IOWA | Health and Human Services

Iowa PDL New Drug Review

Proprietary Name: Harliku®
Common Name: nitisinone
PDL Category: Gastrointestinal Agent

Pharmacology/Usage: Nitisinone, the active ingredient of Harliku®, is a competitive inhibitor of hydroxyphenyl-pyruvate dioxygenase, an enzyme upstream of homogentisate 1,2-dioxygenase (HGD) in the tyrosine catabolic pathway.

Nitisinone inhibits catabolism of the amino acid tyrosine and can result in elevated plasma levels of tyrosine in patients with alkaptonuria (AKU). Treatment with nitisinone does not require routine dietary restriction in patients with AKU; however, patients who develop keratopathies should be monitored and dietary restriction of tyrosine and phenylalanine should be implemented.

Indication: For the reduction of urine homogentisic acid (HGA) in adult patients with alkaptonuria (AKU).

There is no pregnancy category for this medication; however, the risk summary indicates that available data from published case reports with use in pregnant women are not sufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Tablets: 2mg.

Recommended Dosage: The recommended dosage is 2mg PO QD, with or without food. If a dose is missed, do not administer two doses at once to make up for a missed dose. Take the next dose at the scheduled time.

Drug Interactions: Nitisinone is a moderate CYP2C9 inhibitor. Reduce the dosage of the co-administered drug metabolized by CYP2C9 by half. Additional dosage adjustments may be needed to maintain therapeutic drug concentrations where minimal concentration changes may lead to serious adverse reactions. See prescribing information for those drugs.

Nitisinone is an OAT1/OAT3 inhibitor which can lead to increased exposure of the co-administered drug. The concomitant use of Harliku® with OAT1/OAT3 substrates may increase the risk of adverse reactions related to the co-administered drug. See prescribing information for those drugs.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (nitisinone) minus reported % incidence for no treatment. Please note that an incidence of 0% means the incidence was the same as or less than no treatment.* The most frequently reported adverse events included elevated tyrosine levels (95%), keratitis (15%), and thrombocytopenia (10%). Keratitis also includes eye irritation, eye pain, and photophobia.

Treatment with Harliku® may cause elevated plasma tyrosine levels in patients with AKU. Tyrosine levels greater than 500 micromol/L may lead to the following:

- Ocular signs and symptoms including keratitis, corneal opacities, corneal irritation, corneal ulcers, conjunctivitis, eye pain, and photophobia. These ocular adverse reactions have been reported in patients treated with nitisinone. Perform a baseline ophthalmologic examination, including slit-lamp examination, prior to starting Harliku® and regularly thereafter. Patients who develop photophobia, eye pain, or signs of inflammation such as redness, swelling, or burning of the eyes or tyrosine levels are >500 micromol/L during Harliku® treatment should undergo slit-lamp re-examination and immediate measurement of the plasma tyrosine concentration.
- Painful hyperkeratotic plaques on the soles and palms.

There is no routine dietary restriction requirement for AKU patients taking Harliku®. However, in patients who develop keratopathies, monitor plasma tyrosine levels, and implement a diet restricted in tyrosine and phenylalanine to keep the plasma tyrosine level below 500 micromol/L. Consider temporarily interrupting Harliku® until resolution of symptoms.

In clinical trials, patients with hereditary tyrosinemia type 1 (HT-1) treated with another oral formulation of nitisinone and dietary restriction developed reversible leukopenia (3%), thrombocytopenia (3%), or both (1.5%). In addition, 10% of patients in Trial 1 developed thrombocytopenia. No patients developed infections or bleeding as a result of the episodes of leukopenia and thrombocytopenia. Monitor platelet and white blood cell counts during Harliku® therapy.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Cycle Pharmaceuticals Ltd.

Analysis: The efficacy of Harliku® was assessed in an open-label, single center, randomized, no-treatment controlled trial that included adult patients (N=40) diagnosed with AKU. Patients received either Harliku® 2mg QD or no treatment for 3 years.

One patient in the Harliku® group died after experiencing atrial fibrillation and had discontinued treatment one month prior to death, and 2 patients in the no treatment control group discontinued the study early. Of the 40 patients enrolled in the trial, 67.5% were male, 92.5% were White, and the mean age was 51.7 years (range 38 to 68).

Harliku® was effective at reducing levels of urinary HGA. The Harliku® group had an average percent reduction from baseline of 88% after 1 year of treatment, which was sustained through three years of treatment with an average percent reduction from baseline of 91% at year 3. In contrast, the untreated controls had an average increase of 107% from baseline to year 1 and 108% from baseline to year 3.

Place in Therapy: Harliku® is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated for the reduction of urine homogentisic acid (HGA) in adult patients with alkaptonuria (AKU). The efficacy of Harliku® was assessed in an open-label, single center, randomized, no-treatment controlled trial that included adults with AKU. Results suggested that Harliku® was effective at reducing levels of urinary HGA. The Harliku® group had an average percent reduction from baseline of 88% after 1 year of treatment, which was sustained through three years of treatment with an average precent reduction from baseline of 91% at year 3. In contrast, the untreated controls had an average increase of 107% from baseline to year 1 and 108% from baseline to year 3. Harliku® is the only FDA-approved treatment for urinary HGA reduction in adults with AKU.

Summary

It is recommended that Harliku® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Harliku [package insert]. Cambridge, CB3 0FA, United Kingdom; Cycle Pharmaceuticals Ltd; 2025.