PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Syprine Prior Authorization Policy
- Syprine® (trientine hydrochloride capsules – Valeant, generics)

REVIEW DATE: 09/23/2020

OVERVIEW

Trientine, a metal chelator, is indicated for the treatment of patients with Wilson's disease who are intolerant of penicillamine.[1] Trientine and penicillamine are not interchangeable; trientine should be used when treatment with penicillamine is no longer possible because of intolerable or life-endangering side effects. Trientine is not indicated for use in patients with cystinuria, rheumatoid arthritis, or biliary cirrhosis. In general, patients should remain under regular medical supervision while receiving trientine and patients (especially women) should be closely monitored for evidence of iron deficiency anemia. Controlled studies of trientine in pediatric patients are not available; however, it has been used in patients as young as 6 years with no adverse events. Other chelating agents indicated in the treatment of Wilson's disease include penicillamine capsules (Cuprimine®, generics) and Depen® (penicillamine tablets).[5-6] These agents also have other indications for the treatment of cystinuria and treatment of patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy.

Disease Overview

Copper is an essential metal and is an important cofactor for many proteins.[3] However, normal dietary consumption and absorption of copper exceeds the amount that the body needs.[4] Copper homeostasis depends primarily on biliary excretion. Wilson's disease is an inherited disorder in which alterations in cellular copper processing and impaired biliary excretion lead to copper accumulation.[2-4] Copper initially builds up in the liver and eventually is released into the bloodstream and deposited into other organs (e.g., brain, kidneys, and cornea). The majority of patients with Wilson's disease are diagnosed between the ages of 5 and 35 years, with the most common presentations being liver disease, neurological disorder (e.g., tremor, ataxia, dystonia), or psychiatric illness.[3-4] The average prevalence of Wilson's disease is 30 cases per million individuals. Lifelong pharmacologic therapy is the mainstay of treatment for Wilson's disease; without treatment, most patients will die from liver disease or progressive neurologic disease. Liver transplantation is reserved for severe or resistant cases. In patients with Wilson's disease, trientine acts as a general metal chelator and promotes urinary copper excretion.

Guidelines

The American Association for the Study of Liver Diseases (AASLD) provides guidelines for the diagnosis and management of Wilson's disease (2008).[3] It is noted that while the most experience in the treatment of this condition is with penicillamine, trientine is effective for the treatment of Wilson's disease, especially in patients who are intolerant of penicillamine or have clinical features indicating potential intolerance (history of renal disease of any sort, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency). Trientine has been found to be effective initial therapy, even in patients with decompensated liver disease at the outset. The AASLD recommends that initial treatment for symptomatic patients include a chelating agent (penicillamine or trientine). Neurological worsening following therapy initiation appears to be much less common with Syprine than with penicillamine. For the treatment of presymptomatic patients or those on maintenance therapy, chelating agents and zinc are both treatment options. Zinc appears preferable for presymptomatic children under the age of 3 years. In pregnant patients, treatment for Wilson's disease should be continued due to the risk of liver failure with therapy interruption, but dosage reduction is advisable for penicillamine and trientine. Satisfactory outcomes have been shown with continuation of therapy with chelating agents (both penicillamine and trientine) during pregnancy.

Liver transplantation should be considered in patients with acute liver failure due to Wilson's disease and in patients with decompensated cirrhosis unresponsive to chelation therapy.

The European Association for the Study of the Liver (EASL) also published a clinical practice guideline for the treatment of Wilson's disease (2012).[4] Like the AASLD, the EASL acknowledges that numerous studies have demonstrated the effectiveness of penicillamine. The EASL also notes that trientine has been shown to be an effective initial therapy. A chelating agent (penicillamine or trientine) is the recommended initial treatment of symptomatic patients, and again, a chelating agent or zinc may be used for the treatment of presymptomatic patients or patients established on maintenance therapy. In patients with neurological disease established on maintenance therapy either a chelating agent or zinc may be used; zinc may have a role as first-line therapy in these patients. The EASL guidelines also state that despite teratogenicity concerns with penicillamine, treatment of Wilson's disease should be continued during pregnancy as the risks of withdrawing therapy outweigh those of continuing therapy. However, penicillamine and trientine dosage reductions are recommended in pregnant patients.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of trientine. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with trientine as well as the monitoring required for adverse events and long-term efficacy, approval requires trientine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of trientine is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Wilson's Disease.** Approve for 3 years if the patient meets the following criteria (A and B):
   - **A)** Patient meets ONE of the following criteria (i, ii, iii, iv, v or vi):
     - **i.** Patient has tried one penicillamine product and is intolerant to penicillamine therapy, according to the prescriber; OR
       Note: Examples of penicillamine products are Cuprimine® (penicillamine capsules, generics), Depen® (penicillamine tablets, generics).
     - **ii.** Patient has clinical features indicating the potential for intolerance to penicillamine therapy, according to the prescriber; OR
       Note: Specific clinical features include history of any renal disease, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency.
     - **iii.** Patient has a contraindication to penicillamine therapy, according to the prescriber; OR
     - **iv.** Patient has neurologic manifestations of Wilson's disease; OR
     - **v.** Patient is pregnant; OR
     - **vi.** Patient has been started on therapy with trientine (Syprine, generics).
   - **B)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of trientine is not recommended in the following situations:

1. **Biliary Cirrhosis.** Trientine (Syprine, generics) is not indicated for the treatment of biliary cirrhosis.[1]

2. **Cystinuria.** Trientine (Syprine, generics) is not recommended for use in patients with cystinuria.[1] Unlike penicillamine, trientine does not contain a sulfhydryl moiety and therefore it is not capable of binding cysteine.

3. **Rheumatoid Arthritis (RA).** Trientine (Syprine, generics) is not recommended for use in patients with RA.[1] Per the prescribing information, trientine was not found to be effective in improving any clinical or biochemical parameter after 12 weeks of treatment of patients with RA.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Syprine® [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; December 2016.
2. Weiss KH, Thurik F, Gotthardt DN, et al. Efficacy and safety of oral chelators in treatment of patients with Wilson Disease. *Clin Gastroenterol Hepatol*. 2013;11:1028-1035.
3. Roberts EA, Schilsky MI. AASLD Practice Guidelines: Diagnosis and treatment of Wilson Disease: an update. *Hepatology*. 2008;47(6):2089-2111.
4. European Association for Study of the Liver (EASL) clinical practice guidelines: Wilson's disease. *J Hepatol*. 2012;56(3):671-85.
5. Cuprimine® [prescribing information]. Bridgewater, NJ. Aton Pharma. Inc., a division of Valeant Pharmaceuticals North America LLC; March 2018.
6. Depen® [prescribing information]. Somerset, NJ. Meda Pharmaceuticals Inc.; January 2019.