptoms suggesting toxicity.

**Guidelines:**

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

**BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the pharmacy benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

**References:**

Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

<table>
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<tr>
<th>Brand Name</th>
<th>Generic Name</th>
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<tbody>
<tr>
<td>Cuprimine</td>
<td>Penicillamine</td>
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<tr>
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Cross References:

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