Treatment for Alkaptonuria

harliku™
(nitisinone) Tablets

HARLIKU is the **first and only** FDA-approved treatment to reduce homogentisic acid (HGA) in adult patients with alkaptonuria (AKU).

Indications

HARLIKU™ is indicated for the reduction of urine homogentisic acid (HGA) in adult patients with alkaptonuria (AKU).

Important Safety Information

Do not prescribe HARLIKU to patients allergic to nitisinone or any other contained ingredients.

Warnings and Precautions:

Ocular Symptoms and Hyperkeratotic Plaques Due to Elevated Plasma Tyrosine Level:

Ocular signs and symptoms including keratitis, corneal opacities, corneal irritation, corneal ulcers, conjunctivitis, eye pain, and photophobia, have been reported in patients.

• Perform slit-lamp examination prior to treatment and regularly thereafter. Reexamine patients if symptoms develop or tyrosine levels are > 500 micromole/L. Assess plasma tyrosine levels in patients with an abrupt change in neurological status.

• Perform a clinical laboratory assessment, including plasma tyrosine levels, in patients with an abrupt change in neurological status.

Leukopenia and Severe Thrombocytopenia

In clinical trials, patients with hereditary tyrosinemia type 1 (HT-1) treated with another oral formulation of nitisinone and dietary restriction, developed reversible leukopenia, thrombocytopenia, or both. 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.

Adverse Reactions:

The most common adverse reactions (≥1%) reported in patients with AKU taking nitisinone in clinical trials are elevated tyrosine levels, thrombocytopenia and keratitis.

Drug Interactions:

• Nitisinone is a moderate CYP2C9 inhibitor and a weak CYP2E1 inducer. Potential clinical impact of Harliku administration with CYP2C9 substrates. Reduce the dosage of the co-administered drugs metabolized by CYP2C9 by half. Additional dosage adjustments may be needed.

• Nitisinone is an inhibitor of OAT1/OAT3. Potential clinical impact of administration with OAT1/OAT3 substrates. Patients should be monitored for potential adverse reactions.

Use in Specific Populations:

Pregnancy: Limited available data with nitisinone use in pregnant women are not sufficient to determine a drug-associated risk of adverse developmental outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Lactation: The developmental and health benefits of breastfeeding should be considered against the mother's clinical need for HARLIKU, along with potential adverse effects on the breastfed infant from HARLIKU or from the underlying maternal condition.

Pediatric Use: The safety and effectiveness of HARLIKU have not been established in pediatric patients with AKU.

Geriatric Use: Insufficient data from clinical studies of HARLIKU to determine if patients ≥ 65 years of age respond differently. Elderly patients should be cautious reflecting any decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

For more detailed information, please refer to the full Prescribing Information at harliku.com/PI/.

To report SUSPECTED ADVERSE REACTIONS, contact Cycle Pharmaceuticals at 1-855-831-5413, or the FDA at: 1-800-FDA-1088 or www.fda.gov/medwatch.

How Do HARLIKU™ (nitisinone) Tablets Work?

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Nitisinone, the active ingredient in HARLIKU treatment, is effective in significantly reducing symptoms of disease in AKU patients.[1]

It blocks the tyrosine degradation pathway upstream of homogentisate 1,2-dioxygenase (HGD). As a potent inhibitor of 4-hydroxyphenylpyruvic acid dioxygenase (4-HPPD),[2] nitisinone blocks the pathway upstream of HGA production.

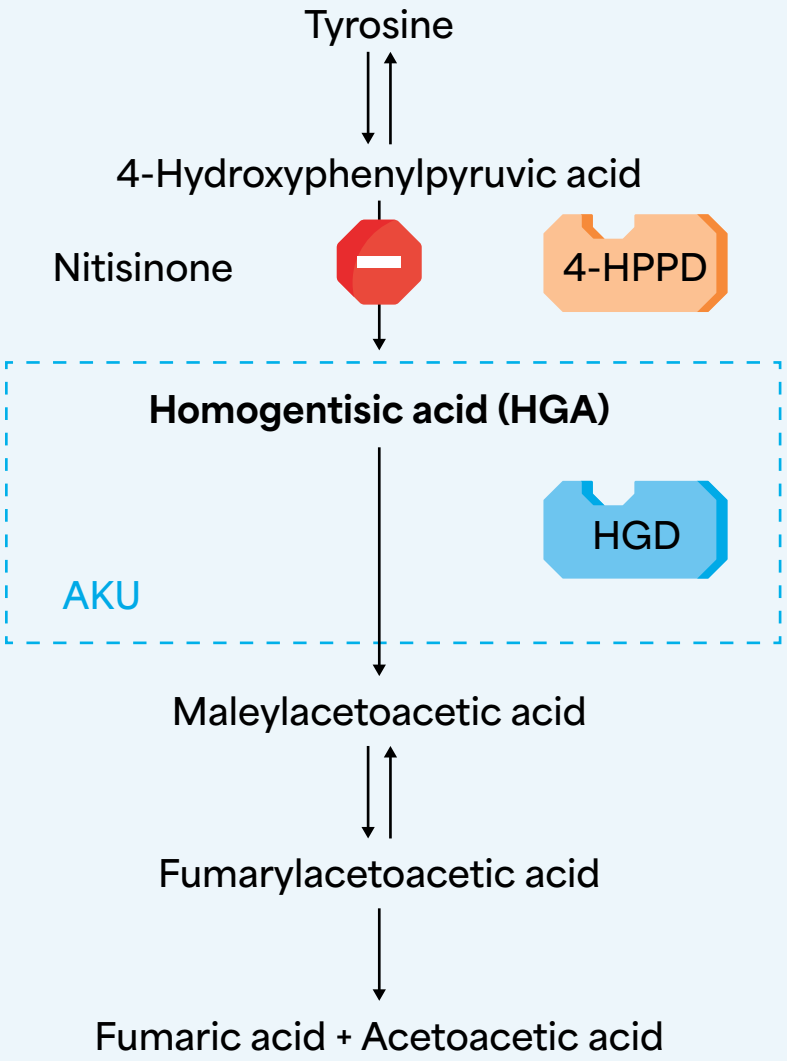

Fig. 1. Tyrosine catabolism pathway. 4-HPPD, 4-hydroxyphenylpyruvate dioxygenase; HGD, homogentisate 1,2-dioxygenase.[4]

Patients with AKU can have an improved quality of life with HARLIKU.[3]

not an actual patient

Key Benefits of Nitisinone:

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Reduces urine HGA levels in AKU patients by up to 97%[3]

Improves quality of life[4]

In an open-label, randomized study of 40 patients, nitisinone-treated patients reported significant improvement in the 36-Item Short-Form Survey (SF-36) domains of physical functioning, pain, and energy and fatigue. (Table 1)[4]

Improves physical functioning[4]

In the open-label, randomized study, after 3 years of nitisinone treatment, patients experienced significant improvement in their distance walked in the 6 Minute Walk Test (6MWT). (Table 1)[4]

Helps with slowing progression of AKU symptoms[1]

In an observational study of 39 patients, the average Alkaptonuria Severity Scoring Index (AKUSSI) change score decreased over the course of treatment, from 0.65 ± 0.15 at baseline to 0.15 ± 0.13 after 3 years of nitisinone, signifying a reduction in the rate of progression.[1]

Table 1. Significant improvements in SF-36 domain scores and 6MWT after three years of nitisinone treatment[4]

Average domain scores and *p*-values from paired analyses within the nitisinone-treated group. No significant differences were observed within the untreated group.

Year of visit (Nitisinone-treated)	SF-36 Pain	SF-36 Energy & Fatigue	SF-36 Physical Functioning	Distance Walked in 6MWT (ft)
Initial	37.03	38.75	38.75	1371
3 year	56.41	52.19	53.44	1527
P-value	0.0025	0.0160	0.0062	0.0061

Prescribing HARLIKU

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Starting a patient on nitisinone has been shown to be beneficial in slowing the clinical progression of AKU.[1]

Give your patient with AKU a brighter future by starting them on HARLIKU before the onset of significant clinical symptoms.[1]

More information

Watch this webinar from National Institutes of Health (NIH) experts, Dr Wendy J. Introne, MD, and Dr William A. Gahl, MD, PhD. They will guide you through diagnostic strategies and the latest developments in evidence-based nitisinone treatment for AKU: **harliku.com/hcp/aku-webinar/**

The following articles have more information about nitisinone*:

Spears, K.R., et al, (2024). Patient-reported outcomes and functional assessments of patients with Alkaptonuria in a 3-year Nitisinone treatment trial. Molecular Genetics and Metabolism, 143(1-2), p.108562. https://pubmed.ncbi.nlm.nih.gov/39121793/

Ranganath, L.R., et al. (2018). Nitisinone arrests ochronosis and decreases rate of progression of Alkaptonuria: Evaluation of the effect of nitisinone in the United Kingdom National Alkaptonuria Centre. Molecular Genetics and Metabolism, 125(1), pp.127-134. https://pubmed.ncbi.nlm.nih.gov/30055994/

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References:

1. Ranganath L, et al, 2018, Nitisinone arrests ochronosis and decreases rate of progression of Alkaptonuria: Evaluation of the effect of nitisinone in the United Kingdom National Alkaptonuria Centre .Mol Genet. https://pubmed.ncbi.nlm.nih.gov/30055994/

2. Zatkova, A., Ranganath, L., & Kadasi, L. 2020. Alkaptonuria: Current Perspectives. The application of clinical genetics, 13, 37-47. doi:10.2147/TACG.S186773

3. HARLIKU (nitisinone) Tablets. Prescribing Information. Cycle Pharmaceuticals Ltd

4. Spears KR, Rossignol F, Perry MB, et al. 2024 Patient-reported outcomes and functional assessments of patients with Alkaptonuria in a 3-year Nitisinone treatment trial. Mol Genet Metab. 143(1-2),108562. doi:10.1016/j.ymgme.2024.108562

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