CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

NITISINONE (Nitisinone Tablets — Cycle Pharmaceuticals Ltd.)
Indication: The treatment of adult and pediatric patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that nitisinone (Nitisinone Tablets) 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.
- The total cost of treatment with nitisinone (Nitisinone Tablets) should not exceed the drug plan cost of other nitisinone products.

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Reasons for the Recommendation

1. HT-1 is a rare disease (worldwide incidence of approximately one in 100,000 live births) that manifests most commonly in infants and is associated with high mortality and morbidity. The available clinical evidence from 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 a historical cohort that received dietary treatment alone. Patients receiving nitisinone also had a reduced risk of liver failure, fewer liver transplantation requirements, lower risk of hepatocellular carcinoma (HCC), fewer porphyric crises, and reduced acute complications of HT-1.
2. Nitisinone Tablets are bioequivalent to the reference nitisinone product, Orfadin.
3. The manufacturer-submitted prices for nitisinone are $12.95 per 2 mg tablet, $25.06 per 5 mg tablet, and $47.40 per 10 mg tablet. Based on these prices, nitisinone (Nitisinone Tablets) is 42% to 53% less expensive than Orfadin, and 12% to 27% less expensive than MDK-Nitisinone, depending on unit strength. CADTH previously reviewed Orfadin, and CDEC recommended that the price of Orfadin be reduced by 74%. To achieve the price for Orfadin suggested by CDEC, the price of Nitisinone Tablets would need to be reduced by 45% to 55% to be equivalent to the price suggested for the other nitisinone products.

Of Note:

- 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 compared with historical controls. Delaying nitisinone treatment initiation (i.e., after two years of age) was associated with an increased probability of HCC and the need for a liver transplant.
- Jurisdictions that do not perform newborn screening for HT-1 may wish to consider the cost-effectiveness of introducing such screening, thereby facilitating early identification of eligible patients.
- 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.

- CDEC noted several important limitations with the studies reviewed by the CADTH Common Drug Review (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.
- CDEC previously recommended two other nitisinone products that are available for the treatment of patients with HT-1: Orfadin and MDK-Nitisinone.

Discussion Points:

- Outcomes reported as being important to patient groups, such as health-related quality of life and lack of 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-hydroxyphenylpyruvate 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 and succinylacetoacetate. Nitisinone (Nitisinone Tablets) is supplied as tablets containing 2 mg, 5 mg, and 10 mg of nitisinone, with the Health Canada–approved initial dosage of nitisinone being 1 mg/kg of body weight per day, in two divided doses orally. The dose of nitisinone should be adjusted individually based on weight, biochemical factors, and enzyme markers. The maximum daily dose 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, bioequivalence data for Nitisinone Tablets and Orfadin, 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

One group, the Canadian Liver Foundation, provided input for this submission. Patient perspectives were obtained from survey via an online questionnaire. The following is a summary of key input from the perspective of the patient group:

- 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 families of patients with HT-1.
- Most respondents reported currently receiving nitisinone products (Orfadin or MDK-Nitisinone). Patients report a quick response to treatment with nitisinone. Nitisinone treatment is considered life-saving and offers the opportunity to lead a more normal life. However, HT-1 still presents many patient challenges, such as adherence to the strict diet, the need to be monitored regularly for progress, long-term complications of the disease (e.g., development of liver cancer), and the anxiety about receiving the medication in a timely fashion, as any interruption in treatment has the potential to have serious consequences.
- The patient group hopes that the current no-cost access to nitisinone therapy, regardless of brand, remains in place to alleviate the financial burden on patients and their families.

- Although no respondents had experience with Nitisinone Tablets, it may benefit patients and their caregivers because it is stored at room temperature and is easier swallow because the tablets are smaller than the capsules.

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 dosage 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 and 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 historical patient population that received dietary treatment alone (N = 108; the time period from which the participants were enrolled was unknown). The Quebec NTBC study (N = 78; patients 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, were used as historical control), early-treatment (N = 24; treatment started within 30 days of 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 — This was presented as “death due to liver failure” and “transplantation due to liver failure” during treatment with nitisinone in the included trials.
- HCC — The measurement of HCC included death due to HCC, transplantation due to HCC, or HCC diagnosed during treatment with nitisinone.
- Liver transplant — The need for a liver transplant due to inadequate response to drug therapy, progressive liver disease, or suspected HCC.
- 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 outcomes in the NTBC study were survival, survival without need for liver transplant, death due to liver failure, HCC, and porphyric crises. The primary outcomes in the Quebec study were 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 before two months of age: The two- and four-year survival rates were 88% and 88%, respectively (historical control: 29% and 29%, respectively).

- Nitisinone started before six months of age: The two- and four-year survival rates were 94% and 94%, respectively (historical control: 74% and 60%, respectively).
- Nitisinone started after six 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 after 30 days of age (28%). Both deaths in the post-transplantation nitisinone-treated group were reported as due to complications unrelated to HT-1.

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. In the historical control, 25% died of liver failure and 6.4% underwent liver transplant due to liver failure.

The Quebec study: None of the patients who started nitisinone after 30 days of age had developed detectable liver disease after more than five years of treatment.

Hepatocellular Carcinoma

The NTBC study: 5% of nitisinone-treated patients versus 8% of patients in the historical control experienced HCC.

The Quebec study: HCC was reported in one patient who started nitisinone after 30 days of age; no HCC was reported in the nitisinone-naive group or the nitisinone group which comprised patients who started on the drug before 30 days of age.

Liver Transplantation

The NTBC study: 13% of nitisinone-treated patients versus 25% of patients in the historical control underwent liver transplantation.

The Quebec study: None of the patients who started nitisinone before 30 days of age, 27% of patients who started nitisinone after 30 days of age, and 71% of nitisinone-naive patients underwent liver transplantation.

Porphyric Crises and Neurological Crises

The NTBC study: One mild porphyric crisis was reported for nitisinone-treated patients versus 10% who died from consequences of porphyria-like crises in the historical control group.

The Quebec study: Nitisinone-naive patients spent 71 months in hospital for neurologic crises versus 17 months for patients who received nitisinone after 30 days of age, and no months were spent in hospital by patients who received nitisinone before 30 days of age.

Hospitalization Resulting From Acute Complications of HT-1

The NTBC study: This outcome was not reported.

The Quebec study: Nitisinone therapy was associated with fewer hospitalizations related to HT-1 complications.

Statistical comparisons between the nitisinone treatment group and the historical control were not conducted for any measured outcomes.

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 with 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 with nitisinone.

Bioequivalence

One randomized, open-label, single-dose, crossover bioequivalence study was conducted for Nitisinone Tablets and Orfadin (reference product). Results of this bioequivalence study showed that a single 10 mg dose of Nitisinone Tablets had pharmacokinetics equivalent to Orfadin in healthy volunteers under fasting conditions. Therefore, Nitisinone Tablets met all potency and bioequivalence requirements necessary to be declared equivalent to Orfadin, based on Health Canada guidelines.

Cost and Cost-Effectiveness

The submitted price of nitisinone (Nitisinone Tablets) differs based on dose: 2 mg ($12.95), 5 mg ($25.06), and 10 mg ($47.40). The recommended initial dose is 1 mg/kg of body weight daily divided into two doses administered orally, up to a maximum of 2 mg/kg daily. At the recommended dose, the annual cost of treatment for a 20 kg patient is $34,626, increasing to $130,343 for a 70 kg patient.

The manufacturer submitted a Markov state–transition model comparing Nitisinone Tablets with diet restriction to diet restriction alone for newborn patients newly diagnosed with HT-1. The model consisted of seven health states: HT-1 with or without symptoms, acute liver failure, HCC or cirrhosis, liver transplantation, post-liver transplantation, neurological crises, and death. Efficacy data to inform the health state transitions were taken directly from the Quebec nitisinone study by Larochelle et al. Utility values for the health states were sourced from published literature. The perspective was that of a Canadian health care payer with a time horizon of 20 years and a cycle length of one year. A discount of 1.5% was applied to costs and outcomes. In its base case, the manufacturer estimated that the addition of Nitisinone Tablets to dietary restriction versus dietary restriction alone would result in an incremental cost-utility ratio (ICUR) of $138,658 per quality-adjusted life-year (QALY) gained.

CDR identified several key limitations with the manufacturer's submission:

- The manufacturer assumed all patients would be identified and treated at birth, which does not include the entire population indicated by Health Canada and may not appropriately estimate the cost-effectiveness of nitisinone therapy in patients who are identified and initiate treatment at a later time.
- The manufacturer modelled a 20-year time horizon, which does not adequately reflect the lifelong nature of HT-1 treatment.
- The manufacturer directly incorporated the outcomes of 51 patients with HT-1 from the Quebec study rather than estimating transition probabilities using the data from the study, hampering the flexibility and generalizability of the estimates and artificially reducing uncertainty in the probabilistic analyses.
- Mortality in cycles after liver transplantation was not considered in the model. Not considering all-cause and other-cause mortality over time limits the assessment of the long-term cost-effectiveness of nitisinone.
- Utilities were derived from a different population (an adult population of chronic hepatitis B patients), which may not be generalizable to pediatric patients with HT-1.
- The manufacturer assumed that the use of supplements necessary for the restriction of dietary tyrosine and phenylalanine would be equal between groups and could therefore be excluded, which is unlikely to be the case given the longer life expectancy and lack of liver transplantation in the nitisinone-treated group.

CDR conducted a reanalysis incorporating utilities from a chronic hepatitis C population, as well as the cost of dietary restriction, resulting in an estimated ICUR of $149,197 per QALY. However, this likely underestimates the ICUR for Nitisinone Tablets (i.e., biases the results in favour of Nitisinone Tablets) due to its 20-year time horizon rather than lifetime. CDR was unable to test several limitations, such as a lifetime time horizon or alternate assumptions around the long-term outcomes of patients using nitisinone therapy, such as the eventual need for a liver transplant, especially among patients whose HT-1 was not identified in the first month of life.

At the submitted price, Nitisinone Tablets are 42% to 53% less expensive than the submitted price for Orfadin, and 12% to 27% less expensive than that of MDK-Nitisinone, depending on unit strength. However, to be equivalent to the price reduction suggested by CDEC for other nitisinone products, the price of Nitisinone Tablets would need to be reduced by 45% to 55%.

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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

July 18, 2018 Meeting

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None