CADTH

CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

**Nitisinone (ORFADIN — Sobi Canada Inc.)**
Indication: The treatment of adult and pediatric patients with hereditary tyrosinemia type-1 in combination with a dietary restriction of tyrosine and phenylalanine.

**RECOMMENDATION:**
The CADTH Canadian Drug Expert Committee (CDEC) recommends that nitisinone (Orfadin) be reimbursed for the treatment of adult and pediatric patients with hereditary tyrosinemia type-1 in combination with dietary restriction of tyrosine and phenylalanine, if the following criterion and conditions are met:

**Criterion:**
- For use in patients with an established diagnosis of hereditary tyrosinemia type-1.

**Conditions:**
- The drug is prescribed by a physician with experience in the diagnosis and management of hereditary tyrosinemia type-1.
- Price reduction of at least 74%.


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**Redactions:** Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

# Nitisinone (Orfadin — Sobi Canada Inc.)

Indication: Hereditary tyrosinemia type-1 (HT-1).

## Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that nitisinone (Orfadin) be reimbursed for the treatment of adult and pediatric patients with HT-1 in combination with a dietary restriction of tyrosine and phenylalanine, if the following criterion and conditions are met:

## Criterion:

- For use in patients with an established diagnosis of HT-1.

## Conditions:

- The drug is prescribed by a physician with experience in the diagnosis and management of HT-1.
- Price reduction of at least 74%.

## Reasons for the Recommendation:

1. HT-1 is a rare disease (worldwide incidence of approximately 1 in 100,000 live births) that manifests most commonly in infants and is associated with high mortality and morbidity. Nitisinone is the only treatment approved for HT-1 in Canada and therefore it addresses an unmet need for this condition.
2. Two open-label, single-arm studies (NTBC [N = 207] and Quebec [N = 78]) demonstrated an association between treatment with nitisinone (in combination with dietary restriction of tyrosine and phenylalanine) and improved survival in patients with HT-1, as compared with an historical cohort that received dietary treatment alone. Nitisinone was also associated with reduced risk of liver failure, fewer liver transplantation requirements, lower risk of hepatocellular carcinoma, fewer porphyric crises, and reduced acute complications of HT-1.
3. The incremental cost-effectiveness of treatment with nitisinone plus dietary restriction of tyrosine and phenylalanine (initiated prior to 1 month of age), as compared with dietary restriction alone, was estimated to be greater than $300,000 per quality-adjusted life-year (QALY) using a manufacturer-submitted cost-utility model and after re-analysis of the model by the CADTH Common Drug Review (CDR). However, there is considerable uncertainty associated with this estimate related to both limitations with the clinical data and features of the manufacturer-submitted cost-utility model. Therefore, at the submitted price ($22.50 per 2 mg capsule, $53.30 per 5 mg capsule, $100 per 10 mg capsule, and $193.33 per 20 mg capsule) treatment of patients with HT-1 with nitisinone is not considered to be cost-effective. A price reduction of at least 74% (for all nitisinone strengths) would be required to increase the probability that nitisinone will be cost-effective in infants one month old or younger, while a higher price reduction would likely be required for nitisinone to be cost-effective in all populations.

## Of Note:

1. Evidence from the NTBC and Quebec studies indicated that patients with an earlier diagnosis and treatment initiation with nitisinone (before six months of age) had a higher probability of survival and reduced morbidity as compared with historical controls. Delaying nitisinone treatment initiation (i.e., after two years of age) was associated with an increased probability of hepatocellular carcinoma and the requirement of liver transplant.
2. Jurisdictions that do not perform newborn screening for HT-1 may wish to also consider the cost-effectiveness of introducing such screening, thereby facilitating early identification of eligible patients.
3. CDEC heard from a clinician with experience in the diagnosis and management of HT-1 that these patients require a multidisciplinary health care approach to managing their disease. Outcomes for these patients are more likely to be improved if they receive nitisinone in combination with coordinated care from other health professionals (e.g., dieticians to help manage dietary requirements) at centres with health care teams that have experience in managing patients with HT-1.

4. CDEC noted several important limitations with the studies reviewed by CDR, including the open-label design and lack of a direct comparator. In addition, no absolute or relative measures of effect with formal statistical comparisons were performed on the outcomes between nitisinone plus dietary restriction versus dietary restriction alone leading to uncertainty of the magnitude of any benefit with nitisinone versus dietary restriction. These limitations made it difficult to assess the comparative clinical benefit of nitisinone.
5. Two other nitisinone products have received Health Canada approval, but have not yet been evaluated by CDEC.

## Discussion Points:

- Outcomes reported as being important to patient groups such as health-related quality of life and cognitive deficits were not measured in the included trials.
- Patient adherence to recommended treatment regimens (combination of nitisinone therapy and restricted diet) was not reported in the included trials. Patient adherence to treatment was considered challenging by the patient groups.

## Background:

Nitisinone has a Health Canada indication for the treatment of adult and pediatric patients with HT-1 in combination with a dietary restriction of tyrosine and phenylalanine. Nitisinone is a competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme upstream of fumarylacetoacetate hydrolase in the tyrosine catabolic pathway. It prevents the accumulation of the catabolic intermediates, which can be converted to the toxic metabolites, succinylacetone (SA) and succinylacetoacetate. Nitisinone (Orfadin) is supplied as capsules containing 2 mg, 5 mg, 10 mg or 20 mg of nitisinone, with the Health Canada-approved initial dose of nitisinone being 1 mg/kg body weight per day, in two divided doses orally. The drug is also available as an oral suspension (4 mg/mL), which was not included in the manufacturer's submission to CDR. The dose of nitisinone should be adjusted individually based on weight, biochemical factors, and enzyme markers. The maximum daily dosage of nitisinone is 2 mg/kg.

## Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of non-randomized studies of nitisinone submitted by the manufacturer and a critique of the manufacturer's pharmacoeconomic evaluation. CDEC also considered input from a clinical expert with experience treating patients with HT-1, and information submitted by patient groups about outcomes and issues important to patients and caregivers who are affected by HT-1.

### Patient Input Information

Two groups responded to the call for patient input: the Canadian Liver Foundation and the Canadian Organization for Rare Disorders. The following is a summary of key input from the perspective of the patient groups:

- HT-1 is a rare, inborn genetic error of metabolism associated with a severe form of liver disease in infancy or early childhood. In its acute form, without drug or transplant treatment, death from hepatic failure occurs frequently within three to nine months of age. The clinical manifestations of chronic HT-1 are less severe, but these children may develop liver cancer or liver failure and require a liver transplant. Patients' and caregivers' lives frequently revolve around the burdens of this disease. Financial, social, and emotional strains may be experienced by the family of patients with HT-1.
- Early detection of HT-1 (within days of birth) and prompt treatment program are associated with the best chance of survival and the fewest long-term complications.
- Most respondents from both patient groups are currently receiving nitisinone (Orfadin or a bioequivalent version of the same drug) or had used it in the past. Nitisinone treatment is considered life-saving and offers the opportunity to lead a more normal life. However, HT-1 still presents many challenges, such as adherence to the strict diet, need to be monitored regularly for progress, chance of cognitive delay, drug-related side-effects, long-term complications of the disease (e.g., development of liver cancer), and financial impact on the family and individual.

- Responders from both patient groups expressed concerns about the challenges of receiving the medication in a timely fashion as any interruption in treatment has the potential to have serious consequences. The submission of one group further highlighted the frustration when an uncommunicated switch from one manufacturer of nitisinone to the other was implemented in Canada, and respondents were left wondering and worrying about the efficacy of the drug.
- Patients expressed that the cost to patients should remain low or non-existent, and that universal accessibility and interruption-free availability of nitisinone is critical, during any transition to the Public Drug Plans in Canada and throughout a patient's lifetime.

## Clinical Trials

The systematic review included two single-arm, open-label trials (NTBC and Quebec studies) of patients with HT-1.

The NTBC Study (N = 207 with a starting dose of 0.6 mg/kg/day to 1 mg/kg/day in the main analysis; patients were enrolled between 1991 and 1997) was a phase II to III trial that assessed the efficacy and safety of nitisinone for the treatment of patients with HT-1. Patients with prior liver transplants were excluded. Patients were compared with a group of historical patient population that received dietary treatment alone (N = 108, time period from which the participants were enrolled was unknown). The Quebec NTBC Study (N = 78, born between 1984 and 2004) was a phase II trial of patients with HT-1. Patients were categorized as nitisinone-naive (N = 28, patients born between 1984 and 1994 when nitisinone was not available in Quebec, used as historical control), early-treatment (N = 24, treatment started before 30 days after birth) and late-treatment (N = 26, treatment started more than 30 days after birth).

## Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Survival — in the NTBC Study, survival was measured as overall survival, survival without need for liver transplantation, and death due to liver failure during treatment with nitisinone. In the Quebec Study, survival data were reported as death before and after transplantation.
- Liver failure — presented as "death due to liver failure" and "transplantation due to liver failure" during the treatment with nitisinone in the included trials.
- Hepatocellular carcinoma (HCC) — measurement of HCC included death due to HCC, transplantation due to HCC, or HCC diagnosed during treatment with nitisinone.
- Liver transplant — need for liver transplant due to inadequate response to drug therapy, progressive liver disease, or suspected HCC was reported.
- Porphyric crises or neurological crises — "porphyric crises" were reported in the NTBC Study. "Neurological crises" were reported in the Quebec study. The two terms are considered interchangeable by the clinical expert.
- Hospitalization due to complications of HT-1 — this included hospitalizations for preventive treatment and observation during infections.
- Serious adverse events, total adverse events, withdrawal due to adverse events, and death.

The primary outcome in the NTBC Study was survival, survival without need for liver transplant, death due to liver failure, HCC, and porphyric crises. The primary outcome in the Quebec study was hospitalization due to acute complications of HT-1, survival, liver transplant, and neurological crises.

Health-related quality of life was not studied in the included trials.

## Efficacy

Survival probability

*The NTBC Study:* Overall: two- and four-year overall survival rates were 96% and 93% respectively for patients who received nitisinone:

- Nitisinone started < 2 months of age: the two- and four-year survival rates were 88% and 88% respectively (historical control: 29% and 29% respectively)
- Nitisinone started < 6 months of age: the two- and four-year survival rates were 94% and 94% respectively (historical control: 74% and 60% respectively)
- Nitisinone started > 6 months of age: the two- and four-year survival rates were 97% and 93% respectively (historical control: 96% and 96% respectively)

*The Quebec Study:* All (100%) nitisinone-treated patients versus 71% of nitisinone-naive patients were alive before liver transplant. Following liver transplantation, there were two deaths each in the nitisinone-naive (10%) and in the group of patients who started nitisinone > 30 days of age groups (28%). Both deaths in the post-transplantation nitisinone-treated group were reported as due to complications unrelated to HT1.

**Liver failure**

*The NTBC Study*: seven patients (3.4%) died of liver failure and seven patients (3.4%) underwent liver transplant due to liver failure; compared with historical control in which 25% died of liver failure and 6.4% underwent liver transplant due to liver failure.

*The Quebec Study*: none of patients who started nitisinone < 30 days of age had developed detectable liver disease after more than five years of treatment.

**HCC**

*The NTBC Study*: 5% of nitisinone-treated patients versus 8% for historical control experienced HCC.

*The Quebec Study*: HCC was reported in one patient who started nitisinone > 30 days of age group; no HCC was reported in nitisinone-naive group or the nitisinone group started < 30 days of age.

**Liver transplantation**

*The NTBC Study*: 13% of nitisinone-treated patients versus 25% in historical control underwent a liver transplantation.

*The Quebec Study*: none of patients who started nitisinone < 30 days of age, 27% of patients who started nitisinone > 30 days of age, and 71% of nitisinone-naive patients underwent a liver transplantation.

**Porphyric crises and neurological crises**

*The NTBC Study*: one mild porphyric crisis was reported for nitisinone-treated patients versus 10% died from consequences of porphyria-like crises in historical control.

*The Quebec Study*: 71 months were spent in hospital for neurologic crises for nitisinone-naive patients versus17 months for patients received nitisinone > 30 days of age and no months in hospital for patients received nitisinone < 30 days of age.

**Hospitalization resulting from acute complications of HT-1**

*The NTBC Study*: Outcome not reported.

*The Quebec Study*: nitisinone therapy was associated with fewer hospitalizations related to HT-1 complications.

Statistical comparisons between nitisinone treatment group and historical control were not conducted for any outcome measures.

## Harms (Safety and Tolerability)

In the NTBC Study, eye disorders were the most common adverse events (31 events observed in 14 patients). In the Quebec study, one patient developed photophobia and corneal crystals, which disappeared within 24 hours of strict dietary restriction. Three cases of severe thrombocytopenia were deemed to be related to treatment of nitisinone. No patients withdrew from the study due to adverse events. Ten deaths in the NTBC Study and two deaths in the Quebec study were reported during treatment of nitisinone.

## Cost and Cost-Effectiveness

The manufacturer submitted the following price for nitisinone capsules: 2 mg ($22.50), 5 mg ($53.30), 10 mg ($100), and 20 mg ($193.33). The recommended dose is 1 mg/kg body weight daily, up to a maximum of 2 mg/kg body weight, divided in two doses. At the Health Canada-recommended dose, the annual cost of treatment is $70,614 in a 20 kg patient, increasing to $267,850 in a 75 kg patient.

The manufacturer submitted a cost-utility analysis comparing nitisinone (1mg/kg) plus best supportive care (BSC; dietary restriction) versus BSC alone in a subset of the population indicated, that is for the treatment of newborns who are identified and treated within one month of birth, either through a newborn screening program; or physical examination, patient history, and specialized tests (including urine SA levels). Comparative treatment effect was derived from a Quebec study of newborns followed for up to 14 years. The manufacturer used a three state, semi-Markov cohort where all patients start in the health state “diagnosed with HT-1” and could transition to a liver transplant state (with associated tunnel states) and a death state. A lifetime time horizon was used and the analysis was from a health ministry perspective.

The manufacturer estimated the addition of nitisinone to BSC versus BSC alone would result in an incremental cost-utility ratio (ICUR) of $320,985 per QALY.

CDR identified several key limitations with the manufacturer’s economic submission, including:

- The manufacturer assumed all newborns are identified and treated early (within 30 days), and that no treated patients would require liver transplant or die prematurely from disease, which is questionable given screening programs may not be available or may not identify 100% of infants with HT-1.
- A relatively short-term study was used by the manufacturer to inform the clinical inputs, which may not capture long-term events in patients with HT-1. The results of the model are contingent on continued benefit from treatment over an average life time of approximately 80 years.
- The utility values used for pediatric patients are uncertain as they are based on male adult patients with decompensated cirrhosis due to chronic hepatitis B infection.
- The manufacturer did not include the cost of diet in the nitisinone group, or the potential for hepatocellular carcinoma and other relevant complications in patients with HT-1.
- The results are highly sensitive to nitisinone dose, but this parameter could not be varied over time or tested probabilistically.

CADTH undertook a re-analysis that included diet costs for both treatment groups; considered alternate utility values assumed to be more generalizable to patients with HT-1; and a greater proportion of nitisinone patients requiring liver transplantation. This resulted in an ICUR of $377,025 per QALY for nitisinone plus BSC compared with BSC alone for patients captured in the model population. The likelihood that nitisinone is cost-effective at a willingness-to-pay threshold of $200,000 per QALY was 0%. A price reduction of at least 74% (for all nitisinone strengths) would be required for nitisinone to achieve an ICUR less than $100,000 per QALY based on the CADTH base case.

CADTH was unable to test several limitations, and noted the lack of long-term information for patients receiving nitisinone increased the uncertainty of the magnitude of the likely clinical benefit. The ICUR for nitisinone plus BSC compared with BSC alone is unknown in the patient population treated after one month of age.

## CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

## January 17, 2018 Meeting

## Regrets:

None

## Conflicts of Interest:

None