uridine triacetate (Xuriden™)

Policy # 00507
Original Effective Date: 05/18/2016
Current Effective Date: 06/14/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider uridine triacetate (Xuriden™)‡ for the treatment of hereditary orotic aciduria to be **eligible for coverage.****

Patient Selection Criterion
Coverage eligibility for uridine triacetate (Xuriden) for the treatment of hereditary orotic aciduria will be considered when the following criterion is met:

- Patient has a documented diagnosis of hereditary orotic aciduria.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of uridine triacetate (Xuriden) when patient selection criteria are not met to be **investigational.***

Background/Overview

Xuriden is a pyrimidine analog for uridine replacement indicated for the treatment of hereditary orotic aciduria. Xuriden is an acetylated form of uridine. After oral administration, the Xuriden is de-acetylated by esterases in the body, yielding uridine in the circulation. Xuriden is supplied as oral granules in 2 gram packets. The starting dose of Xuriden is 60 mg/kg once daily. The dose may be increased to 120 mg/kg once daily (not to exceed 8 grams) for insufficient efficacy.

Hereditary Orotic Aciduria
Hereditary orotic aciduria (uridine monophosphate synthase deficiency) is a rare congenital autosomal recessive disorder of pyrimidine metabolism caused by a defect in uridine monophosphate synthase (UMPS). The UMPS gene encodes uridine 5′monophosphate synthase, an enzyme that catalyzes the final two steps of the pyrimidine biosynthetic pathway. This enzyme deficiency leads to a lack of uridine and an overproduction of orotic acid. The buildup of orotic acid causes clinical manifestations of megaloblastic anemia, orotic crystalluria and nephropathy, cardiac malformations, strabismus, recurrent infections, and delays in physical and intellectual development. Once uridine is introduced into the system, feedback inhibition occurs and the overproduction of orotic acid is reduced.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Xuriden was approved in September of 2015 for the treatment of hereditary orotic aciduria.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Xuriden was evaluated in an open label study in 4 patients with hereditary orotic aciduria. Three of the patients were treated previously with uridine and then transitioned to Xuriden. The dose of Xuriden provided to patients in this trial was 60 mg/kg once daily and the duration of the study was 6 weeks. The endpoints studied were the patients' pre-specified hematologic parameters during the trial period. These parameters varied for each patient, but examples include: neutrophil count and percent neutrophils, white blood cell count, and mean corpuscular volume. The primary endpoint for those that were on uridine was the stability of the hematologic parameter, and for the treatment naïve patient, the primary endpoint was improvement of the hematologic parameter. Secondary endpoints were urine orotic acid and orotidine levels and growth (height/weight) for all patients. After six weeks of treatment, Patients 1 and 3 met the pre-specified

criteria for stability of the hematologic parameter. When Patient 2 was switched from uridine to Xuriden treatment, the pre-specified criteria for white blood cell count remained stable; however documentation of a low white blood cell count prior to uridine initiation was not available. Patient 4 did not meet the pre-specified endpoint of improvement of the hematologic parameter. At baseline, three patients had normal urine orotic acid levels and all four patients had normal urine orotidine levels. Three patients who had achieved normal urine orotic acid levels when they were treated with uridine maintained normal levels 6 weeks after transitioning to Xuriden. All four patients had normal urine orotidine levels at baseline which remained stable after 6 weeks of treatment with Xuriden. The treatment effect of Xuriden on growth was assessed in the three pediatric patients (Patients 1, 3, and 4). At baseline, weight and height measurements were at or below the lower limit of normal for age (below 5th percentile for age) for Patients 1 and 4; height and weight measurements were within the normal range for age for Patient 3. After 6 months of treatment, Patients 1 and 3 experienced improved weight growth, as reflected in increases in their weight-for-age percentiles and weight velocity percentiles; Patient 4's weight growth remained stable (i.e., weight percentile for age and weight velocity percentile for age was unchanged). Height growth remained stable in all three patients (i.e., height percentiles for age and height velocity percentiles for age were unchanged).

The package insert also refers to 19 case reports over the years in patients with hereditary orotic aciduria. Most of the patients were diagnosed at a young age. All of the patients presented with a significantly elevated level of urinary orotic acid. Fifteen of the nineteen had megaloblastic anemia, 8 with leukopenia, and at least 2 with neutropenia. These patients were treated with exogenous uridine and the hematologic parameters were improved within 2-3 weeks in most cases. The urinary orotic acid levels were significantly reduced within 1-2 weeks of uridine therapy. Fluctuations did occur, but levels were always at much lower levels than before treatment. Improvement in body weight was also noted. Effects of exogenous uridine were maintained over months and years as long as treatment continued and was adjusted per body weight increases. If the exogenous uridine was stopped, the orotic aciduria and hematologic abnormalities would resurface. Body growth also receded if the uridine was interrupted.

References

1. Xuriden [package insert]. Wellstat Therapeutics. Gaithersburg, Maryland. September 2015.

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05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. New policy.
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2019	Medical Policy Committee review
05/15/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2022

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.