uridine triacetate (Xuriden®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO216

Description

Uridine triacetate (Xuriden) is a pyrimidine analog for uridine replacement indicated in adult and pediatric patients for the treatment of hereditary orotic aciduria (HOA).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
uridine triacetate (Xuriden)	2 g/packet	Hereditary orotic aciduria	240 g/30 days

Initial Evaluation

I. Uridine triacetate (Xuriden) may be considered medically necessary when the following criteria are met:
   A. Member is diagnosed with **hereditary orotic aciduria (HOA)** by a provider specializing in the patient's diagnosis or in consultation with a geneticist, hematologist or specialist in metabolic disorders; **AND**
   B. Member has at least ONE of the following diagnostic criteria:
      1. Molecular genetic test indicating variations in uridine monophosphate synthetase (UMPS) gene; **OR**
      2. Urine test indicating high levels of orotic acid and/or orotidine; **AND**
   C. Member has severe disease as defined by one or more of the following:
      1. Hematologic abnormalities (e.g. megaloblastic anemia, neutropenia, leukopenia); **OR**
      2. Renal tract obstruction (due to aggregation of orotic acid crystals); **OR**
      3. Immune dysfunction; **OR**
      4. Congenital anomalies; **OR**
      5. Physical and intellectual developmental delays; **AND**
   D. Provider attestation that member does not have ornithine transcarbamoylase (OTC) deficiency; **AND**
      1. Blood ammonia levels are within normal limits

II. Uridine triacetate (Xuriden) is considered investigational when used for all other conditions, including but not limited to:
   A. Fluoropyrimidine overdose/overexposure

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescriber attestation that the member has exhibited stability or improvement in disease symptoms [e.g., improvement in hematologic status, improvement in growth]

Supporting Evidence

I. HOA is an extremely rare genetic disorder affecting both men and women, with fewer than 25 cases of patients with this disorder worldwide have been reported in the medical literature. It is caused by variations in the uridine monophosphate synthase (UMPS) gene which is responsible for producing an enzyme that catalyzes the last two steps of the pyrimidine biosynthesis pathway. One of these two final steps is to convert orotic acid into another chemical substance. Because of the variation in the UMPS gene, individuals with this disorder have low levels of the enzyme needed to breakdown orotic acid and subsequently have a reduced production of uridine, a nucleotide involved in multiple essential physiological functions including biosynthesis of RNA, synthesis of glycogen and glycoprotein, phospholipid synthesis, and DNA synthesis.
II. The exact mechanism by which orotic acid buildup and uridine monophosphate synthase deficiency leads to signs and symptoms of the disease is not completely understood. Orotic acid is believed to improve the metabolism of folic acid and vitamin B12 and may play a role in gene transcription.
III. HOA is a clinically heterogenous disorder and individuals who retain some UMPS activity may be asymptomatic or only mildly affected. Features of more severe disease include megaloblastic anemia that is not responsive to treatment with vitamin B12 or folic acid, neutropenia, renal tract obstruction (due to aggregation of orotic acid crystals), immune dysfunction, congenital anomalies, and physical and intellectual developmental delays.
IV. Diagnosis of HOA is confirmed by assessment of symptoms, family history, a urine test indicating high levels of orotic acid and/or orotidine, and a molecular genetic test indicating variations in uridine monophosphate synthetase (UMPS) gene. Not all patients will present with elevated orotic acid and/or orotidine urine levels; however, this is the most common laboratory abnormality seen in 80%-99% of patients. Deferential diagnosis of HOA includes urea cycle disorders one of which may

also present with high blood levels of orotic acid, this disorder is known as ornithine transcarbamoylase (OTC) deficiency. OTC can be distinguished from HOA by evaluation of blood ammonia levels. Patients with HOA will have normal blood ammonia levels, whereas, patients with OTC deficiencies tend to have elevated ammonia levels.

V. Nucleotide replacement has been the mainstay of treatment of HOA. Case reports document rapid hematologic response with administration of uridine. Some patients treated with uridine have reached adulthood and some who have been treated with uridine lifelong have fathered or given birth to normal children. Supportive therapies include blood transfusions, intravenous hydration and electrolyte replacement, and treatment for renal and infectious disease complications.

VI. FDA approval of uridine triacetate (Xuriden) was based on collective evidence from case reports, pharmacokinetic studies, safety studies, and one Phase III, open-label, single-arm, six-week clinical trial and its six-month extension phase. The efficacy was evaluated in a Phase III trial which enrolled four patients with HOA (three male, one female; age range three to 19 years). Three patients were previously treated with uridine and were switched to uridine triacetate (Xuriden). One patient was treatment naïve. The study evaluated stability or improvement in patients' hematologic parameters in the initial six-week period and the extension phase. By week six, three previously treated patients met the primary endpoint and maintained stability of their hematologic parameters, while one treatment naïve patient failed to meet the primary endpoint – improvement in hematologic parameters. The secondary endpoint was improved growth parameters (height and weight). Effect on growth was assessed in three patients and remained unchanged after 24 months of treatment.

VII. Uridine triacetate (Xuriden) is the only FDA approved therapy for HOA. The National Organization for Rare Disease Disorders and other expert opinions recommend treatment with uridine triacetate (Xuriden).

VIII. Uridine triacetate (Xuriden) should not be used for the treatment of fluoropyrimidine overdose/overexposure. A different formulation of uridine triacetate (Vistogard) has been approved by the FDA for the treatment of this condition.

Investigational or Not Medically Necessary Uses

I. Uridine triacetate (Xuriden) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Fluoropyrimidine overdose/overexposure

References

1. Xuriden [Prescribing Information]. Wellstat Therapeutics Corporation: Rockville, MD. September 2015.
2. FDA. Xuriden (uridine triacetate) oral granules. Medical Review Letter. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208169Orig1s000TOC.cfm. Accessed December 30, 2020.

3. National Organization for Rare Disorders. Hereditary Orotic Aciduria. Available at https://rarediseases.org/rare-diseases/hereditary-orotic-aciduria/. Accessed December 30, 2020.
4. Wellstat Therapeutics. Open-Label Study of Uridine Triacetate in Pediatric Patients with Hereditary Orotic Aciduria. Available at https://clinicaltrials.gov/ct2/show/NCT02110147. Accessed December 30, 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	01/2021