CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

Nitisinone (MDK-Nitisinone — MendeliKABs Inc.)
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 (MDK-Nitisinone) 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:

Clinical 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 (MDK-Nitisinone) should not exceed the drug plan cost of other nitisinone products.

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

Conditions

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- The total cost of treatment with nitisinone (MDK-Nitisinone) should not exceed the drug plan cost of other nitisinone products.

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 came from two open-label, single-arm studies, NTBC (N = 207) and Quebec (N = 78), which 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. Nitisinone was also associated with 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. The manufacturer-submitted prices for nitisinone are: $14.78 per 2 mg capsule, $34.18 per 5 mg capsule, $64.70 per 10 mg capsule, and $128.10 per 20 mg capsule. The manufacturer-submitted economic analysis was insufficient to adequately estimate the cost-effectiveness of MDK-Nitisinone plus dietary restriction compared with dietary restriction alone in Canadian patients with HT-1. The CADTH Common Drug Review (CDR) was unable to conduct reanalyses to provide an estimated incremental cost-utility ratio (ICUR). However, MDK-Nitisinone is bioequivalent to the reference nitisinone product, Orfadin.

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 HCC and the requirement of liver transplant.
2. 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.
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 for nitisinone plus dietary restriction versus dietary restriction alone, leading to uncertainty of the magnitude of any benefit. These limitations made it difficult to assess the comparative clinical benefit of nitisinone.
5. CDEC previously provided a recommendation on the reference nitisinone product, Orfadin (January 2018). One other nitisinone product has received Health Canada approval, but it has not yet been evaluated by CDEC.

6. The incremental cost-effectiveness of treatment with Orfadin plus dietary restriction of tyrosine and phenylalanine (initiated prior to one month of age), 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 reanalysis of the model by CDR. At the submitted prices of both reviewed nitisinone products, MDK-Nitisinone is less expensive by approximately 35%. Given that CDEC recommended a price reduction of at least 74% to make the reference product (Orfadin) cost-effective, a price reduction of at least 60% (for all MDK-Nitisinone strengths) would be required to increase the probability that MDK-Nitisinone will be cost-effective in infants one month old or younger (in line with the price condition included for Orfadin). A higher price reduction would likely be required for MDK-Nitisinone to be cost-effective in all populations, as noted previously in the Orfadin recommendation.

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-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 (MDK-Nitisinone) is supplied as capsules containing 2 mg, 5 mg, 10 mg, or 20 mg of nitisinone, with the Health Canada–approved initial dosage of nitisinone being 1 mg/kg 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 MDK-Nitisinone with 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

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 families of patients with HT-1.
- Early detection of HT-1 (within days of birth) and prompt treatment 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 patient 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.

- 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 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, 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 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 — presented as "death due to liver failure" and "transplantation due to liver failure" during treatment with nitisinone in the included trials.
- 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.
- 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 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 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 after 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 after 30 days of age; no HCC was reported in nitisinone-naive group or the nitisinone group that started before 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 before 30 days of age, 27% of patients who started nitisinone after 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% who 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 versus 17 months for patients who received nitisinone after 30 days of age and no months in hospital for patients who received nitisinone before 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 the nitisinone treatment group and 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 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.

Bioequivalence

One randomized, blinded, one-way parallel bioequivalence study comparing the pharmacokinetics and safety of MDK-Nitisinone (test product) and Orfadin (reference product) following a 10 mg single dose in healthy participants under fasting conditions was considered. The test product, 10 mg capsule MDK-Nitisinone, met all potency and bioequivalence requirements to be declared equivalent to the reference product, Orfadin, based on Health Canada guidelines.

Cost and Cost-Effectiveness

The manufacturer submitted the following prices for nitisinone capsules: 2 mg ($14.78), 5 mg ($34.18), 10 mg ($64.70), and 20 mg ($128.10). Based on the Health Canada–recommended daily dosage of nitisinone of 1 mg/kg/day, the estimated cost of treatment in the first year of life is $18,998 per patient, derived using World Health Organization growth chart median weight by age. The annual cost per year of treatment for a 75 kg patient is $179,124.

The manufacturer submitted a cost-utility analysis comparing nitisinone plus dietary restriction of tyrosine and phenylalanine with dietary restriction alone in infants less than 30 days of age with HT-1 over a six-year time horizon, from a public health care system perspective. The economic analysis incorporated three health states: nitisinone treatment; no nitisinone treatment before liver transplant; and no nitisinone treatment after liver transplant. All patients in the no-nitisinone groups transitioned from pre- to post-liver transplant state at age 2. Patients in the nitisinone group remained in the "nitisinone treatment" health state, and no mortality rate was applied to either group. Clinical effectiveness was based on a Quebec cohort study.

The manufacturer multiplied the number of years spent in each health state by the assigned utility of the state, estimating that the addition of nitisinone to dietary restriction would result in an ICUR of $62,823 per QALY.

CDR identified several major limitations with the manufacturer's economic submission:

- The manufacturer's model did not align with clinical data or accepted economic analysis methods. Clinical status, transition probabilities, event probabilities, event-related consequences, and mortality were not considered or not considered appropriately.
- The six-year time horizon was insufficient to adequately capture long-term events in patients with HT-1 and underestimates the cost of therapy in patients older than six years of age.
- The generalizability of the utility values used for pediatric HT-1 patients is uncertain, as they are based on an adult population with cirrhosis due to chronic hepatitis B.
- Costing in the model was based on a Quebec costing study and presented in an aggregated, non-transparent manner, making it difficult to examine resource use or detect potential double counting.
- Costs were reported to be discounted by 3% to 5% in the Quebec costing study. However, QALYs were not discounted in the model, leading to an underestimate of the ICUR.

The manufacturer's economic model was insufficient to adequately estimate the cost-effectiveness of MDK-Nitisinone plus dietary restriction compared with dietary restriction alone in Canadian patients with HT-1; CDR was unable to conduct reanalyses to provide an estimated ICUR.

Two other nitisinone products have recently been approved for use by Health Canada; one has recently been reviewed by CADTH (Orfadin), while the other is currently under review. Given the clinical data indicating these treatments are comparable, whether MDK-Nitisinone delivers value for money will depend on its cost relative to other nitisinone products.

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.

March 21, 2018 year Meeting

Regrets

None.

Conflicts of Interest

None.