Subject: Nitisinone (Orfadin, Nityr)	Original Effective Date: 7/10/2018
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Review Date:	
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Nitisinone (Orfadin, Nityr)** for the treatment **hereditary tyrosinemia type 1 (HT-1), a rare, genetic pediatric disease,** when appropriate criteria are met.

The intent of the **Nitisinone (Orfadin, Nityr)** policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

- **Hereditary Tyrosinemia Type 1 (HT-1)**
  - HT-1 is a rare, autosomal recessive genetic disorder (*estimated birth prevalence: 1 in 12,000 to 1 in 100,000 individuals of northern European descent*) caused by mutations in the gene responsible for formation of fumarylacetoacetate hydrolase (FAH), which catalyzes the last step in tyrosine metabolism. In normal, unaffected individuals, excess amounts of the amino acid tyrosine are degraded in several steps. In HT-1, however, one of the enzymes in this degradation, fumarylacetoacetase hydrolase (FAH), is deficient. FAH deficiency results in accumulation of upstream toxic metabolites, causing liver and kidney failure and developmental delays. Before the advent of liver transplantation, HT-1 was invariably fatal, usually as a result of liver failure or hepatocellular carcinoma.
  - Untreated tyrosinemia type I usually presents either in young infants with severe liver involvement or later in the first year with liver dysfunction and renal tubular dysfunction associated with growth failure and rickets. Untreated children may have repeated, often unrecognized, neurologic crises lasting one to seven days that can include change in mental status, abdominal pain, peripheral neuropathy, and/or respiratory failure requiring mechanical ventilation. Death in the untreated child usually occurs before age ten years, typically from liver failure, neurologic crisis, or hepatocellular carcinoma. (Sniderman King L, et al.)

- Combined treatment with nitisinone and a low-tyrosine diet has resulted in a greater than 90% survival rate, normal growth, improved liver function, prevention of cirrhosis, correction of renal tubular acidosis, and improvement in secondary rickets. (Sniderman King L, et al.)
  - Low-protein, tyrosine- and phenylalanine-restricted diet plus nitisinone is first-line treatment for tyrosinemia type 1
  - Dietary restrictions, consists of foods with low or absent phenylalanine and tyrosine and restriction of natural protein, results in decreased tyrosine levels. However, this approach does not stop the production of SA, prevent the progression of liver or renal disease, or reduce the risk of developing hepatocellular carcinoma or neurologic abnormalities. Dietary restrictions must be continued and monitored indefinitely.
  - **Nitisinone (Orfadin, Nityr)**
    - Nitisinone is the medical treatment of choice for hereditary tyrosinemia type 1 (HT-1) (Grompe M.) and is the first drug approved for the treatment of HT-1. The treatment of adult and pediatric patients with hereditary tyrosinemia type-1 in combination with a dietary restriction of tyrosine and phenylalanine.
    - Nitisinone inhibits one of the first enzymes in this tyrosine degradation pathway [4-hydroxyphenyl-pyruvate dioxygenase (HPD)] to limit the formation and accumulation of the toxic metabolites.
    - It is available in two bioequivalent brands, **Orfadin (capsules and suspension) and Nityr (tablets).**
  - Prior to the availability of nitisinone, the only definitive therapy for tyrosinemia type I was liver transplantation, which now should be reserved for those children who have severe liver failure at presentation and fail to respond to nitisinone therapy or have documented evidence of malignant changes in hepatic tissue.

- **The long-term risk of developing neurologic problems on nitisinone therapy is unknown.** This is a concern because neurologic complications develop in some patients with inherited HPD deficiency, the same enzyme affected by nitisinone (Origuchi Y, et al.; Giardini O et al). A study of long-term outcomes of nitisinone treatment in France showed cognitive impairment in 35 percent of patients (Masurel-Paulet A, et al.). A subsequent Dutch study demonstrated that some patients experience cognitive decline over time despite nitisinone treatment and despite dietary control of tyrosine levels (Bendadi F, et al.). It is not known whether this phenotype is related to elevated tyrosine, phenylalanine deficiency, or caused by other factors.

- Adverse effects occurring in 1% or more of patients receiving nitisinone include hepatic neoplasms, liver failure, thrombocytopenia, leukopenia, conjunctivitis, corneal opacity, keratitis, photophobia, blepharitis, ocular pain, cataracts, porphyria, epistaxis, pruritus, exfoliative dermatitis, dry skin, maculopapular rash, and alopecia.

- Nitisinone has significantly improved the prognosis for those with HT1. However because newborn screening is only available in a few countries most patients still present clinically. **Early treatment with nitisinone and strict diet is essential.** Careful long term monitoring and management is required. **Prospective, controlled treatment studies are needed to develop evidence-based guidelines for the future management of HT1.**

CLASSIFICATION: Reversible inhibitor of hydroxyphenylpyruvate; 4-Hydroxyphenylpyruvate Dioxygenase Inhibitor

Nitisinone competitively inhibits 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme present early in the tyrosine degradation pathway, thereby preventing the build-up of the toxic metabolites.

FDA INDICATIONS

HEREDITARY TYROSINEMIA TYPE 1
Treatment of hereditary tyrosinemia type 1 as an adjunct to dietary restriction of tyrosine and phenylalanine in adult and pediatric patients.

- *Orphan drug designation: Treatment of tyrosinemia type 1: Orfadin was designated an Orphan Drug in May 1995 by the Office for Orphan Product Development. Orphan products are developed to treat rare diseases - there are less than 100 children in the United States with HT-1.*

Available in two bioequivalent brands, Orfadin (capsules and suspension) and Nityr (tablets)
Refrigeration

- Orfadin (capsules and suspension) requires refrigeration.
- Nityr is the first formulation of nitisinone treatment for HT-1 that does not require refrigeration. Nityr tablets may be stored at room temperature.

Dosing and Administration

- Nityr (tablets) may be administered without regard to meals
- Orfadin (suspension) without regard to meals and Orfadin (capsules) should be administered at least 1 hour prior to, or 2 hours after a meal
- Oral suspension contains a unique warning for adverse reactions caused by glycerol, an inactive ingredient of this formulation. Oral doses of glycerol of 10 grams or more (contained in single doses of Orfadin more than 20 mL) have been reported to cause headache, upset stomach, and diarrhea; patients who are unable to tolerate the suspension should consider switching to capsules.
- Both the Orfadin capsules and Nityr tablets may be dissolved in water or applesauce for easier administration.
- Both products should be dosed twice daily in patients under five years of age, however Orfadin may be administered once daily in patients five years of age and older who have undetectable serum and urine succinylacetone concentrations after a minimum of 4 weeks on a stable dosage of nitisinone.

Available as:

- Capsule, Oral:
  Orfadin: 2 mg, 5 mg, 10 mg, 20 mg
- Suspension, Oral:
  Orfadin: 4 mg/mL (90 mL) [contains polysorbate 80, sodium benzoate]
- Tablet, Oral:
  Nityr: 2 mg, 5 mg, 10 mg

FDA Approved:
Orfadin (capsules): January 2002
Orfadin (oral suspension): April 2016
Nityr (tables): July 2017

Black Box Warnings: None at the time of this writing

REMS: None at the time of this writing

RECOMMENDATIONS/COVERAGE CRITERIA

Nitisinone (Orfadin, Nityr) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or in consultation with, a specialist in metabolic or genetic disease, or in the treatment of **hereditary tyrosinemia type 1 (HT-1)** or in consultation with this specialist. Submit consultation notes if applicable.

  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]
Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis

- ❒ Diagnosis of **hereditary tyrosinemia type 1 (HT-1)** confirmed by biochemical testing or DNA testing: [ONE]
  - ❍ Detection of succinylacetone in urine: Elevated urinary or plasma succinylacetone (SA) levels
  - ❍ DNA testing: Mutation in the fumarylacetoacetate hydrolase (FAH) gene

  Informational Note: Detection of succinylacetone (SA: the principal metabolite of FAA) in urine, blood, or amniotic fluid is the most reliable diagnostic test for HT-1. Genetic testing for disease-causing mutations is also available and may be useful for prenatal diagnosis and reproductive counseling, but is not essential for clinical management.

- ❒ **Baseline** liver evaluation and ophthamalogic testing

  NOTE: Ophthalmologic examination and hepatic imaging (magnetic resonance imaging is preferred) should be performed annually

3. Age/Gender/Restrictions [ALL]

- ❒ Laboratory monitoring will be conducted regularly, as appropriate throughout therapy, including but not limited to: [ALL]
  - ❍ Dietary tyrosine and phenylalanine
  - ❍ Urine or plasma succinylacetone, liver function parameters, and alpha-fetoprotein levels (in addition, at initiation or if there is a deterioration of the individual's clinical condition, may also monitor urine 5-aminolevulinate and erythrocyte porphobilinogen-synthase activity)

    NOTE: Follow-up urinary or plasma succinylacetone levels required for continuation of treatment requests (a <u>decrease</u> from baseline while on treatment with nitisinone)

- ❍ Body weight; slit-lamp examination (prior to initiation of therapy and in patients who develop symptoms of ocular toxicity)
- ❍ Plasma tyrosine (as clinically indicated with side effects; concentrations should be kept <500 micromole/L to avoid toxicity)
- ❍ Platelet and white blood cell counts (regularly during therapy)

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ Prescribed as an **adjunct to dietary restriction of tyrosine and phenylalanine** as dietary restrictions of tyrosine and phenylalanine alone sufficient to maintain the urinary succinylacetone at or below detectable levels
- ❒ Member currently placed on a liver transplantation waiting list, or member will likely become a candidate for liver transplantation within the next year.

  NOTE: If yes, please provide information to Molina Healthcare as authorization should be provided for a length sufficient up to time of transplant.
- ❒ **For Orfadin requests:** Clinical evidence or medical record documenting the use of **Nityr** will be ineffective or cause an adverse reaction to the member

  NOTE: This specific criterion is an additional Company requirement for coverage of the requested medication. Request will not be authorized if criterion is not met.

5. Contraindications*Exclusions/Discontinuations

**There are no contraindications listed in the manufacturer's labeling and the manufacturer states that no drug interaction studies have been conducted to date.*

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to nitisinone or any component of the formulation

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Nitisinone (Orfadin, Nityr) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria [ALL]

- ❑ Member currently meets ALL initial coverage criteria
- ❑ Subsequent authorizations will require the Member to have an office visit and re-assessment for this condition annually to determine if continuation of treatment with requested medication is medically necessary. Chart notes or consultation notes (if applicable) must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Compliance [ALL]

- ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance), including: [ALL]
  - ❍ Adherent to the prescribed medication regimen
  - ❍ Tolerance to therapy
  - ❍ No severe adverse reactions or drug toxicity

NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

NOTE: History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY

3. Labs/Reports/Documentation required [ALL]

Nitisinone (Orfadin, Nityr) therapy may be authorized with continued clinical need and **positive clinical response** as evidenced by the following: [ALL]

- ❒ Urinary or plasma succinylacetone (SA) levels have **decreased from baseline** while on treatment with nitisinone

EXCEPTION: If the nitisinone levels is between the recommended range (40 and 60 µmol/L), monitoring plasma/urine succinylacetone may not be considered necessary. Submit blood nitisinone levels (must be between 40 and 60 µmol/L).

- *Nitisinone is generally prescribed at 1.0 mg/kg/day; individual requirements may vary. Dosage should be adjusted to maintain blood nitisinone levels between 40 and 60 µmol/L, which theoretically blocks more than 99% of p-HPPD activity. Rarely, an individual may require higher blood levels of nitisinone (70 µmol/L) to suppress succinylacetone excretion. As long as blood concentration of nitisinone is within the therapeutic range, urine succinylacetone does not need to be measured. (Sniderman King L et al.).*

- ❒ Monitoring of hepatic and ophthamalogic side effects testing (recommended once annually or as clinically appropriate for member's condition)

  NOTE: Periodic monitoring with imaging studies (ultrasound, computerized tomography, magnetic resonance imaging) and laboratory tests (serum α-fetoprotein) should be performed in patients receiving nitisinone for treatment of tyrosinemia type.

  Informational Note: Ophthalmologic examination should be performed prior to initiating Orfadin treatment; patients who develop ocular adverse reactions or exhibit an abrupt change in neurologic status should undergo ophthalmologic re-examination and immediate measurement of plasma tyrosine concentrations. Orfadin dosing should not be adjusted in order to lower plasma tyrosine concentrations; concomitant restriction of dietary tyrosine and phenylalanine should be maintained and dietary intake reassessed.

- ❒ Plasma tyrosine level is maintained **below 500 µmol/L (micromol/L)** to reduce risk of ocular symptoms, developmental delay, or hyperkeratotic plaques
  - *International workshop group recommends plasma tyrosine level < 400 µmol/L (3.6 mg/dL) as target (Orphanet J Rare Dis 2014 Aug 1;9:107)*
  - *Treatment with Orfadin may cause an increase in plasma tyrosine levels, which at levels > 500 µmol/L may lead to ocular signs and symptoms (e.g., corneal ulcers, corneal opacities, conjunctivitis, keratitis, eye pain, photophobia), varying degrees of intellectual disability and developmental delay, and painful hyperkeratotic plaques on the soles and palms.*

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity, including but not limited to: [ANY]
  - ❍ **Ocular Effects**. Corneal ulcers, corneal opacities, keratitis, conjunctivitis, ocular pain, and photophobia have been reported in patients receiving nitisinone. Slit-lamp examination should be performed prior to initiation of nitisinone therapy; patients who develop photophobia, ocular pain, or signs of ocular inflammation (e.g., ocular redness, swelling, burning) during therapy with the drug should be promptly evaluated by slit-lamp examination and by measurement of plasma tyrosine concentration.
  - ❍ **Hepatic Effects**. Liver failure or hepatic neoplasms may occur in patients with tyrosinemia type 1.
  - ❍ **Plasma Tyrosine Concentrations**. Elevation of plasma tyrosine concentrations can result from inadequate restriction of tyrosine and phenylalanine intake in patients receiving nitisinone; plasma tyrosine concentrations should be maintained below 500 µmol/L to avoid toxic effects to the eyes, skin, and nervous system. If plasma tyrosine concentrations exceed 500 µmol/L, a more-restricted diet should be implemented; nitisinone dosage should not be adjusted to reduce plasma tyrosine concentrations.
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms

Contraindications/Exclusions/Discontinuations

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to nitisinone or any component of the formulation

5. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ALL]

Tyrosinemia Type I; Adjunct

- ❒ 1mg/kg/day to 2mg/kg/day in divided doses. Initial: 0.5 mg/kg orally twice daily; if succinylacetone is detectable after 4 weeks, increase to 0.75 mg/kg twice daily. *Titrate the dose based on biochemical and/or chemical response, as described in the full prescribing information.*

  NOTE: Must be used in conjunction with a diet restricted in tyrosine and phenylalanine. Titrate dose as needed based on biochemical and/or clinical response. If the biochemical response is satisfactory, the dosage should be adjusted only according to body weight gain. Do not adjust dose according to plasma tyrosine concentration.

- ❒ Adult and pediatric patients: Maximum dose of 2 mg/kg/day

2. Authorization Limit [ALL]

- ❒ Quantity limit: 1 mg/kg orally twice daily (2 mg/kg/day)
- ❒ Dispensing limit: Only a 1-month supply may be dispensed at a time
- ❒ Duration authorization: [ALL]
  - ❍ Initial: 6 months
  - ❍ Continuation: 6 months
- ❒ Continuation of treatment: Re-authorization is required every **6 months** to determine effectiveness of therapy and continued need based on documented positive clinical response. Subsequent renewals will be authorized upon verification of marked clinical improvement demonstrated by objective improvement in these selected markers. *Refer to 'Continuation of Therapy' section.*

3. Route of Administration [ALL]

- ❒ Orfadin (nitisinone) is considered a **self-administered** medication
  - ◆ *Orfadin (nitisinone is deemed appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility will not be authorized.*
- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider. These agents must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

This policy addresses the coverage of **Nitisinone (Orfadin, Nityr)** for the treatment **hereditary tyrosinemia type 1** when appropriate criteria are met.

All other uses of **Nitisinone (Orfadin, Nityr)** that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

SUMMARY OF CLINICAL EVIDENCE

Hereditary Tyrosinemia

- Hereditary tyrosinemia is an inborn error of amino acid metabolism characterized by elevated tyrosine levels in fluids and tissues. *Dynamed 2018*

- Occurs as 3 different types, caused by 3 different gene mutations, each affecting a different enzyme involved in tyrosine metabolism*Dynamed 2018*
  - **Type 1** is characterized by liver and renal dysfunction, growth failure, rickets, neurologic crises, and hepatocellular carcinoma
  - **Type 2** is characterized by ocular and cutaneous changes and developmental delay
  - **Type 3** (rare) may be asymptomatic or characterized by ataxia and mild cognitive delay

PIVOTAL TRIAL

EFFICACY

- The efficacy of Orfadin was evaluated in an open-label, uncontrolled study of 207 patients with hereditary tyrosinemia type I (HT-1), ages 0 to 22 years (median age 9 months) at the time of enrollment.

  All patients were treated with Orfadin (nitisinone):
  - In addition to dietary restriction of tyramine and phenylalanine
  - At a starting dose of 0.3-0.5 mg/kg twice daily, and the dose was increased in some patients to 1 mg/kg twice daily based on biochemical and clinical response

  Median duration of treatment was 22 months (range <1 month to 80 months). The long-term effect of Orfadin on hepatic function was not assessed in the clinical trial.

  Efficacy was assessed by comparing survival and incidence of liver transplant to historical controls: 2 and 4 year survival probabilities were compared to historical controls treated with dietary restriction alone.

  Results
  - **Patients presenting with HT-1 younger than 2 months of age who were treated with nitisinone and dietary restriction had both 2 and 4 year survival probabilities of 88%.** In comparison, historical control patients presenting with HT-1 younger than 2 months of age and treated with dietary restriction alone had both 2 and 4 year survival probabilities of 29%.
  - **Patients presenting with HT-1 between ages 2 and 4 months and treated with nitisinone and dietary restriction had both 2 and 4 year survival probabilities of 94%.** Historical controls in this group had 2 and 4 year survival probabilities of 74% and 60%, respectively.
  - The long-term effect of nitisinone on hepatic function was not assessed.
  - Significant reductions in the incidence of early-onset liver failure and of porphyria-like neurologic crises. In a subgroup of patients with renal impairment prior to initiation of nitisinone therapy, indicators of renal function (e.g., urinary excretion of amino acids, serum phosphate concentrations, urinary α_1-microglobulin) were within normal ranges following 1 year of therapy with the drug.
  - Effects on urine and plasma succinylacetone, porphyrin metabolism, and urinary alpha-1-microglobulin showed statistically significant improvements in nitisinone-treated patients compared to pre-treatment baseline.

- The safety and efficacy of Nityr have been established based on studies of another oral formulation of nitisinone in patients with HT-1. Nityr was also approved based on this open-label, uncontrolled study of 207 patients with HT1.

Recommendations for the Management of Tyrosinaemia Type 1

Orphanet Journal of Rare Diseases, 2013 (Volume 8, Number 1)

- **Low-protein, tyrosine- and phenylalanine-restricted diet** plus **nitisinone** is first-line treatment for tyrosinemia type 1; low-protein (tyrosine- and phenylalanine-restricted diet alone is first-line treatment for tyrosinemia types 2 and 3)

- Management of Tyrosinemia Type 1

A. If not in acute liver failure
   - Start **nitisinone** 1 mg/kg/day orally and **low-protein, tyrosine- and phenylalanine-restricted diet** as soon as tyrosinemia type 1 confirmed, or if highly suspected, start as soon as diagnostic tests sent to lab (do not delay while awaiting test results)
   - Assess treatment response
     - Succinylacetone should be undetectable, and clinical condition, liver function, and coagulation should improve within 1 week
       - If good response, **monitor** regularly with liver function tests, alpha-fetoprotein (AFP), coagulation studies, quantitative plasma amino acids, quantitative blood or urine succinylacetone, and liver imaging
         - if AFP normal or decreasing steadily, continue monitoring
         - if AFP increases or fails to decrease steadily, monitor more closely and check for changes on liver imaging
         - if AFP increasing or imaging shows nodules > 10 mm, refer to liver specialist and consider transplant
       - If poor response
         - if liver function fails to normalize or succinylacetone detectable at 1 week, check compliance and dosing, and if both are appropriate, increase nitisinone to 2 mg/kg/day
         - if succinylacetone undetectable but clinical response otherwise poor, refer to liver specialist and consider transplant

B. If in acute liver failure
   - Approach is similar to that used in patients without acute liver failure, but early management must be individualized based on disease severity and treatment response
   - Provide **supportive measures** such as **fluid and electrolytes** as needed
   - Start **nitisinone** 2 mg/kg/day orally and low-protein, tyrosine- and phenylalanine-restricted diet as soon as tyrosinemia type 1 confirmed, or if highly suspected, start as soon as diagnostic tests sent to lab (do not delay while awaiting test results)
     - reduce nitisinone to 1 mg/kg/day after 48 hours, or allow dose to fall gradually with growth to 1 mg/kg/day
     - assess treatment response as above, but monitor ammonia and glucose in addition to liver function, coagulation, and succinylacetone
     - response times are variable, but likely longer than in less severely ill patients
   - Consider **liver transplant** for signs of deteriorating liver function such as progressive jaundice, hyperammonemia, encephalopathy, or worsening coagulopathy

Follow-up
   - nitisinone and low-protein, tyrosine- and phenylalanine-restricted diet must be continued indefinitely
   - should include ongoing close clinical, blood, urine, and imaging monitoring to ensure compliance and early detection of hepatocellular carcinoma and other complications

DEFINITIONS

Hereditary tyrosinemia type 1: A metabolic disorder in which an enzyme critical for the breakdown of the amino acid tyrosine is missing. This allows abnormal amounts of tyrosine to accumulate in the body and act like as a poison causing damage, especially in the liver.

APPENDIX

N/A

CODING INFORMATION

The codes listed in the policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

CPT	Description
NA	

HCPCS	Description
J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10	Description [For dates of service *on or after* 10/01/2015]
E70.21	Tyrosinemia

*CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

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Policy History	MCPC
Policy Developed *Peer Review: AMR Peer Review Network. 4/21/2018. Practicing Physician. Board certified in Clinical Genetics, Pediatrics*	7/10/2018

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