NITISINONE CAPSULES

Administration of Nitisinone Capsules:

adult and pediatric patients with hereditary tyrosinemia type 1 (HT-1) in combination with safely and effectively. See full prescribing information for NITISINONE CAPSULES.

Cap and “Novitium 2 mg” on body, filled with white to off white powder blend.

Dosage and Administration

Recommended Dosage (2.1)

The recommended starting dosage is 0.5 mg orally twice daily.

Administered (2.2)

• Maintain dietary restriction of tyrosine and phenylalanine

For patients who have difficulties swallowing capsules, the capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use.

Dosage Forms and Strengths

Capsules: 2 mg, 5 mg, 10 mg (3).

NITISINONE CAPSULES

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration

Starting Dosage

The recommended starting dosage of Nitisinone capsules is 0.5 mg administered orally twice daily.

Dosage Titration

Titrate the dosage in each individual patient based on biochemical and/or clinical response.

• Monitor plasma and/or urine succinylacetone concentrations, liver function parameters and alpha fetoprotein levels.

• If succinylacetone is still detectable in blood or urine 4 weeks after the start of nitisinone treatment, increase the nitisinone dosage to 0.75 mg twice daily. A maximum total dosage of 2 mg twice daily may be needed based on the evaluation of all biochemical parameters.

• If the biochemical response is satisfactory (undetectable blood and/or urine succinylacetone), the dosage may be adjusted only to body weight and not according to plasma tyrosine levels.

• During initiation of therapy, or if there is a deterioration in the patient's condition, it may be necessary to follow all available biochemical parameters (i.e. plasma and/or urine succinylacetone, plasma 5 amino- acidiminolevulinic acid (ALA) and tyrosine/phenylalanine (PBG)/synthetic activity).

• Maintain plasma tyrosine levels below 500 micromol/l, by dietary restriction of tyrosine and phenylalanine intake (see Warnings and Precautions (5.1)). In patients who develop plasma tyrosine levels above 500 micromol/l, assess dietary restriction of tyrosine and phenylalanine intake and the contents suspended in a small amount of water, formula or apple sauce immediately before use.

3 DOSAGE FORMS AND STRENGTHS

Nitisinone Capsules are available as:

• 2 mg: White opaque hard gelatin capsule shell Size #3, imprinted with black ink as “008” on cap and “Novitium 2 mg” on body, filled with white to off white powder blend.

• 5 mg: White opaque hard gelatin capsule shell Size #3, imprinted with black ink as “008” on cap and “Novitium 5 mg” on body, filled with white to off white powder blend.

• 10 mg: White opaque hard gelatin capsule Shell Size #3, imprinted with black ink as “010” on cap and “Novitium 10 mg” on body, filled with white to off white powder blend.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Plasma Tyrosine Levels, Ocular Symptoms, Developmental Delay and Hyperphenylalaninemia

Nitisinone is an inhibitor of 4-hydroxyphenylpyruvate dioxygenase, an enzyme in the tyrosine metabolic pathway (see Clinical Pharmacology (12.1)). Therefore, treatment with nitisinone may cause an increase in plasma tyrosine levels in patients with HT-1. The incidence of initial biochemical reduction in dietary tyrosines and phenylalanine while on nitisinone treatment. Do not adjust nitisinone dosage in order to lower the plasma tyrosine concentration. Maintain plasma tyrosine levels below 500 micromol/l. Inadequate reduction of tyrosine and phenylalanine intake can lead to elevations in plasma tyrosine levels and levels greater than 500 micromol/l may lead to the following:

• Ocular signs and symptoms including corneal abrasions, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia have been reported in patients treated with nitisinone (see Adverse Reactions (6.1)). In a clinical study in a non-HT-1 population without dietary restriction and reported tyrosine levels >500 micromol/l, both symptomatic and asymptomatic keratopathies have been observed. Therefore, perform a baseline slit-lampophthalmoscopy examination including slit-lamp examination prior to initiating nitisinone treatment and regularly thereafter. Patients who develop photophobia, eye pain, or signs of inflammation such as swelling, oozing, or burning of the affected eye should undergo ophthalmologic examination and measurement of the plasma tyrosine concentration. If nitisinone should elicit slit-lamp examination and immediate measurement of the plasma tyrosine concentration.

• Variable degrees of intellectual disability and developmental delay. In patients treated with nitisinone who exhibit an abrupt change in neurologic status, perform a clinical laboratory assessment including plasma tyrosine levels. Perform hypertensive praxis on the soles and palms.

In patients with HT-1 treated with dietary restrictions and nitisinone who develop elevated plasma tyrosine levels, assess dietary tyrosine and phenylalanine intake.

5.2 Leukopenia and Severe Thrombocytopenia

In clinical trials, patients treated with nitisinone and diet restriction developed transient leukopenia (3%), thrombocytopenia (3%), or both (1%) (see Adverse Reactions (6.1)). No patients developed infections or bleeding as a result of the episodes of leukopenia and thrombocytopenia. Monitor platelet and white blood cell counts during nitisinone therapy.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Nitisinone was studied in one open-label, uncontrolled study of 207 patients with HT-1, ages 0 to 22 years at enrollment (median age 9 months) who were diagnosed with HT-1 by the presence of succinylacetone in the urine or plasma. The starting dosage of nitisinone was 0.3 to 0.5 mg/kg twice daily, and the dose was increased in some patients to 1 mg/kg/m² twice daily, based on plasma tyrosine levels and PK/PD production. The recommended starting dosage of nitisinone is 0.5 mg/kg twice daily (see Dosage and Administration (2.1)). Mean duration of therapy was 74 months (range 23 to 139 months). The most serious adverse reactions reported during nitisinone treatment were leukopenia, thrombocytopenia, pyrexia, and ocular/visual complaints associated with elevated plasma tyrosine levels (see Warnings and Precautions (5.1)). Fourteen patients experienced ocular/visual events. The duration of the symptoms varied from 5 days to 2 weeks. Six patients had thrombocytopenia, three of which had platelet counts <20,000/µL; and seven patients had leukopenia, seven of which had white blood cell counts <2,000/µL.

6.2 Adverse Reactions

The most common adverse reactions reported in clinical studies of nitisinone treatment were leukopenia, thrombocytopenia, pyrexia, and ocular/visual complaints associated with elevated plasma tyrosine levels (see Warnings and Precautions (5.1)). Twenty-five patients experienced ocular/visual events. The duration of the symptoms varied from 5 days to 2 weeks. Six patients had thrombocytopenia, three of which had platelet counts <20,000/µL, and seven patients had leukopenia, seven of which had white blood cell counts <2,000/µL.

6.3 Laboratory Findings

The results of clinical chemistry analyses performed during nitisinone treatment were generally similar to those expected in patients with HT-1. The most common laboratory findings were elevations in alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. The frequency of these findings is typical of patients with HT-1. No clinically significant test results were observed in patients treated with nitisinone. The most common abnormalities observed were increases in liver chemistry enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin), decreases in serum albumin and serum globulin, and elevations in ketone bodies and urine lactate. The most common laboratory abnormalities in the plasma and/or urine found in patients treated with nitisinone were elevations in succinylacetone and tyrosine. These elevations were lower than those observed in patients with HT-1. The most common laboratory abnormalities observed in patients treated with nitisinone were elevations in succinylacetone, tyrosine, and uric acid. The most common abnormalities observed were increases in liver chemistry enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin), decreases in serum albumin and serum globulin, and elevations in ketone bodies and urine lactate. The most common laboratory abnormalities in the plasma and/or urine found in patients treated with nitisinone were elevations in succinylacetone and tyrosine. These elevations were lower than those observed in patients with HT-1. The most common laboratory abnormalities observed in patients treated with nitisinone were elevations in succinylacetone, tyrosine, and uric acid. These elevations were lower than those observed in patients with HT-1.

6.4 Postmarketing Experience

There were no data on the presence of nitisinone in human milk, nor the effects of nitisinone on milk production. Data suggest that nitisinone is present in rat milk due to findings of lower ocular toxicity and body weight seen in drug-naive nursing rat pups. The use of nitisinone in pediatric patients is supported by evidence from one open-label, uncontrolled clinical study conducted in 207 patients with HT-1 ages 0 to 22 years (median age 9 months) (see Clinical Studies (14)).
8.5 Geriatric Use
Clinical studies of nitisinone did not include sufficient numbers of elderly patients. In general, dose selection in the elderly should be cautious, and should be based on age-related changes in renal function, and on the severity of the condition being treated. In general, aging of itself requires no dose adjustment.

10 OVERDOSAGE
Accidental ingestion of nitisinone by individuals eating normal diets not restricted in tyrosine and phenylalanine will result in elevated tyrosine levels in healthy subjects given a single 1 mg dose of nitisinone. The plasma tyrosine level reached a maximum of 1200 micromol/l at 48 to 120 hours after dosing. After a washout period of 14 days, the mean value of plasma tyrosine was still 888 micromol/l. Repeat follow-up samples obtained from volunteers several weeks later showed tyrosine values back to normal. There were no reports of changes in vital signs or laboratory data of any clinical significance. One patient reported sensitivity to sunlight. Hyper-tyrosinemia has been reported with nitisinone treatment (see Warnings and Precautions (5.1)).

11 DESCRIPTION
Nitisinone capsules contain nitisinone, which is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of heterozygous tyrosinemia type 1 (HT-1) [see Warnings and Precautions (5.1)]. Nitisinone orients as white to yellow colored powder. It is practically insoluble in water and sparingly soluble in 2M Sodium Hydroxide. Ethanol and Methanol.

Chemically, nitisinone is 2-(2-tert-butyl-4-fluorophenyl)cyano)cyclohex-1-ene-1,3-dione, and the structural formula is:

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\text{F}_2\text{C}
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\text{O} \quad \text{O}
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\text{NO}_2 \quad \text{N}
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Inert ingredients in the formulation are: Citric acid anhydrous, hydroxypropyl, mannitol and stearyl acid. The empty hard gelatin capsules contain gelatin, sodium (sal) and titanium dioxide.

The capsules shells are impregnated in edible ink which contain black iron oxide, potassium hydroxide, propylene glycol, shells and strong ammonia solution.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Nitisinone is a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase, an enzyme responsible for converting 4-hydroxyphenylpyruvate to 4-hydroxyphenylacetic acid (HPAA) and then succinylacetone in the tyrosine metabolic pathway. By inhibiting the catalytic intermediates of tyrosine metabolism, nitisinone reduces the accumulation of the catalytic intermediates 4-oxo-4-carboxynaphthoic acid and 4-hydroxyphenylacetic acid.

In patients with HT-1, these catalytic intermediates are converted to the toxic metabolites succinylacetone and succinylacetate, which are responsible for the observed liver and kidney toxicity. Succinylacetone can also inhibit the pyruvate synthase pathway leading to the accumulation of 5-enolpyruvate, a neurotoxin responsible for the psychomotor characteristics of HT-1.

12.2 Pharmacodynamics
In a clinical study, patients with HT-1 were diagnosed by the presence of succinylacetone in urine or plasma and treated with nitisinone (see Clinical Study (4)). In all 186 patients whose urine succinylacetone was measured, the urinary succinylacetone concentration decreased to less than 1 mmol/mol creatinine, the lower limit of quantitation, the mean time to normalization of urine succinylacetone was 0.3 months. The probability of recurrence of abnormal values of urine succinylacetone was 1% at a urine concentration of 37 micromol/l, (90% confidence interval: 29, 51 micromol/l). In 87% (156/172) of patients whose plasma succinylacetone was measured, the plasma succinylacetone concentration decreased to less than 0.1 mmol/l, the lower limit of quantitation. The mean time to normalization of plasma succinylacetone was 3.9 months.

Nitisinone inhibits catalysis of the amino acid tyrosine and can result in elevated plasma levels of tyrosine. Therefore, treatment with nitisinone requires restriction of the dietary intake of tyrosine and phenylalanine to prevent the toxicity associated with elevated plasma levels of tyrosine (see Warnings and Precautions (5.1)). Additional pediatric use information is approved for Swedish Orphan Biovitrum AB’s DigiFab (nitisinone) capsules. However, due to Swedish Orphan Biovitrum AB’s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

12.3 Pharmacokinetics
The single-dose pharmacokinetics of nitisinone have been studied for nitisinone capsules in healthy adult subjects and the multiple-dose pharmacokinetics have been studied for nitisinone capsules in healthy subjects.

Absorption
The pharmacokinetic characteristics following single oral administration of nitisinone 30 mg under fasting conditions are shown in Table 3. The multiple-dose characteristics of nitisinone 80 mg daily can be seen in Table 4. Study-steady (50) was reached within 14 days doing in all subjects.

13 CLINICAL STUDIES
The efficacy and safety of nitisinone in patients with HT-1 was evaluated in one open-label, uncontrolled study of 207 patients with HT-1, ages 0 to 22 years at enrollment (median age 9 months). Patients were diagnosed with HT-1 by the presence of succinylacetone in urine or plasma. All patients were treated with nitisinone at a starting dose of 0.3 to 0.5 mg/kg twice daily, and the dose was increased in some patients to 1 mg/kg twice daily based on weight, liver and kidney function tests, platelet count, serum amino acids, urinary phenolic acid, plasma and urine succinylacetate, erythrocyte P50-synthetic, and serum 5-ALA. The median duration of treatment was 22 months (range less than 1 month to 80 months). Efficacy was assessed by comparison of survival and incidence of liver transplant to historical controls.

For patients presenting with HT-1 younger than 2 years of age who were treated with dietary restriction and nitisinone, 2 and 4 year survival probabilities were 88% and 88%, respectively. Data from histological controls showed that patients presenting with HT-1 younger than 2 years of age at time of treatment and dietary treatment alone had 2 and 4-year survival probabilities of 29% and 25%, respectively. For patients presenting with HT-1 younger than 2 years of age who were treated with dietary restriction and nitisinone, 2 and 4-year survival probabilities were 34% and 44%, respectively. Data from histological controls showed that patients presenting with HT-1 between 2 months and 6 months of age treated with dietary restriction alone had 2 and 4-year survival probabilities of 74% and 60%, respectively. The effects of nitisinone on urine and plasma succinylacetate, porphyrin metabolism, and urinary alpha-1-microglobulin were also assessed in a clinical study.

Porphyrin-like crises were reported in 3 patients (0.3% of cases per year) during the clinical study. This compares to an incidence of 5 to 20% of cases per year expected as part of the natural history of the disorder. An assessment of porphyrin-like crises was performed because these events are commonly reported in patients with HT-1 who are not treated with nitisinone. Urinary alpha-1-microglobulin, a proposed marker of proximal tubular dysfunction, was measured in 100 patients at baseline. The overall mean pretreatment level was 4.3 grams/microglobulin. After one year of treatment in a subgroup of patients (n=100), the mean alpha-1-microglobulin decreased by 1.5 grams/microglobulin. In patients 24 months of age and younger in whom multiple values were available (n=65), median alpha-1-microglobulin levels decreased from 6.5 to 3.0 grams/microglobulin (reference value for age less than or equal to 12 years of age).

16 HOW SUPPLIED/STORAGE AND HANDLING
Nitisinone Capsules 2 mg for oral administration containing 2 mg of nitisinone, are supplied as follows:

White Oragard hard gelatin capsule shell size #3, imprinted with black ink as “000” on cap and “Nitisin 2 mg” on body, filled with white to off white powder blend.

NDC 0254-3402-02 Bottles of 60 capsules with child-resistant closure and tamper resistant induction sealing

Nitisinone Capsules 5 mg for oral administration containing 5 mg of nitisinone, are supplied as follows:

White Oragard hard gelatin capsule shell size #3, imprinted with black ink as “010” on cap and “Nitisin 5 mg” on body, filled with white to off white powder blend.

NDC 0254-3021-02 Bottles of 60 capsules with child-resistant closure and tamper resistant induction sealing

Store at room temperature between 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C and 30°C (59°F and 86°F) (see USP Controlled Room Temperature).