IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Syprine (trientine) is a copper chelator that binds to and facilitates the excretion of copper. It is orally administered and is used to lower copper levels in patients with Wilson’s disease, a genetic condition that affects about one in every 30,000 births.
Policy/Criteria

I. Most contracts require prior authorization approval of trientine (Syprine) prior to coverage. Trientine (Syprine) may be considered medically necessary when criteria A and B, below, are met:

A. Documentation of a diagnosis of Wilson’s disease when established by or in consultation with a specialist in gastroenterology.

AND

B. Treatment with penicillamine is not tolerated or is contraindicated.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers trientine (Syprine) to be a self-administered medication.

B. When prior authorization is approved, trientine (Syprine) may be authorized using the following dosing schedules:
   a. For patients >12 years of age: 240 capsules per 30 days (maximum dose of 2,000 mg/day).
   b. For patients ≤ 12 years of age: 180 capsules per 30 days (maximum dose of 1,500 mg/day).

C. Authorization may be reviewed at least annually to confirm that the medication is effective. Documentation by chart notes of disease stability or improvement in symptoms must be provided.

III. Trientine (Syprine) is considered investigational when used for all other conditions, including, but not limited to:

A. Rheumatoid arthritis

B. Cystinuria

C. Left-ventricular hypertrophy in patients with diabetes

D. Dermatitis
Position Statement

- **Trientine (Syprine)** is a copper chelator, approved for patients with Wilson’s disease who are intolerant of penicillamine.
- Wilson’s disease, also known as hepatolenticular degeneration, is a genetic disorder in which copper is not adequately excreted. The accumulation of copper typically begins in the liver; however brain involvement is also common. Once the diagnosis is made, treatment is life-long, unless the patient receives a liver transplant.
- Penicillamine (Cuprimine®, Depen Titratabs®) is the most commonly used chelator to treat Wilson’s disease; trientine (Syprine) was originally developed to provide an alternative treatment option to patients who cannot tolerate penicillamine.
- Penicillamine is recognized by treatment guidelines as an effective first-line treatment, and it is commonly used for this purpose. Roughly 30% of patients experience intolerable adverse events that require treatment discontinuation.
- Treatment guidelines recognize trientine as an effective option for patients who are intolerant of penicillamine and as first-line use in patients who have not tried penicillamine; however, these recommendations are based on low-quality, retrospective case reports.[1-3]
- Both penicillamine and trientine have been available since the 1960’s. Neither drug is well-studied nor have they been directly compared. FDA approval was based on small, non-randomized clinical trials. Low quality case studies/case series and clinical experience suggest that the two drugs are similarly effective.[3,4]
- Penicillamine is the preferred treatment option for Wilson’s disease. Although none of the treatment options are well-studied, penicillamine appears to be similar in efficacy to trientine and significantly more affordable. While some adverse events may preclude the use of penicillamine, there is extensive clinical experience with penicillamine and side effects are well characterized, thus, trientine should be reserved for patients who cannot tolerate penicillamine.

Clinical Efficacy

- Prescribing information for trientine (Syprine) describes two clinical trials in 41 patients with Wilson’s disease, who were intolerant of penicillamine. Dosing regimens varied across both studies, with doses ranging from 450 to 2,400 mg per day.
  - 34 patients experienced an improvement in global response, four saw no change, two were lost to follow-up, and one patient’s condition deteriorated.
  - One patient who initially improved experienced a recurrence of systemic lupus erythematosus, leading to the discontinuation of trientine.[5,6]
Investigational uses:

Rheumatoid arthritis
In 15 patients with rheumatoid arthritis, trientine was reported not to be effective in improving chemical or biochemical parameter after 12 weeks of treatment.[6]

Cystinuria
In contrast to penicillamine, the absence of a sulfhydryl moiety renders it incapable of binding cysteine and therefore, is of no use in cystinuria.[6]

Left-ventricular hypertrophy (LVH) in patients with diabetes
In 15 patients with LVH and diabetes, treatment with trientine reduced left ventricular mass indexed to body surface area compared to placebo. Larger, high quality clinical trials are necessary to confirm clinical benefit of trientine in diabetic patients with LVH.[7]

Dermatitis
A clinical trial in nickel-sensitive patients with hand dermatitis found that treatment with trientine 300mg daily did not result in a detectable increase in urinary nickel excretion.[8]

Safety
- Adverse reactions observed in clinical studies include iron deficiency, and systemic lupus erythematosus.[6]
- Post-marketing reports of dystonia, muscular spasms, myasthenia gravis, and neurological worsening have also been noted.[4,6]
- Most patients who have been treated with trientine have previously been treated with penicillamine, and a causal relationship between these adverse events and trientine use has not been established.[3,4]

Dosing
- Systemic evaluation of dose and/or interval between doses has not been done. Based on limited clinical experience, the recommended initial dose of trientine is 500-750 mg/day for pediatric patients and 750-1,250 mg/day for adults given in divided doses two, three or four times daily.[6]
- The daily dose of trientine should only be increased when clinical response is inadequate or the concentration of free serum copper is persistently above 20 mcg/dL.[6]
- The maximum recommended dose is 2,000 mg/day for adults or 1,500 mg/day of patients age 12 and under.[6]
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<thead>
<tr>
<th>Codes</th>
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<tr>
<td>ICD-9</td>
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**References**