HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 June 2007

ORFADIN 2 mg, capsules
Bottle of 60 capsules (CIP: 365 937-2)

ORFADIN 5 mg, capsules
Bottle of 60 capsules (CIP: 365 938-9)

ORFADIN 10 mg, capsules
Bottle of 60 capsules (CIP: 365 939-5)

Applicant: SWEDISH ORPHAN INTERNATIONAL AB

Nitisinone

ATC code: A16AX04

List I
Medicine for hospital prescription only

Date of Marketing Authorisation (MA): 21 February 2005 (variation of 28 August 2006)
European Marketing Authorisation based on the centralised procedure, and granted under exceptional circumstances

Date of designation as an orphan drug: 29 December 2000

Reason for request: Inclusion on the list of medicines approved for hospital use.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

Nitisinone

1.2. Background

Nitisinone is a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase, an enzyme upstream of fumarylacetoacetate hydrolase in the tyrosine catabolic pathway.

1.3. Indication

Treatment of patients with a confirmed diagnosis of type 1 hereditary tyrosinaemia (HT-1), in association with a low tyrosine and phenylalanine diet.

1.4. Dosage

Nitisinone treatment should be initiated and supervised by a physician experienced in the treatment of HT-1 patients. Treatment of all genotypes of the disease should be initiated as early as possible to increase overall survival and avoid complications such as liver failure, liver cancer and renal disease. Adjunct to the nitisinone treatment, a diet deficient in phenylalanine and tyrosine is required and should be followed by monitoring of plasma amino acids (see sections 4.4 and 4.8 of the SPC).
The dose of nitisinone should be adjusted individually.
The recommended initial dose is 1 mg/kg body weight/day divided in 2 doses administered orally. The capsule may be opened and the content suspended in a small amount of water or formula diet immediately before intake.

Dose adjustment
During regular monitoring, it is appropriate to follow urine succinylacetone, liver function test values and alpha-fetoprotein levels (see section 4.4 of the SPC). If urine succinylacetone is still detectable one month after the start of nitisinone treatment, the nitisinone dose should be increased to 1.5 mg/kg body weight/day divided in 2 doses. A dose of 2 mg/kg body weight/day may be needed based on the evaluation of all biochemical parameters. This dose should be considered as a maximal dose for all patients.
If the biochemical response is satisfactory, the dose should be adjusted only according to body weight gain.
However, in addition to the tests above, during the initiation of therapy or if there is a deterioration, it may be necessary to follow more closely all available biochemical parameters (i.e. plasma succinylacetone, urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

A : Digestive tract and metabolism
A16 : Other products associated with the digestive tract and metabolism
A16A : Other medicinal products for the digestive tract and metabolism
A16AX : Various medicinal products for the digestive tract and metabolism
A16AX04 : Nitisinone

2.2. Medicines in the same therapeutic category

ORFADIN is the only drug which has been approved to date for the treatment of Type 1 hereditary tyrosinaemia (HT-1).

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The documentation of the clinical efficacy of nitisinone, in association with a low tyrosine and phenylalanine diet, in the treatment of type 1 hereditary tyrosinaemia (HT-1) is based on an international cohort of patients treated in a compassionate trial (NTBC Study).

The MA was granted on the basis of initial data obtained from a cohort of 207 patients (median baseline age: 9 months) recruited in this programme and treated for a median period of 22.2 months (min: 0.1 month - max: 77.9 months)[1,2].

The monitoring and inclusion of the patients were continued, and a supplementary analysis conducted, on the basis of a final cohort of 566 patients exposed to the treatment for a mean period of 4.3 years (maximum 13 years), that is to say a total follow-up of 2331 person-years.

The mean age at the start of treatment was 1.7 years (range: 0-21.7 years). Nitisinone was administered orally, twice daily. The initial recommended daily dose was 1 mg/kg of body weight (although some patients initially received a dose of 0.6 mg/kg/day), and could be adjusted where necessary on the basis of the individual response to the treatment.

The effect of nitisinone on survival and the risk of developing hepatocellular carcinoma has been studied and compared with the historical data observed with dietary restrictions alone (study by Van Spronsen et al., 1994: N=108)[3]. The incidence of the renal complications (renal tubular disease) and neurological complications often observed in these patients was also compared with the historical data.

- *Effect on survival*

The survival analysis submitted by the manufacturer related to the initial cohort of 207 patients treated for a maximum of 12.9 years (table 1).

Seveteen patients died during the treatment. Patients who dropped out of the study for reasons other than death (48 liver transplants, 2 lost to follow-up, 1 discontinuance of treatment) were censured starting from the date of discontinuance of treatment.

Table 1: Number of patients according to duration of follow-up

Duration of follow-up in years	Age at start of treatment (in months)			Total
	0 - 2	> 2 - 6	> 6	
0	16	64	127	207
1	14	57	111	182
2	13	55	103	171
5	13	50	87	150
7	10	32	65	107
10	- -	6	17	23
12	- -	1	1	2

[1] NTBC Study: Swedish Orphan AB Report No. 2000 010 02.
[2] Inclusion period: between February 23, 1991 and August 21, 1997.
[3] Van Spronsen et al. Hereditary tyrosinemia Type I: A new clinical classification with difference in prognosis on dietary treatment. Hepatology. 1994;20:1187-91

Table 2: Probability of survival on the basis of age at start of treatment

Age at the start of treatment or diagnosis	Probability of survival (%)**							
	Treatment with nitisinone N=207 patients recruited				Historical control* (Dietary restriction only) N=108 patients recruited			
	1 year	2 years	5 years	10 years	1 year	2 years	5 years	10 years
< 2 months	88	88	82	--	38	29	28	--
2-6 months	94	94	95	95	74	74	51	34
> 6 months	97	95	92	86	96	96	93	59

* historical data (Van Spronsen et al., 1994) on treatment involving dietary restrictions only.

** **this comparison must be considered merely indicative, because it is not directly supported by statistical tests designed to establish the robustness of the comparison with the historical data.**

The probability of survival seems to have improved, especially in patients who began the treatment before the age of 6 months.

- *Effect on the risk of developing hepatocellular carcinoma*

The analysis presented by the manufacturer relates to 566 patients exposed to treatment with nitisinone (maximum duration of exposure = 13 years). A total of 23 cases (4.1%) of hepatocellular carcinoma were reported in this population.

Table 3: incidence of hepatocellular carcinoma (HCC)

	Age at start of treatment < 12 months	Age at start of treatment > 12 months
Patients without HCC	365	161
Patients with HCC	3	20

The risk of developing hepatocellular carcinoma seems to be lower (2.3 to 3.7 times less) with nitisinone than the historical data, especially if the treatment begins before the age of 12 months (risk 13.5 times lower). Indeed with dietary restrictions only, the occurrence of hepatocellular carcinoma is described in 18% of the children before the age of two years.

- Effect on the incidence of renal and neurological complications

Of all the patients (n= 566) exposed to nitisinone for a mean period of 4.3 years (maximum 13 years), that is to say a total follow-up of 2331 person-years, only one developed renal tubular disease with rickets, and no patients presented acute neurological events (polyneuritis, pseudo-Guillain-Barré syndrome, or dystonic pain crises).

3.2. Adverse effects

No patient dropped out of the trial due to an adverse event considered to have a possible causal link with the treatment. Visual disorders (conjunctivitis, corneal opacity, keratitis, photophobia and eye pain), classed as non-severe, were the adverse events most frequently observed, and were reversed spontaneously or after strict compliance with a low tyrosine and phenylalanine diet.

Haematological symptoms (granulocytopenia, leucopenia, thrombocytopenia and leucocytosis) and cutaneous symptoms (itching, exfoliative dermatitis and erythematous rash) were also reported during treatment with nitisinone.

Special warnings and precautions for use relating to the risk of visual and haematological disorders are included in the SPC (paragraph 4.4). According to the SPC, there is also a risk of convulsions during treatment, but this was not observed during the trials.

3.3. Conclusion

Although their evidence level is not optimal, the data resulting from analysis of a cohort of patients (NTBC Study) suffering from type 1 hereditary tyrosinaemia (HT-1) show that treatment with nitisinone combined with a low tyrosine and phenylalanine diet produces better results than dietary restrictions alone (Van Spronsen et al.,1994)[4]. The probability of survival seems to have improved, especially in patients who began the treatment before the age of 6 months; in this population higher mortality is seen if dietary restrictions are the only measure introduced[4]. The risk of developing hepatocellular carcinoma also seems to be lower, especially if the treatment begins before the age of 12 months. Moreover, the treatment seems to effectively prevent renal complications (renal tubular disease) and acute neurological events (polyneuritis, pseudo-Guillain-Barré syndrome, dystonic pain crises) often observed in these patients.

The Committee regrets the absence of a sensitivity analysis designed to establish the robustness of the comparisons with the historical data.

The tolerance of the product is acceptable provided that the warnings and precautions for use are complied with: leucopenia and thrombocytopenia must be carefully monitored, and visual disorders due to the formation of tyrosine crystals must be prevented by strict observance of a low phenylalanine and tyrosine diet, and monitoring of the plasma tyrosine levels[5]. There is also a risk of convulsions during the treatment.

4 CONCLUSIONS OF THE TRANSPARENCY COMMITTEE

4.1. Actual Benefit

Type 1 hereditary tyrosinaemia (HT-1) is a metabolic disorder which affects the tyrosine catabolism pathway. It is caused by loss of fumarylacetoacetate hydrolase activity. It is classed as an orphan disease due to the number of patients affected by it (1 case in every 100,000 to 120,000 births). It is a serious disorder, which leads to a deterioration in the quality of life, and can be life-threatening.

ORFADIN is a first-line treatment.
The efficacy/adverse effects ratio of this medicinal product is high.

There is no alternative medication.

Public health benefit

Type 1 hereditary tyrosinaemia is a serious disorder, which represents a low public health burden in view of its rarity (orphan disease).

As improving the management of orphan diseases is one of the priorities identified (under the Rare Disease Plan), the treatment of this disorder constitutes a public health need.

[4] Van Spronsen et al. Hereditary tyrosinemia Type I: A new clinical classification with difference in prognosis on dietary treatment. Hepatology. 1994 ;20:1187-91

[5] Special warnings and precautions for use relating to the risk of visual and haematological disorders are included in the SPC (paragraph 4.4).

Although its evidence level is not optimal, ORFADIN should considerably improve the health of the population of patients suffering from HT-1. ORFADIN probably has an impact on the reduction of mortality in these patients and on morbidity (reduced risk of developing hepatocellular carcinoma and prevention of renal and neurological complications). ORFADIN should therefore provide a response to the public health need.
The transferability of the results depends mainly on compliance with a strict low tyrosine and phenylalanine diet.
In view of the small number of patients concerned, the population impact of ORFADIN on the reduction of morbidity and mortality is bound to be low.
Consequently, having regard to the response provided by ORFADIN to the need identified, the public health benefit of this proprietary product is moderate.

In the current state of knowledge, its actual benefit is substantial.

4.2. Improvement in actual benefit

Taking into account the clinical data described above, the Committee considers that ORFADIN, in association with a low tyrosine and phenylalanine diet, provides an important improvement in actual benefit (IAB II) compared with diet alone, in the treatment of patients suffering from type 1 hereditary tyrosinaemia (HT-1).

4.3. Therapeutic use

The diagnosis of type 1 hereditary tyrosinaemia (HT-1) is based on the finding in the blood and urine of an accumulation of succinylacetoacetate and succinylacetone secondary to the fumarylacetoacetase deficiency which constitutes the primary deficiency in this disorder. Moreover, there is nearly always increased urinary excretion of δ-aminolevulinic acid resulting from inhibition of δ-aminolevulinate hydratase by succinylacetone. This secondary inhibition of porphyrin metabolism is probably responsible for the acute neurological symptoms often observed in these patients (polyneuritis, pseudo-Guillain-Barré syndrome, dystonic pain crises)[6].
Nitisinone (ORFADIN) is currently the first-line treatment for this disorder. This treatment should be commenced urgently, associated with a low tyrosine and phenylalanine diet, as soon as the diagnosis is confirmed, and sometimes as soon as it is suspected (situations where the confirmation tests cannot be obtained on an emergency basis).

According to the experts, a liver transplant is essentially indicated in 2 situations:

- on an emergency basis in patients suffering from acute hepatocellular insufficiency if treatment with ORFADIN is unsuccessful,
- secondarily in patients who are stable during treatment with ORFADIN but develop a complication (hepatocarcinoma or cirrhosis).

[6] J-M Saudubray, P. de Lonlay, C. Beyler, C. Barnerias, G. Touati. Maladies héréditaires du métabolisme. Chapter 428: Déficit héréditaires du catabolisme des acides aminés: amino-acidopathies, aciduries organique. In: pierre Godeau: Traité de Médecine. Paris, Flammarion, Médecine-Sciences, 2004: 1692-1700.

4.4. Target population

The target population comprises all patients with a confirmed diagnosis of type 1 hereditary tyrosinaemia (HT-1).

The incidence of the illness ranges between 1/100,000 and 1/120,000 live births[7].

In France, ORFADIN has been available to patients since 1991. Between 1991 and February 2005, 49 patients were treated with ORFADIN in France[8] in the context of the compassionate programme, which represents a cumulative rate of 3.5 patients per year. By extrapolation, the total number of patients should not exceed approximately 100 in the next ten years, on the assumption that no patient discontinues the treatment.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services for the indications and at the dosages specified in the MA.

[7] Orphanet: Tyrosinémie héréditaire de type I. *In:* http://www.orpha.net/data/patho/FR/fr-tyr.html
[8] According to the manufacturer's data.