XURIDEN™ (uridine triacetate) oral granules

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms “experimental” and “investigational” are considered to be interchangeable.

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Description:

Xuriden (uridine triacetate) is a pyrimidine analog indicated for uridine replacement therapy for the treatment of hereditary orotic aciduria (HOA). Uridine triacetate is an acetylated form of uridine. Following oral administration, uridine triacetate is deacetylated by nonspecific esterases to uridine. The safety and effectiveness of Xuriden (uridine triacetate) was evaluated in a six-week, open-label trial in four patients with HOA. There has also been a retrospective review of the clinical course of 18 patients with HOA treated with uridine triacetate. The estimated birth prevalence is < 1:1,000,000, the disorder has been identified in less than 20 patients worldwide, with only four known patients in the United States. Uridine triacetate is also available as Vistogard® 10 gram granule packet that is indicated for the emergency treatment of fluorouracil or capecitabine overdose or overexposure. Xuriden™ is available as 2 gram granule packets.

HOA is a rare congenital autosomal recessive metabolic disorder in infants and children caused by a deficiency in uridine 5’-monophosphate (UMP) synthase. Deficiency of UMP synthase results in the inability to normally synthesize uridine nucleotides (a necessary component of ribonucleic acid) and causes developmental delays,
failure to gain weight / failure to thrive, hematologic abnormalities (such as megaloblastic anemia with anisocytosis, poikilocytosis, and moderate hypochromia, and leukopenia), and excessive urinary excretion of orotic acid crystals, which can lead to urinary obstruction. The anemia does not respond to iron, folic acid or vitamin B12.

Other treatments for HOA include therapy with uridine supplements. Xuriden (uridine triacetate) delivers 4-7 times more uridine than oral administration of uridine itself.

The urea cycle is the body’s primary system for removing waste nitrogen produced by the metabolism of protein and other nitrogen-containing molecules. Several enzymes, each encoded by a different gene, are involved in the urea cycle; mutations in any of the urea cycle genes may cause a urea cycle defect.

Orotic acid may be elevated in patients with urea cycle disorders and other causes of elevated ammonia. Elevated levels of urine orotic acid are seen in ornithine transcarbamylase (OTC) deficiency, citrullinemia type I, argininosuccinate lyase deficiency, arginase deficiency, llysinuric protein intolerance, and hyperornithinemia-hyperammonemia-homocitrullinemia. Elevated levels of urine orotic acid can also be due to purine nucleoside phosphorylase deficiency, Rett syndrome, Reye syndrome, Lesch-Nyhan syndrome, certain cases of pervasive developmental delay, and drugs such as allopurinol and 6-azauridine. Pregnant women may have higher than normal orotic acid excretion; and orotic aciduria has also been reported in traumatized individuals as a marker of catabolism.

Definitions:

Other causes of Urinary Orotic Acid Excretion:

- Urea cycle disorders
  - Ornithine transcarbamylase (OTC) deficiency
  - Citrullinemia
  - Argininosuccinic aciduria
  - Arginase deficiency
- Pyrimidine and pyrimidine metabolism disorders
  - Uridine monophosphate synthase deficiency (UMPS, hereditary orotic aciduria)
    - UMPS, type I
    - UMPS, type II
  - Hereditary orotic aciduria without megaloblastic anemia (OAWA)
  - Purine nucleoside phosphorylase (PNP) deficiency
- Drugs (via inhibition of orotidine-5'-monophosphate decarboxylase)
  - Allopurinol
  - 6-azauridine
- Severe Traumatic injuries
  - Motor vehicle accidents, accidental falls, and/or crush injuries
  - Multiple bone fractures, head injuries, and/or extensive soft-tissue damage
  - Gunshot wounds to the abdomen, chest and face
  - Sepsis and severe abdominal trauma - abdominal compartment syndrome
  - Non-accidental trauma, child abuse and/or penetrating injuries
- Other disorders/syndromes
XURIDEN™ (uridine triacetate) oral granules (cont.)

Lysinuric protein intolerance
Hyperornithinemia, hyperammonemia, and homocitrullinuria (HHH) syndrome
Rett syndrome
Reye syndrome
Lesch-Nyhan syndrome
Pervasive developmental delay (PPD)

Drug related events:

**Ineffective / failure**
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

**Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance**
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual’s outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

*Allergic reaction / hypersensitivity* – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

*Intolerance* – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

**Contraindication**
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental
Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Xuriden requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- **Initial therapy:** FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Xuriden is considered **medically necessary** when ALL of the following criteria are met:

  1. Individual is 2 months of age or older
  2. Provider is a specialist in inborn errors of metabolism or metabolic diseases
  3. Medical record documentation of a confirmed diagnosis of hereditary orotic aciduria with all of the following features:
     - Megaloblastic anemia unresponsive to iron, folic acid, or vitamin B12
     - Excessive urinary excretion of orotic acid
  4. **ALL** of the following baseline tests have been completed before initiation of treatment:
     - Complete blood count with differential
     - Urinalysis for orotic acid and orotidine levels
     - Ammonia level
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- **Continuation of coverage (renewal request):** Xuriden is considered *medically necessary* with documentation of **ALL** of the following:
  1. The individual has benefited from therapy but remains at high risk
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any contraindications or other exclusions to its continued use

- Xuriden for all other indications not previously listed is considered *experimental or investigational* based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

  This includes but is not limited to:
  - Hyperammonemia
  - Urea cycle disorder
  - Lysinuric protein intolerance
  - Hyperornithinemia, hyperammonemia, and homocitrullinuria (HHH) syndrome
  - Rett syndrome
  - Reye syndrome
  - Lesch-Nyhan syndrome
  - Pervasive developmental delay (PPD)
  - Purine nucleoside phosphorylase (PNP) deficiency
  - Severe traumatic injuries

**Resources:**


Anonymous: In Brief: Uridine Triacetate (Xuriden) for Hereditary Orotic Aciduria (online only). The Medical Letter on Drugs and Therapeutics. March 28, 2016 Issue 1491
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FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>XURIDEN is a pyrimidine analog for uridine replacement indicated for the</td>
<td>Recommended Dosage:</td>
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<tr>
<td>treatment of hereditary orotic aciduria.</td>
<td>• The starting dosage is 60 mg/kg once daily; the dose may be increased to 120 mg/kg (not to exceed 8 grams) once daily for insufficient efficacy.</td>
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<td></td>
<td>• See the full prescribing information for 60 mg/kg and 120 mg/kg weight-based dosing tables.</td>
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<td>Preparation and Administration</td>
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<td>• Measure the dose using either a scale accurate to at least 0.1 gram, or a graduated teaspoon, accurate to the fraction of the dose to be administered.</td>
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<tr>
<td></td>
<td>• Administer the dose with food (applesauce, pudding or yogurt) or in milk or infant formula. See full prescribing information for preparation and administration instructions.</td>
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