

CENTER FOR DRUG EVALUATION AND RESEARCH

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FINAL PRINTED LABELING

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ORFADIN® capsules
(nitisinone)**DESCRIPTION**

Orfadin® capsules contain nitisinone, which is a synthetic reversible inhibitor of 4-hydroxyphenylpyruvate dioxygenase used in the treatment of hereditary tyrosinemia type 1 (HT-1).

Nitisinone occurs as white to yellowish-white, crystalline powder. It is practically insoluble in water, soluble in 2M sodium hydroxide and in methanol, and sparingly soluble in alcohol.

Chemically, nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione, and the structural formula is:

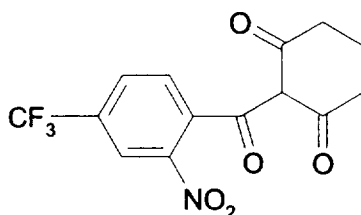


Figure 1.

The molecular formula is $C_{14}H_{10}F_3NO_5$ with a relative mass of 329.23

Orfadin® is a hard white-opaque capsule, marked as 2 mg, 5 mg or 10 mg strengths of nitisinone and is intended for oral administration. Each capsule contains 2 mg, 5 mg or 10 mg nitisinone, plus pregelatinized starch. The capsule shell is gelatin and titanium dioxide and the imprint is an iron oxide.

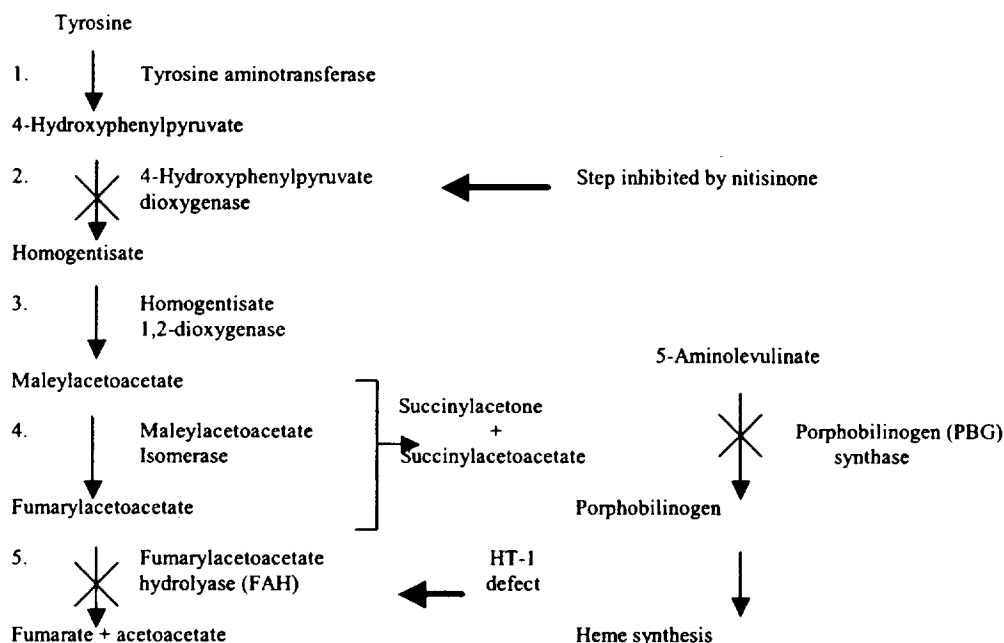
CLINICAL PHARMACOLOGY**Clinical Presentation of Hereditary Tyrosinemia Type 1 (HT-1)**

Hereditary tyrosinemia type 1 occurs due to a deficiency in fumarylacetoacetase (FAH), the final enzyme in the tyrosine catabolic pathway (see Fig. 2).

This disorder is characterized by progressive liver failure, increased risk of hepatocellular carcinoma, coagulopathy, painful neurologic crises, and renal tubular dysfunction resulting in rickets. The clinical phenotype is variable. Most patients present before 6 months of age with the acute form of the disease. These children exhibit symptoms of acute liver failure, recurrent bleeding and have a high risk of mortality within the first year of life. In the subacute form, children present with symptoms between 6 and 12 months of age and have a less rapid progression of liver disease. In the chronic form, symptoms do not appear until after one year of age and these patients have a more gradual progression to liver failure. Patients with chronic HT-1 are at increased risk of developing hepatocellular carcinoma and progressive renal tubular dysfunction resulting in secondary hypophosphatemia and rickets. Patients with all forms of the disease are at risk of painful porphyria-like neurologic crises, which occur in 5-20% of patients per year as part of the natural history of the disorder. Dietary restriction of tyrosine and phenylalanine may improve liver and kidney function but does not prevent the progression of the disease. Liver transplant can correct most of the metabolic effects of the

disorder except for the renal tubular dysfunction, which may be due to the local production of toxic metabolites in the kidney.

Figure 2. Biochemical pathway of tyrosine degradation and its association with porphyrin synthesis in HT-1.



Mechanism of Action of Nitisinone

Nitisinone is a competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme upstream of FAH in the tyrosine catabolic pathway (see Fig. 2). By inhibiting the normal catabolism of tyrosine in patients with HT-1, nitisinone prevents the accumulation of the catabolic intermediates maleylacetoacetate and fumarylacetoacetate. In patients with HT-1, these catabolic intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate, which are responsible for the observed liver and kidney toxicity. Succinylacetone can also inhibit the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate, a neurotoxin responsible for the porphyric crises characteristic of HT-1 (See Fig. 2).

Since nitisinone inhibits catabolism of tyrosine, use of this drug can result in elevated plasma levels of this amino acid. Treatment with nitisinone, therefore, requires restriction of the dietary intake of tyrosine and phenylalanine to prevent the toxicity associated with elevated plasma levels of tyrosine (see WARNINGS).

Pharmacokinetics and Drug Metabolism

Limited information exists on the metabolism, distribution, and excretion of nitisinone in rats. Nitisinone was greater than 90% bioavailable following oral administration of the labeled compound in rats and was distributed to different organs, particularly the liver and kidney, where radioactivity remained for 7 days after administration. Nitisinone was biotransformed in rats and excreted via the urine.

No pharmacokinetic studies of nitisinone have been conducted in children or HT-1 patients.

Absorption

The single-dose pharmacokinetics of nitisinone have been studied in ten healthy male volunteers aged 19-39 years (median 32 years). Nitisinone, 1 mg/kg body weight, was administered as a capsule and a liquid. The median time for maximum plasma concentration was 3 hours for the capsule and 15 minutes for the liquid. The capsule and liquid formulation were found to be bioequivalent based on an analysis of area under the plasma concentration-time curve and maximum plasma concentration (C_{max}).

Metabolism

No information on the metabolism of nitisinone in humans is available.

Excretion

The mean terminal plasma half-life of nitisinone in healthy male volunteers was 54 hours.

The effect of food on the pharmacokinetics of nitisinone has not been studied.

Special Populations

Geriatric – No pharmacokinetic studies of nitisinone have been performed in geriatric patients.

Gender – The effect of gender on the pharmacokinetics of nitisinone has not been studied.

Race – The effect of race on the pharmacokinetics of nitisinone has not been studied.

Renal Insufficiency - The effect of renal insufficiency on the pharmacokinetics of nitisinone has not been studied.

Hepatic Dysfunction - The effect of hepatic dysfunction on the pharmacokinetics of nitisinone has not been studied.

Drug-Drug Interactions

No drug-drug interaction studies have been conducted with nitisinone.

CLINICAL STUDIES

An open-label study of the use of nitisinone in patients with HT-1 was conducted by 96 investigators at 87 hospitals in 25 countries. The data presented were obtained over a period covering more than six years and are derived from 207 patients with a diagnosis of HT-1 verified by the presence of succinylacetone in the urine or plasma. The median age of patients at enrollment was 9 months (range birth to 21.7 years, see Table 1).

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Table 1. Characteristics of the Study Population

	N	Treatment time in months (Median)
Total population	207	22
Females	93	23
Males	114	21
<i>Age at start of nitisinone therapy</i>		
0-24 months	142	20
> 24 months	65	28

The median duration of treatment was 22 months with a range of 0.1 months to 78 months.

Biochemical Effects of Nitisinone Treatment

The efficacy of nitisinone as an inhibitor of 4-hydroxy-phenylpyruvate dioxygenase was inferred by the effects of treatment on the following biochemical parameters: urine succinylacetone, plasma succinylacetone, and erythrocyte porphobilinogen synthase (PBG) activity. For all 186 patients for whom data are available, the excretion of succinylacetone in urine was reduced to a level below the reference limit, which represents the sensitivity of the analytical procedure. The median time to normalization was 0.3 months. For most patients for whom data are available (150/172=87%) the plasma concentration of succinylacetone decreased to a level below the reference. The median time to normalization was 3.9 months. For all 180 patients for whom data are available, the porphobilinogen synthase activity of erythrocytes increased to within reference limits. The median time to normalization was 0.3 months. The differences in these indices compared to the start of nitisinone treatment were statistically significant ($p<0.001$).

Effects on Overall Survival

Available data for historical controls show that patients presenting with HT-1 under 2 months of age and treated with dietary restrictions alone had 2 and 4-year survival probabilities of 29% and 29%, respectively. This compares to 2 and 4-year survival probabilities of 88% and 88%, respectively, for patients presenting with HT-1 under 2 months of age and treated with dietary restrictions and nitisinone in this study. Data for historical controls show that patients presenting with HT-1 under 6 months of age had 2 and 4-year survival probabilities of 74% and 60%, respectively. This compares to 2 and 4-year survival probabilities of 94% and 94%, respectively, for patients presenting with HT-1 under 6 months of age and treated with dietary restrictions and nitisinone in this study.

Effects on Incidence of Liver Transplantation or Death due to Liver Failure

Although the long term prognosis of patients treated with nitisinone with regard to hepatic function is not yet known, the results of this clinical study suggest a marked reduction (>75%) in the risk of early onset liver failure that characterizes the natural history of HT-1.

Effect on Porphyrin Metabolism

Three cases of porphyric crisis, one of which was fatal, were observed in three patients during the clinical study and in continued clinical follow-up (0.3% cases per year). This compares to the incidence of 5-20% cases per year expected as part of the natural history of the disorder.

Effect on Renal Function

Renal function was investigated specifically in the subgroup of patients exhibiting signs of renal dysfunction prior to treatment. At the one-year visit, both urine excretion of amino acids and serum concentration of phosphate were within the reference range in this subgroup.

Urinary alpha-1-microglobulin, used to estimate tubular function, was increased at the start of the study in this subgroup but was within the normal reference limits after 1 year of treatment.

INDICATIONS AND USAGE

Orfadin® capsules (nitisinone) are indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1.

CONTRAINDICATIONS

None known.

WARNINGS

High Plasma Tyrosine Levels

Inadequate restriction of tyrosine and phenylalanine intake can result in elevations in plasma tyrosine. Plasma tyrosine levels should be kept below 500 $\mu\text{mol/L}$ in order to avoid toxic effects to the eyes (corneal ulcers, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia), skin (painful hyperkeratotic plaques on the soles and palms), and nervous system (variable degrees of mental retardation and developmental delay). In most patients, eye symptoms were transient, lasting less than one week. Six patients had prolonged episodes lasting 16 to 672 days (see **PRECAUTIONS, General**).

Transient Thrombocytopenia and Leucopenia

Patients treated with nitisinone and dietary restriction in clinical trials were observed to develop transient thrombocytopenia (3%), leucopenia (3%) or both (1.5%). One patient, who developed both leucopenia and thrombocytopenia, improved after the dose of nitisinone was decreased from 2 mg/kg to 1 mg/kg. Another patient, who developed thrombocytopenia, had nitisinone stopped for 2 weeks, but platelet values continued to be low for 3 months and slowly returned to normal after 5 months. In all other patients, platelet values and white blood cell counts normalized gradually without documented change in nitisinone dose. No patients developed infections or bleeding as a result of the episodes of leucopenia and thrombocytopenia. Platelet and white blood cell counts should be monitored regularly during nitisinone therapy.

PRECAUTIONS

General

Ophthalmologic Care of Patients Treated with Nitisinone (see **WARNINGS**)

- Slit-lamp examination of the eyes should be performed before initiation of nitisinone treatment.
- Patients who develop photophobia, eye pain or signs of inflammation such as redness, swelling, or burning of the eyes during treatment with nitisinone should undergo slit-lamp reexamination and immediate measurement of the plasma tyrosine concentration.
- A more restricted diet should be implemented if the plasma tyrosine level is above 500 $\mu\text{mol/L}$.
- Nitisinone dosage should not be adjusted in order to lower the plasma tyrosine concentration, since the HT-1 metabolic defect may result in deterioration of the patient's clinical condition.

Risk of Porphyric Crises, Liver Failure, and Hepatic Neoplasms

Patients with hereditary tyrosinemia type 1 are at increased risk of developing porphyric crises, liver failure, or hepatic neoplasms requiring liver transplantation. These complications of HT-1 were observed in patients treated with nitisinone for a median of 22 months during the clinical trial (liver transplantation 13%, liver failure 7%, malignant hepatic neoplasms 5%, benign hepatic neoplasms 3%, porphyria 0.5%). **Regular liver monitoring by imaging (ultrasound, computerized tomography, magnetic resonance imaging) and laboratory tests, including serum alpha-fetoprotein concentration is recommended. An increase in serum alpha-fetoprotein concentration may be a sign of inadequate treatment, but patients with increasing alpha-fetoprotein or signs of nodules of the liver during treatment with nitisinone should always be evaluated for hepatic malignancy.**

Information for Patients

Patients and their parents or caregivers should be advised of the need to maintain dietary restriction of tyrosine and phenylalanine when taking nitisinone to treat hereditary tyrosinemia type 1.

Patients and their parents or caregivers should be advised to report promptly unexplained eye symptoms, rash, jaundice, or excessive bleeding (see **WARNINGS** and **ADVERSE REACTIONS**).

Laboratory Tests

- Plasma nitisinone concentration, urine and plasma succinylacetone levels, urine 5-ALA levels, and erythrocyte PBG-synthase activity were used during clinical trials to guide drug dosage. The probability of recurrence of abnormal values of urine succinylacetone was 1% at a nitisinone concentration of 37 $\mu\text{mol/L}$ (95% confidence interval: 23-51 $\mu\text{mol/L}$). Assays for plasma nitisinone concentration, plasma succinyl acetone, urine 5-ALA, and erythrocyte PBG-synthase activity are not routinely available in the U.S. However, urine succinylacetone levels can be used to guide drug dose adjustment (see **DOSAGE** and **ADMINISTRATION**).
- Serum alpha-fetoprotein concentrations are generally markedly elevated at the time of diagnosis, and gradually decrease during the course of nitisinone treatment. Increases during therapy may be a sign of inadequate treatment. An exponential increase in serum alpha-fetoprotein concentration should be promptly evaluated for potential liver neoplasia.
- Platelet and white blood cell counts should be monitored regularly because of the risk of transient thrombocytopenia and leukopenia (see **WARNINGS**).
- Serum phosphate should be measured as a screening test for patients with renal involvement at risk of secondary hypophosphatemia and rickets.
- Plasma tyrosine levels should be kept below 500 $\mu\text{mol/L}$ in order to avoid toxic effects (see **WARNINGS**).

Drug Interactions

No drug-drug interaction studies have been conducted with nitisinone.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals have not been performed to evaluate the carcinogenic potential of nitisinone. Nitisinone was not mutagenic in the Ames test. In a single dose-group study in rats given 100 mg/kg/day (12 times the recommended clinical dose based on relative body surface area), reduced litter size, decreased pup weight at birth and decreased survival of pups after birth was demonstrated.

Pregnancy Category C:

Adequate reproductive toxicity studies have not been conducted with nitisinone. It is not known if nitisinone can produce harm to the fetus if administered to pregnant women. Nitisinone should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Although the exposure was not quantified, naive pups that were exposed to Orfadin™ via breast milk showed signs of ocular toxicity and lower body weight. This suggests that Orfadin™ is excreted via breast milk in rats. It is not known whether nitisinone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitisinone is administered to a nursing woman.

Pediatric Use

Nitisinone has been studied in patients ranging in age from birth to 21.7 years. The median age of enrolment in a study of 207 patients with HT-1 was 9 months.

Geriatric Use

Clinical studies of nitisinone did not include any subjects aged 65 and over to determine whether they respond differently from younger subjects. HT-1 is presently a disease of the pediatric population. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this patient population.

ADVERSE REACTIONS

In a clinical trial of 207 patients treated with nitisinone for HT-1, the most frequent adverse effects, regardless of causality assessment, occurred in the following organ systems:

Liver and Biliary System: hepatic neoplasm 8%, liver failure 7%.

Visual System: conjunctivitis 2%, corneal opacity 2%, keratitis 2%, photophobia 2%, blepharitis 1%, eye pain 1%, cataracts 1%.

Hemic and Lymphatic: thrombocytopenia 3%, leucopenia 3%, porphyria 1%, epistaxis 1%.

Skin and Appendages: pruritis 1%, exfoliative dermatitis 1%, dry skin 1%, maculopapular rash 1%, alopecia 1%.

Adverse reactions that occurred in less than 1% of the patients, regardless of causality assessment, are:

Body as a Whole: death.

Nervous System: seizures, brain tumor, encephalopathy, headache, hyperkinesia.

Cardiovascular: cyanosis.

Digestive System: abdominal pain, diarrhea, enanthema, gastritis, gastroenteritis, gastrointestinal hemorrhage, melena, tooth discoloration.

Liver and Biliary System: elevated hepatic enzymes, hepatic function disorder, liver enlargement.

Metabolic and Nutritional Disorders: dehydration, hypoglycemia, thirst.

Resistance Mechanism Disorder: infection, septicemia, otitis.

Respiratory: bronchitis, respiratory insufficiency.

Musculoskeletal System: pathologic fracture.

Female Reproductive: amenorrhea.

Psychiatric: nervousness, somnolence.

OVERDOSAGE

Accidental ingestion of this drug by individuals eating normal diets not restricted in tyrosine and phenylalanine will result in elevated tyrosine levels. In volunteers given a single 1 mg/kg dose of nitisinone, the plasma tyrosine level reached a maximum of 1200 $\mu\text{mol/L}$ from 48 to 120 hours after dosing. After a washout period of 14 days, the mean value of plasma tyrosine was still 808 $\mu\text{mol/L}$. Fasted follow-up samples obtained from volunteers several weeks later showed tyrosine values back to normal. Nitisinone was generally well tolerated in these studies. There were no reports of changes in vital signs or laboratory data of any clinical significance. One patient did report sensitivity to sunlight. Tyrosinemia has been associated with toxicity to eyes, skin, and the nervous system (see **WARNINGS**).

No information about specific treatment of overdose is available. Restriction of tyrosine and phenylalanine in the diet should limit toxicity associated with tyrosinemia. Patients should be monitored for potential adverse events (see **ADVERSE REACTIONS**).

DOSAGE and ADMINISTRATION

Treatment with nitisinone should be initiated by a physician experienced in the treatment of hereditary tyrosinemia type 1.

The dose of nitisinone should be adjusted in each patient. The recommended initial dose is 1 mg/kg/day divided for morning and evening administration. Since an effect of food is unknown, nitisinone should be taken at least one hour before a meal. Because of the long half-life of nitisinone, the total dose may be split unevenly as convenient in order to limit the total number of capsules given at each administration. A nutritionist skilled in managing children with inborn errors of metabolism should be employed to design a low-protein diet deficient in tyrosine and phenylalanine. For young children, capsules may be opened and the contents suspended in a small amount of water, formula, or apple sauce immediately before use.

Dose Adjustment

Nitisinone treatment should block the flux through the tyrosine degradation pathway at the level of 4-hydroxy-phenylpyruvate dioxygenase. Treatment should lead to normalized porphyrin metabolism (i.e., normal erythrocyte PBG-synthase activity and urine 5-ALA). Succinylacetone should not be detectable in urine or plasma. If the biochemical parameters (except plasma succinylacetone) are not normalized within one month after start of nitisinone treatment, the dose should be increased to 1.5 mg/kg/day. For plasma succinylacetone, it may take up to three months before the level is normalized after the start of nitisinone treatment. Since plasma nitisinone concentration, plasma succinylacetone, urine 5-ALA, and erythrocyte PBG-synthase activity are not routinely available, it is appropriate during regular monitoring to follow urine succinylacetone, liver function tests, alpha-fetoprotein, and serum tyrosine, and phenylalanine levels. However, during the initiation of therapy and during acute exacerbations, it may be necessary to follow more closely all available biochemical parameters

(see Laboratory Tests). A dose of 2 mg/kg/day may be needed, especially in infants, once liver function has improved. This dose should be considered as a maximal dose for all patients.

HOW SUPPLIED

Orfadin™ capsules are white and marked in black with "NTBC" and identified as 2mg, 5mg or 10mg strengths of nitisinone. The capsules are packaged in a high density (HD) polyethylene container with a tamper-resistant low density (LD) polyethylene snap-on cap. Each bottle contains 60 capsules.

Orfadin® is available as:

2 mg white capsules imprinted "NTBC 2 mg" in black ink. NDC 66607-10026.

5 mg white capsules imprinted "NTBC 5 mg" in black ink. NDC 66607-10056.

10 mg white capsules imprinted "NTBC 10 mg" in black ink. NDC 66607-10106.

Storage

Store refrigerated, 2 - 8°C (36 - 46°F).

Caution: Rx only

Manufactured by:

Apoteket AB, Sweden;

for

SWEDISH ORPHAN INTERNATIONAL AB,
Sweden.

Distributed by:

Rare Disease Therapeutics, Inc.

1101 Kermit Drive

Nashville, TN 37217

Phone number: 615-399-0700

Revised January 2002

Orfadin® owned by

SWEDISH ORPHAN INTERNATIONAL AB,
Sweden.

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Rx only	Orfadin® Capsules	60 capsules
See Package Insert	(nifedipine)	
Store refrigerated 2-8° C (36-46° F)	2 mg	
	For Oral Use	
Manufactured by: Apoteket AB, Sweden, for SWEDISH ORPHAN INTERNATIONAL AB, Sweden.		Distributed by: Rare Diseases Therapeutics Inc., 1101 Kermit Drive Suite 608 Nashville, Tennessee 37217
		103-1 NDC 66607-10026 Expiration Date: Lot:

Rx only	Orfadin® Capsules	60 capsules
See Package Insert	(nifedipine)	
Store refrigerated 2-8° C (36-46° F)	5 mg	
	For Oral Use	
Manufactured by: Apoteket AB, Sweden, for SWEDISH ORPHAN INTERNATIONAL AB, Sweden.		Distributed by: Rare Diseases Therapeutics Inc., 1101 Kermit Drive Suite 608 Nashville, Tennessee 37217
		104-1 NDC 66607-10056 Expiration Date: Lot:

Rx only	Orfadin® Capsules	60 capsules
See Package Insert	(nifedipine)	
Store refrigerated 2-8° C (36-46° F)	10 mg	
	For Oral Use	
Manufactured by: Apoteket AB, Sweden, for SWEDISH ORPHAN INTERNATIONAL AB, Sweden.		Distributed by: Rare Diseases Therapeutics Inc., 1101 Kermit Drive Suite 608 Nashville, Tennessee 37217
		105-1 NDC 66607-10106 Expiration Date: Lot:

Orfadin® Capsules	
(nifedipine)	
10 mg	
For Oral Use	
Rx only Store refrigerated 2-8° C (36-46° F)	See Package Insert
Manufactured by: Apoteket AB, Sweden, for SWEDISH ORPHAN INTERNATIONAL AB, Sweden.	
Distributed by: Rare Diseases Therapeutics Inc., 1101 Kermit Drive Suite 608, Nashville, Tennessee 37217	
60 capsules	NDC 66607-10106
Expiration Date:	
Lot:	108-1

Orfadin® Capsules	
(nifedipine)	
2 mg	
For Oral Use	
Rx only Store refrigerated 2-8° C (36-46° F)	See Package Insert
Manufactured by: Apoteket AB, Sweden, for SWEDISH ORPHAN INTERNATIONAL AB, Sweden.	
Distributed by: Rare Diseases Therapeutics Inc., 1101 Kermit Drive Suite 608, Nashville, Tennessee 37217	
60 capsules	NDC 66607-10026
Expiration Date:	
Lot:	106-1

Orfadin® Capsules	
(nifedipine)	
5 mg	
For Oral Use	
Rx only Store refrigerated 2-8° C (36-46° F)	See Package Insert
Manufactured by: Apoteket AB, Sweden, for SWEDISH ORPHAN INTERNATIONAL AB, Sweden.	
Distributed by: Rare Diseases Therapeutics Inc., 1101 Kermit Drive Suite 608, Nashville, Tennessee 37217	
60 capsules	NDC 66607-10056
Expiration Date:	
Lot:	107-1

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Labeling