BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

VISTOGARD® (uridine triacetate)
XURIDEN™ (uridine triacetate)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for VISTOGARD (uridine triacetate)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in the diagnosis or in consultation with an Oncologist

Indication
- Emergency treatment of **ONE** of the following:
  - Following a fluorouracil or capecitabine overdose regardless if symptoms present

- Early-onset, severe or life-threatening toxicity affecting cardiac or central nervous system, and/or unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours after fluorouracil or capecitabine administration

Age Requirement
- 1 year of age or older

Baseline Clinical Evaluation
- Will not be used for non-emergent treatment of adverse reactions associated with fluorouracil or capecitabine
- Will not be used more than 96 hours following the end of fluorouracil or capecitabine administration

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the United States Food and Drug Administration (FDA)

Safety
- No concomitant use with Xuriden (uridine triacetate)

Documentation Requirements
- A completed request form must be submitted, including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- Used every 6 hours for 20 doses OR end of plan year

Medical Necessity Requirements for XURIDEN (uridine triacetate)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in the diagnosis or in consultation with a Geneticist, Endocrinologist, Pediatrician, Hematologist, or Specialist in Metabolic Disorders

Indication
- Hereditary orotic aciduria

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Age Requirement
- 2 months of age or older

Baseline Clinical Evaluation
- Megaloblastic anemia unresponsive to iron, folic acid, or vitamin B12
- Excessive urinary excretion of orotic acid
- Complete blood count with differential
- Urinalysis for orotic acid and orotidine levels

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the United States Food and Drug Administration (FDA)

Safety
- No concomitant use with Vistogard (uridine triacetate)

Documentation Requirements
- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (complete blood count with differential, urinalysis for orotic acid and orotidine levels)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)
Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification
- Continues to be seen by a physician specializing in or is in consultation with a Geneticist, Endocrinologist, Pediatrician, Hematologist, or Specialist in Metabolic Disorders

Clinical Response
- Achieved and maintains stable complete blood count
- Reduced urine orotic acid levels
- Reduced urine orotidine levels

Adherence
- Adherence to the prescribed therapy regimen has been documented

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Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant use with Vistogard (uridine triacetate)

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

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. Vistogard is not used for non-emergent treatment of adverse reactions associated with fluorouracil or capecitabine because it may diminish the efficacy of these drugs. Vistogard is also not used more than 96 hours following the end of fluorouracil or capecitabine administration as the efficacy and safety have not been established.
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, lysinuric 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:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

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

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

Resources:

Xuriden (uridine triacetate) granules product information, revised by BTG International, Inc. 08-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Vistogard (uridine triacetate) granules product information, revised by BTG International, Inc. 10-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Sutton VR. Inborn errors of metabolism: Epidemiology, pathogenesis, and clinical features. In: UpToDate, Kaplan SL, Kremen J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025.Topic last updated October 26, 2023. Accessed March 10, 2025.

National Organization for Rare Disorders (NORD). Hereditary orotic aciduria. Last updated September 06, 2018. Published 2018. Accessed April 12, 2023. Re-evaluated March 10, 2025.