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CADTH COMMON DRUG REVIEW

# Pharmacoeconomic Review Report

## Nitisinone (Nitisinone Tablets)

(Cycle Pharmaceuticals Ltd.)

Indication: For the treatment of patients with hereditary tyrosinemia type 1 in combination with dietary restriction of tyrosine and phenylalanine.


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

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# Abbreviations

| | |
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| **AE** | adverse event |
| **CDR** | CADTH Common Drug Review |
| **HCC** | hepatocellular carcinoma |
| **HT-1** | hepatorenal tyrosinemia type 1 |
| **ICUR** | incremental cost-utility ratio |
| **INESSS** | l'Institut national d'excellence en santé et en services sociaux |
| **LF** | liver failure |
| **LT** | liver transplantation |
| **NEC** | neurological crises |
| **QALY** | quality-adjusted life-year |

## Table 1: Summary of the Manufacturer's Economic Submission

| | |
|---|---|
| **Drug Product** | Nitisinone Tablets |
| **Study Question** | What is the economic impact of Nitisinone Tablets for the treatment of HT-1 in Canada? |
| **Type of Economic Evaluation** | Cost-utility analysis |
| **Target Population** | Newborns diagnosed with HT-1 at birth through screening, with immediate initiation of treatment |
| **Treatment** | Nitisinone 1 mg/kg/day divided into two doses, with dietary restriction of tyrosine and phenylalanine via nutritional supplements |
| **Outcome(s)** | QALYs |
| **Comparator(s)** | Dietary restriction of tyrosine and phenylalanine (termed "dietary restriction alone") |
| **Perspective** | Canadian public health care payer |
| **Time Horizon** | 20 years |
| **Results for Base Case** | Probabilistic median ICUR reported: $138,871 per QALY |
| **Key Limitations** | • Modelled population 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.<br>• The manufacturer modelled a 20-year time horizon, which does not adequately reflect the lifelong nature of HT-1.<br>• The model directly incorporated the outcomes of 51 patients with HT-1 from the Larochelle study rather than estimating transition probabilities using the data from Larochelle, hampering the flexibility and generalizability of the estimates and artificially reducing uncertainty in the probabilistic analyses.<br>• Mortality in cycles after liver transplantation was not considered. Not considering all-cause and other-cause mortality over time impedes assessment of the long-term cost-effectiveness of Nitisinone Tablets. Additionally, the model lacked flexibility in transition probabilities to estimate the cost-effectiveness of nitisinone over a lifetime horizon.<br>• 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.<br>• The manufacturer assumed the use of the 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 Estimate** | • CDR's base case incorporated utilities from a CHC population as well as the cost of dietary restriction, resulting in an estimated ICUR of $149,197 per QALY.<br>• However, this likely overestimates the cost-effectiveness of Nitisinone Tablets (i.e., biases the results in favour of Nitisinone Tablets) due to its 20-year time horizon rather than lifetime.<br>• At the submitted price, Nitisinone Tablets is 42% to 53% less expensive than Orfadin, and 12% to 27% less expensive than MDK-Nitisinone, depending on unit strength.<br>• 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 = CADTH Canadian Drug Expert Committee; CDR = CADTH Common Drug Review; CHC = chronic hepatitis C; HT-1 = hereditary tyrosinemia type 1; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

| | |
|---|---|
| **Drug** | Nitisinone (Nitisinone Tablets) |
| **Indication** | For the treatment of patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. |
| **Reimbursement Request** | As per indication |
| **Dosage Form** | 2 mg, 5 mg, and 10 mg oral tablets |
| **NOC Date** | November 4, 2016 |
| **Manufacturer** | Cycle Pharmaceuticals Ltd. |

# Executive Summary

## Background

Nitisinone (Nitisinone Tablets) is indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.[1] Nitisinone Tablets are available in 2 mg, 5 mg, and 10 mg strengths. The submitted price of nitisinone is based on dose: 2 mg ($12.95), 5 mg ($25.06), and 10 mg ($47.40).[2] The recommended initial dose is 1 mg/kg body weight daily divided into two doses, administered orally. Patients whose plasma and urine succinylacetone are still detectable one month after starting treatment should be increased to 1.5 mg/kg/day, with a maximum of 2 mg/kg/day, based on the evaluation of all clinical parameters. If biochemical response is satisfactory, dosage should only be adjusted according to body weight.

The CADTH Common Drug Review (CDR) previously reviewed another brand of nitisinone (Orfadin) for the treatment of HT-1; the CADTH Canadian Drug Expert Committee (CDEC) recommended that nitisinone (Orfadin) be reimbursed for the treatment of adult and pediatric patients with an established diagnosis of HT-1 in combination with dietary restriction of tyrosine and phenylalanine if the following conditions are met: the drug is prescribed by a physician with experience in the diagnosis and management of HT-1, and the price is reduced by at least 74%.[3] CDR recently reviewed a third nitisinone product (MDK-Nitisinone), with a similar recommendation, noting that the cost of MDK-Nitisinone should not exceed the cost of other nitisinone products.[4]

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 (HT-1), acute liver failure (LF), hepatocellular carcinoma or cirrhosis (HCC/cirrhosis), liver transplantation (LT), post–liver transplantation (post-LT), neurological crises (NEC), 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. Resource use and costs were derived from predominantly Canadian sources. 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, and no half-cycle correction was applied. The manufacturer included a deterministic and

probabilistic analysis with 5,000 simulations from both a health care payer and societal perspective for each analysis.

In their probabilistic base case, the manufacturer estimated that the addition of Nitisinone Tablets to dietary restriction versus dietary restriction alone would produce an additional 6.47 quality-adjusted life-years (QALYs) over the 20-year time horizon at an additional cost of $896,823, resulting in an incremental cost-utility ratio (ICUR) of $138,658 per QALY gained.

## Summary of Identified Limitations and Key Results

CDR identified several key limitations with the model submitted by the manufacturer, several of which were identified in the previous nitisinone submissions.

Firstly, the modelled population assumed all patients would be identified and treated within one month of birth, which does not align with the population indicated by Health Canada or the manufacturer's reimbursement request, and may not appropriately estimate the cost-effectiveness of nitisinone therapy in patients who are identified later and initiate treatment more slowly.

Secondly, the manufacturer undertook their analysis using a 20-year time horizon, which does not adequately reflect the lifelong nature of HT-1. This shorter time horizon also likely underestimates the ICUR of Nitisinone Tablets in combination with dietary restrictions compared with dietary restrictions alone, based on information provided in the manufacturer's scenario analyses.

Thirdly, the model directly incorporated the outcomes of 51 patients with HT-1 from the Larochelle study rather than estimating transition probabilities using the data from that study, which limited the flexibility of the model and artificially reduced the uncertainty in the probabilistic analyses. The manufacturer assumed that all patients in the nitisinone group remained in the HT-1 health state for the duration of the 20-year model, while surviving patients in the diet restriction–alone group remained in the post–liver transplant health state without risk of further complication or mortality. Both of these assumptions are highly uncertain.

Additionally, by incorporating outcomes found only in the 51 patients from the Larochelle trial, the manufacturer did not account for all-cause mortality, nor mortality in cycles after LT; the exclusion of other-cause mortality and a general lack of flexibility in transition probabilities precluded alteration of the model to estimate the cost-effectiveness of nitisinone over a lifetime horizon.

Furthermore, 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 or the best source of data available.

Finally, the manufacturer assumed the use of the 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 LT in the nitisinone-treated group.

CDR undertook reanalyses that incorporated the cost of dietary supplements for all HT-1 patients who had neither received liver transplants nor died. CDR also incorporated utilities derived from an adult population of patients with chronic hepatitis C, which the clinical expert

consulted by CDR considered to be a more relevant proxy for patients with HT-1. Incorporating both of these changes resulted in an ICUR of $149,197 per QALY. CDR was unable to test several limitations within its reanalyses, 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 liver transplant, especially among patients who were not identified in the first month of life.

While the current model has some strengths compared with the submitted model for Orfadin,[5] including defining health states based on health status rather than treatment assignment and the consideration of HCC, the shorter time horizon used in the current analysis is inappropriate. As HT-1 is a chronic condition requiring lifelong therapy generally starting soon after birth, a lifetime time horizon is appropriate. When adding Nitisinone Tablets to dietary restriction compared with dietary restriction alone, the ICUR increases as the time horizon does ($4,303 per QALY at five years and $66,410 per QALY at 10 years, compared with $149,197 per QALY over 20 years); it is likely Nitisinone Tablets would appear less cost-effective over a lifetime time horizon (greater than 20 years).

## Conclusions

In patients with HT-1 identified and treated at birth, CDR's reanalysis reported an ICUR of $149,197 per QALY for Nitisinone Tablets plus dietary restriction compared with dietary restriction alone over a 20-year time horizon. The manufacturer used the same clinical data to inform the model as previously considered in the Orfadin and MDK-Nitisinone reviews; however, the use of direct data, rather than modelled transition probabilities based on study data, limits the flexibility of the model in exploring alternate assumptions around outcomes and artificially reduces uncertainty in the probabilistic analyses. Additionally, while the current model has some strengths in comparison with the one submitted for Orfadin,[5] the estimated ICUR is likely underestimated due to limiting the time horizon to 20 years rather than lifetime.

The submitted price of Nitisinone Tablets is 42% to 53% less than Orfadin, and 12% to 27% less expensive than MDK-Nitisinone, depending on unit strength. However, CDEC recommended that the price of Orfadin be reduced by 74% in their February 2018 recommendation. To achieve the price of Orfadin suggested by CDEC, the price of Nitisinone Tablets would need to be reduced by 45% to 55% to be equivalent to the suggested price of the other nitisinone products.

# Information on the Pharmacoeconomic Submission

## Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a Markov state–transition model comparing Nitisinone Tablets with diet restriction to diet restriction alone for newborn patients newly diagnosed with hepatorenal tyrosinemia type 1 (HT-1). The model consisted of seven health states: HT-1 with or without symptoms (HT-1), acute liver failure (LF), hepatocellular carcinoma or cirrhosis (HCC/cirrhosis), liver transplantation (LT), post–liver transplantation (post-LT), neurological crises (NEC), and death. 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, and no half-cycle correction was applied. The manufacturer included a deterministic and probabilistic analysis with 5,000 simulations from both a health care payer and societal perspective for each analysis.

## Manufacturer's Base Case

All patients started in the HT-1 health state, and each cycle, patients could move from HT-1 to the HCC/cirrhosis, NEC, or LF health states, which were all transient. The duration of NEC was assumed to be 28 days and could occur more than once per patient in a cycle, while the duration of LF was 21 days. Patients transitioning to the HCC/cirrhosis health state were assumed to undergo LT the following cycle. The LT state was considered to be instantaneous within the model, having neither an assigned duration nor disutility. Patients in the NEC health state could return to the HT-1 state, undergo LT, or die, all within the same cycle, while patients in the HCC/cirrhosis or LF state could transition to the LT state or die (Figure 1).

Baseline characteristics, efficacy, and health state transitions were derived from a Quebec-based cohort study (Larochelle, 2012)[6] of 78 newborns followed for up to 14 years. In that study, patients received nitisinone within 30 days of birth ("early;" n = 24), after 30 days of birth ("late;" n = 26), or remained untreated ("untreated;" n = 28). The model only considered early and untreated patients, as it was assumed that all patients would be screened for HT-1 at birth. One untreated patient in the Larochelle study was excluded from the manufacturer's model because they were not diagnosed with HT-1 until presenting with cirrhosis and HCC; they received a single week of nitisinone therapy prior to liver transplantation. As no early-treated patient experienced the clinical manifestations of HT-1, all 24 patients in the nitisinone group remain in the HT-1 health state for the duration of the model. Patients in the diet-alone group transitioned through the other health states in accordance with the time of onset of the events experienced by the 27 remaining untreated patients in the Larochelle study, rather than according to transition probabilities derived from the study. By the end of the Larochelle study, all diet restriction–alone patients had either died or received LT; no further mortality or events were assumed to happen to them for the remainder of the model's time horizon.

Health-related quality of life for the non-transient health states was derived from a Canadian cohort study of adults (60% men, 75% of Asian or Southeast Asian ethnicity, average age: 50 years) with chronic hepatitis B measured with the EuroQol 5-Dimensions questionnaire

(EQ-5D). Transient health states were associated with disutilities contingent upon their assumed duration (Table 10 in Appendix 5).

Assumptions regarding resource use and costs were derived from Larochelle[6] for general HT-1 and nitisinone monitoring costs; the Ontario Case Costing Initiative and the Ontario Schedule of Benefits for Physician Services for costs associated with LF, LT, and NEC; and a hepatitis B costing study for costs associated with HCC/cirrhosis.[7] Cost of nitisinone therapy was provided by the manufacturer, with weight-based dosing derived from World Health Organization (WHO) growth charts, rounded down to the nearest milligram. The cost of immunosuppression therapy post-LT was based on the treatment protocol from Moini et al. (2015)[8] and Ontario Drug Benefit formulary list prices, while the cost of supplemental nutrition for dietary restriction was assumed equal between groups and not included. See Table 11 and Table 12 in Appendix 5 for further details.

The manufacturer's base-case analysis was presented as both deterministic and probabilistic results from a health care payer perspective (Table 2). The probabilistic analysis of the addition of nitisinone to diet restriction alone produced an additional 6.47 quality-adjusted life-years (QALYs) for an additional cost of $896,823 per person, resulting in an incremental cost-utility ratio (ICUR) of $138,658 per QALY (reporting corrected to probabilistic means rather than medians). A further breakdown of costs for the deterministic analysis can be found in Table 13.

## Table 2: Manufacturer's Base-Case Results

| | Costs | Incremental costs | QALYs | Incremental QALYs | ICUR |
|---|---|---|---|---|---|
| **Deterministic** | | | | | |
| Diet alone | $152,381 | $896,891 | 9.565 | 6.47 | $138,689 |
| Nitisinone plus diet | $1,049,273 | | 16.032 | | |
| **Probabilistic**[a] | | | | | |
| Diet alone | $152,512 | $896,823[a] | 9.567 | 6.47[a] | $138,658[a] |
| Nitisinone plus diet | $1,049,335 | | 16.035 | | |

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Table results are based on reported probabilistic means. The manufacturer reported an ICUR based on median probabilistic costs and QALYs: incremental cost of $897,212 and incremental QALYs of 6.46 for an ICUR of $138,871.

Source: Adapted from the manufacturer's pharmacoeconomic submission, Table 17, and Microsoft Excel model.[2]

## Summary of Manufacturer's Sensitivity Analyses

The manufacturer also conducted deterministic sensitivity analyses, varying: weights of children based on the 25th and 75th percentiles of the WHO growth charts, the proportion of male children, utilities for health states, disutilities for transient health states, costs of transient health state events, and costs of monitoring and maintenance in health states. Altering the assumed mean body weight of the cohort, as well as the utility associated with the post-LT state, had the biggest effect on the ICUR.

## Limitations of Manufacturer's Submission

**Modelled population does not align with listing request:** The manufacturer's modelled population assumed all patients were identified and treated within one month of being born, meaning patients would not have experienced physiologic damage from tyrosinemia.

Assessing this subpopulation does not allow for an estimate of relative costs and the health outcomes of patients who are identified more slowly (i.e., those who were not screened at birth or whose screening results were false-negatives) or who do not initiate treatment within one month. The cost-effectiveness of nitisinone initiated in patients who are older than one month of age is not known, but is likely associated with a higher ICUR, given the higher costs associated with late-treated patients[9] and the likelihood that early-treated patients achieve more clinical benefit.[6]

**Time horizon:** The manufacturer's choice of a 20-year time horizon does not adequately reflect the lifelong nature of HT-1, nor the need for continuing therapy, be it nitisinone, anti-rejection therapies after LT, or nutritional supplements required to maintain a tyrosine- and phenylalanine-restricted diet. The cost-effectiveness of nitisinone therapy over a patient's projected lifetime has not been estimated, and the overall lifespan and later quality of life of patients using nitisinone and dietary restriction for the treatment of HT-1 is unknown.

**State transitions based exactly on Larochelle data:** The manufacturer's model exactly replicated the outcomes of 24 patients who were "early-treated" with nitisinone (plus dietary restriction) and the 27 never-treated (with nitisinone) dietary-restriction patients reported in Larochelle,[6] with patients assumed to have stayed in the same health state they were in at the end of the study for the duration of the model time horizon. As such, the model does not incorporate standard transition probabilities between states, hampering the flexibility of the model, especially when considering alternate efficacy assumptions such as a small annual risk of HCC or LF for patients using nitisinone, as found in Arnon et al.[10] It is likely that some patients will require LT even with nitisinone treatment. Additionally, no distributions are modelled, reflecting uncertainty in health state transitions, leading to reduced variation in results of the probabilistic analysis.

**Non-HT-1–associated mortality excluded:** The manufacturer assumes that all mortality is related to HT-1 or to initial mortality subsequent to LT. All-cause mortality and the higher mortality experienced by patients after LT in subsequent years are not incorporated. Additionally, the lack of inclusion of all-cause or other mortality assumptions precludes estimation of the cost-effectiveness of Nitisinone Tablets over a lifetime time horizon.

**Generalizability of utility weights uncertain**: The utilities used by the manufacturer were derived from Woo et al.,[11] a survey of adults (mean age: 54 years) in various stages of chronic hepatitis B infection as measured by the EQ-5D generic health state preference-weight instrument, which reported utilities of 0.92, 0.81, 0.73, and 0.84 for non-cirrhotic chronic hepatitis B infection, HCC, decompensated cirrhosis, and post-LT health states, respectively, which were used by the manufacturer as a proxy for HT-1, HCC, decompensated cirrhosis, and post-LT in the modelled HT-1 population. While acknowledging the uncertainty in modelling a pediatric population using adult utility data, the clinical expert consulted by CDR considered chronic hepatitis C infection to be a more relevant proxy for patients with HT-1, one that is more likely to reflect disease progression and elevated risk of HCC.

**Cost of dietary-restriction supplementation not included**: The manufacturer's assumption that the cost of supplements to support the dietary restriction of phenylalanine and tyrosine would be equal between groups, and thus could be excluded, is inappropriate, given that patients who have died, as well as patients who have undergone LT, no longer require dietary restriction. The exclusion of these costs biases the total cost of therapy in favour of nitisinone.

## CADTH Common Drug Review Reanalyses

Inflexibility within the manufacturer's model limited the ability of the CADTH Common Drug Review (CDR) to conduct reanalyses. Of the limitations described earlier, CDR was able to conduct reanalyses:

- incorporating utility values from patients with chronic hepatitis C rather than chronic hepatitis B
- incorporating the cost of nutritional supplements related to dietary restriction of tyrosine and phenylalanine for all patients who have neither died nor undergone LT. CDR assumed that patients would consume an average of one supplement daily at the Régie de l'assurance maladie du Québec (RAMQ) listed cost of $91.86 per case of six, or $5,588 per patient per year.

### Table 3: CDR Reanalyses Exploring Limitations of the Manufacturer's Model

| | Description | Manufacturer's Base-Case Value | CDR Value | Incremental Cost ($) | Incremental QALYs | ICUR ($) |
|---|---|---|---|---|---|---|
| | **Manufacturer's base case** | Reference | | 897,212 | 6.461 | 138,871 |
| 1 | **Utilities from CHC population[12] rather than CHB[11]** | HT-1: 0.920; HCC/cirrhosis: 0.770; post–liver transplant: 0.840 | HT-1: 0.860; HCC/cirrhosis: 0.670; post–liver transplant: 0.750 | 896,823 | 6.468 | 138,658 |
| 2 | **Dietary supplementation included** | Cost of diet supplementation not included | Patients in HT-1 and HCC states assumed to consume an average of one supplement daily | 963,356 | 6.472 | 148,855 |
| **1+2** | **CDR reference case** | | | 955,483 | 6.404 | 149,197 |

CDR = CADTH Common Drug Review; CHB = chronic hepatitis B; CHC = chronic hepatitis C; HCC = hepatocellular carcinoma; HT-1 = hereditary tyrosinemia type 1; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

CDR noted that the manufacturer's model differs from the model submitted by the manufacturer of Orfadin, another nitisinone product. CDEC recommended that the price of Orfadin be reduced by at least 74%.[3] While the current submission has some strengths when compared with the Orfadin model (e.g., health states defined by health status rather than treatment assignment; inclusion of HCC as an event of interest),[5] it does not model the entirety of a patient's lifetime which, in a chronic condition like HT-1 involving lifelong treatment, is the relevant time horizon. As the ICUR associated with adding Nitisinone Tablets to dietary restriction increases as the time horizon does ($4,303 per QALY based on a five-year time horizon and $66,410 per QALY based on a 10-year time horizon, compared with $149,197 per QALY over 20 years), it is likely that Nitisinone Tablets would be less cost-effective over a lifetime time horizon than has been reported over the 20-year time horizon.

## Table 4: Submitted Prices of Nitisinone Products Compared With Price Reduction Previously Recommended by CDEC

| Nitisinone Brand | Submitted Price ($) | Savings (%) With Nitisinone Tablets | Approximate Prices ($) Implied by CDEC's Recommended Price Reduction for Orfadin[a] | Price Reduction (%) Required to Meet CDEC's Recommendation |
|---|---|---|---|---|
| Nitisinone Tablets | 2 mg: 12.9500<br>5 mg: 25.0600<br>10 mg 47.4000<br>20 mg: 94.8000[b] | Reference | 2 mg: 5.85<br>5 mg 13.86<br>10 mg: 26.00<br>20 mg: 50.27 | 2 mg: 55%<br>5 mg: 45%<br>10 mg: 45%<br>20 mg: 47%[b] |
| Nitisinone capsules (Orfadin)[a] | 2 mg: 22.5000<br>5 mg:53.3000<br>10 mg: 100.0000<br>20 mg:193.3300 | 2 mg: 42%<br>5 mg: 53%<br>10 mg: 53%<br>20 mg: 51%[b] | | 2 mg: 74%<br>5 mg: 74%<br>10 mg: 74%<br>20 mg: 74% |
| Nitisinone capsules (MDK-Nitisinone) | 2 mg: 14.7833<br>5 mg: 34.1833<br>10 mg: 64.7000<br>20 mg: 128.1000 | 2 mg: 12%<br>5 mg: 27%<br>10 mg: 27%<br>20 mg: 26%[b] | | 2 mg: 60%<br>5 mg: 60%<br>10 mg: 60%<br>20 mg: 60% |

CDEC = CADTH Canadian Drug Expert Committee.

[a] CDEC recommended a price reduction of at least 74% as a condition of the reimbursement recommendation for Orfadin nitisinone capsules.[3] This analysis assumes all unit strengths of Orfadin are reduced equally to achieve that recommendation.

[b] Nitisinone Tablets is not available in a 20 mg strength and, thus, two 10 mg tablets are assumed.

Sources: Manufacturer's Submission,[2] Orfadin recommendation,[3] MDK-Nitisinone recommendation.[4]

## Issues for Consideration

**Tablets do not require refrigeration**: Unlike the two available nitisinone capsule products,[13,14] Nitisinone Tablets does not require refrigeration,[1] which may be of greater convenience in terms of storage for patients, caregivers, and health care providers, as well as of benefit to patients who must have their medication shipped to remote communities.

**Screening practices may vary**: The availability and access to screening programs and the accuracy of screening across Canada may differ. Therefore, jurisdictions will have to determine the likelihood that they will be able to identify patients early.

**Use of Quebec data**: While Quebec has the highest number of HT-1 patients in Canada, and thus the most robust available data on the costs and consequences associated with the condition, this very difference increases uncertainty in the transferability of cost-effectiveness results from Quebec to CDR-participating plans. Due to the number of patients presenting with HT-1 in Quebec, systems and resources are available there that may not be present or easily accessible in other jurisdictions, or which may be associated with different costs due to the infrequency of their use.

**Additional strengths and formulations available for competitors**: Both of the other nitisinone products available have a larger unit size (20 mg), which Nitisinone Tablets does not have. Additionally, a 4 mg/mL oral suspension of Orfadin has been approved by Health Canada, however, it has not been reviewed by CDR.[3,13]

## Patient Input

Patient input was received from the Canadian Liver Foundation (CLF). The input was based on the answers to a bilingual online questionnaire offered to patients, caregivers, and health care professionals in September 2017 to collect input on experience with the two nitisinone products previously reviewed, Orfadin[3] and MDK-Nitisinone capsules.[4] Forty-eight people responded, including six patients with HT-1, 36 caregivers, and four health care professionals. None reported experience with Nitisinone Tablets and, thus, CLF had no additional input regarding the drug, considering it medically equivalent to Orfadin. However, CLF noted that the tablets may be of benefit to some patients and their caregivers compared with capsules, as they can be stored at room temperature and the smaller size may be easier to swallow. See CDR Clinical Report, Appendix 1.

## Conclusions

In patients with HT-1 that is identified and treated at birth, CDR's reanalysis reported an ICUR of $149,197 per QALY for Nitisinone Tablets plus dietary restriction compared with dietary restriction alone over a 20-year time horizon. The manufacturer used the same clinical data to inform the model as previously considered in the Orfadin and MDK-Nitisinone reviews, however, the use of direct data, rather than modelled transition probabilities based on study data, limits the flexibility of the model in exploring alternate assumptions around outcomes and artificially reduces uncertainty in the probabilistic analyses. Additionally, while the current model has some strengths in comparison with the one submitted for Orfadin,[5] the estimated ICUR is likely underestimated due to the time horizon being limited to 20 years rather than lifetime.

The submitted price of Nitisinone Tablets is $12.95, $25.06, and $47.40 per 2 mg, 5 mg, and 10 mg tablets, which is 42% to 53% less expensive than Orfadin, and 12% to 27% less expensive than MDK-Nitisinone, depending on unit strength. However, CDEC recommended that the price of Orfadin be reduced by 74% in their February 2018 recommendation. To achieve the price of Orfadin suggested by CDEC, the price of Nitisinone Tablets would need to be reduced by 45% to 55% to be equivalent to the suggested price of the other nitisinone products.

# Appendix 1: Cost Comparison

The comparators presented in Table 5 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

## Table 5: CDR Cost Comparison Table for the Treatment of Hereditary Tyrosinemia Type 1

| Drug/ Comparator | Strength | Dosage Form | Price ($) | Recommended Dose | Average Daily Drug Cost ($) | Average Annual Drug Cost ($) |
|---|---|---|---|---|---|---|
| **Nitisinone Tablets** | **2 mg<br>5 mg<br>10 mg** | **Tablet** | **12.9500[a]<br>25.0600[a]<br>47.4000[a]** | **1 mg/kg per day in two divided doses; may be increased to a maximum of 2 mg/kg per day** | **20 kg patient: 94.80<br>50 kg patient: 239.72<br>75 kg patient: 356.86** | **20 kg patient: 34,626<br>50 kg patient: 87,558<br>75 kg patient: 130,343** |
| Nitisinone (MDK-Nitisinone) | 2 mg<br>5 mg<br>10 mg<br>20 mg[c] | Capsule | 14.7833[b]<br>34.1833[b]<br>64.7000[b]<br>128.1000[b] | | 20 kg patient: 129.40[c]<br>50 kg patient: 327.17[c]<br>75 kg patient: 487.08[c] | 20 kg patient: 47,263[c]<br>50 kg patient: 119,498[c]<br>75 kg patient: 177,907[c] |
| Nitisinone (Orfadin)[d] | 2 mg<br>5 mg<br>10 mg<br>20 mg | Capsule | 22.5000[e]<br>53.3000[e]<br>100.0000[e]<br>193.3300[e] | | 20 kg patient: 193.33[f]<br>50 kg patient: 493.26<br>75 kg patient: 733.33 | 20 kg patient: 70,614[f]<br>50 kg patient: 180,163<br>75 kg patient: 267,850 |

CDEC = CADTH Canadian Drug Expert Committee; CDR = CADTH Common Drug Review.

[a] Manufacturer's submitted price.

[b] CDEC recommendation for MDK-Nitisinone.[4]

[c] A 20 mg capsule of MDK-Nitisinone has been approved by Health Canada, however, it is not yet marketed in Canada;[15] the 20 mg tablet price was thus not considered in daily and annual drug costs.

[d] A 4 mg/mL oral suspension of Orfadin-brand nitisinone has been approved by Health Canada; however, it is not yet marketed in Canada nor has it been reviewed by CDR.[16]

[e] CDEC recommendation for Orfadin.[3]

[f] The assumption was made that children weighing 20 kg likely still receive treatment as an oral liquid or mixed with food and, therefore, despite the product monograph recommending the dose be divided equally, the splitting of a 20 mg capsule is likely the appropriate comparator.[13]

# Appendix 2: Summary of Key Outcomes

## Table 6: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Nitisinone Plus Dietary Restriction Relative to Dietary Restriction Alone?

| Nitisinone plus Diet Versus Diet Alone | Attractive | Slightly Attractive | Equally Attractive | Slightly Unattractive | Unattractive | N/A |
|---|---|---|---|---|---|---|
| **Costs (total)** | | | | | X | |
| **Drug treatment costs alone** | | | | | X | |
| **Clinical outcomes** | X | | | | | |
| **Quality of life** | X | | | | | |
| **CDR reanalysis** | $149,197 per QALY | | | | | |

CDR = CADTH Common Drug Review; N/A = not applicable.

# Appendix 3: Additional Information

## Table 7: Submission Quality

| | Yes/ Good | Somewhat/ Average | No/ Poor |
|---|---|---|---|
| Are the methods and analysis clear and transparent? | X | | |
| Comments | None | | |
| Was the material included (content) sufficient? | X | | |
| Comments | None | | |
| Was the submission well organized and was information easy to locate? | X | | |
| Comments | None | | |

## Table 8: Authors' Information

| Authors of the Pharmacoeconomic Evaluation Submitted to CDR | | | |
|---|---|---|---|
| ☐ Adaptation of global model / Canadian model done by the manufacturer | | | |
| ☐ Adaptation of global model / Canadian model done by a private consultant contracted by the manufacturer | | | |
| ☐ Adaptation of global model / Canadian model done by an academic consultant contracted by the manufacturer | | | |
| ☒ Other (please specify): De novo model developed by a private consultant contracted by the manufacturer | | | |
| | Yes | No | Uncertain |
| Authors signed a letter indicating agreement with entire document | | | X |
| Authors had independent control over the methods and right to publish analysis | | | X |

CDR = CADTH Common Drug Review.

# Appendix 4: Summary of Other HTA Reviews of Drug

Nitisinone Tablets has been reviewed by Quebec's Institut national d'excellence en santé et en services sociaux (INESSS) (Table 9). INESSS also reviewed Orfadin (nitisinone capsules) in 2017, recommending that it be reimbursed for the treatment of HT-1 in combination with dietary restriction of tyrosine and phenylalanine, with the condition that the economic burden be mitigated.[17] Additionally, in 2015, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia rejected a request to list Orfadin on the basis of an uncertain and unacceptably high estimate of cost-effectiveness.[18]

## Table 9: Other HTA Findings

| | INESSS (June 2017)[19] |
|---|---|
| **Treatment** | Nitisinone Tablets, 2 mg, 5 mg, and 10 mg |
| **Price** | Redacted |
| **Similarities with CDR submission** | • Efficacy and safety data from Larochelle<br>• Health state utilities based on various sources, including Woo et al.<br>• Health state definitions appear similar, although details are unclear |
| **Differences with CDR submission** | Time horizon was 10 years rather than 20 years |
| **Manufacturer's results** | Redacted |
| **Issues noted by the review group** | • Ten-year time horizon does not adequately reflect long-term use of product; INESSS preferred a lifetime but accepted a 20-year analysis, given uncertainty<br>• The use of health state utilities from a hepatitis B population is a limitation of the analysis<br>• Dosage use varies by age of patient; INESSS considered a daily dose of 1.75 mg/kg for patients aged ≤ 5 years, 1.25 mg/kg for ages 6 to 12 years, and 0.75 mg/kg for ages 13 and older |
| **Results of reanalyses by the review group (if any)** | INESSS reanalyses, with a 20-year time horizon and doses as shown in the first row of this table, resulted in an ICUR of less than $225,772 per QALY. Altering the assumed dosing resulted in ICURs of between $165,482 and $285,032 per QALY. A reanalysis with redacted methodology estimates the ICUR at $88,764. |
| **Recommendation** | That Nitisinone Tablets be reimbursed for the treatment of HT-1 in combination with dietary restriction of tyrosine and phenylalanine, under the condition that the price be reduced to an acceptable level of cost-effectiveness. Specifics around price reductions were redacted. |

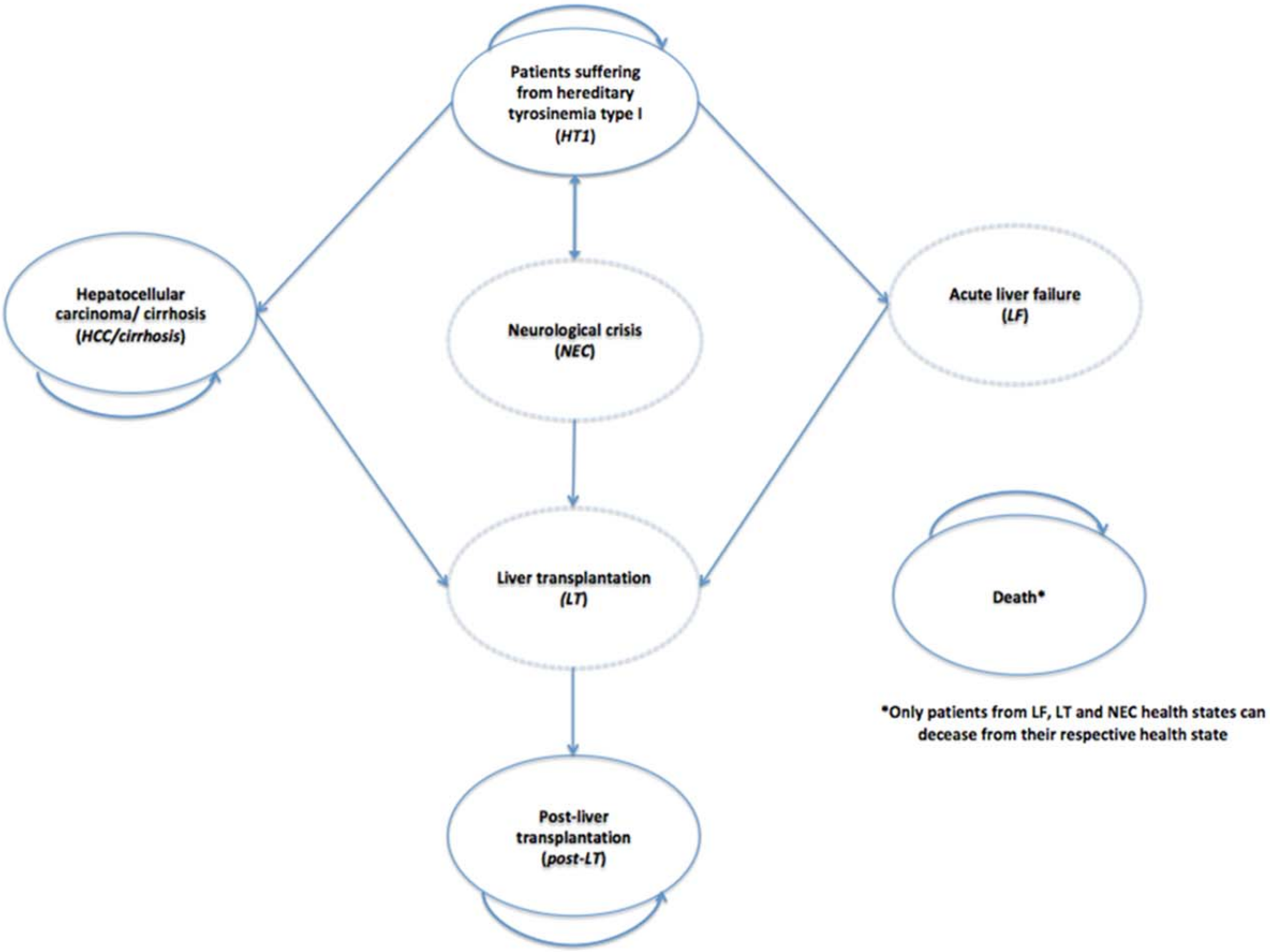
CDR = CADTH Common Drug Review; INESSS = Institut national d'excellence en santé et en services sociaux; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

# Appendix 5: Reviewer Worksheets

## Manufacturer's Model Structure

The manufacturer undertook a Markov state–transition model comparing nitisinone plus dietary restriction with dietary restriction alone in newborn patients with hepatorenal tyrosinemia type 1 (HT-1) as described earlier. Health states and the possible transitions between them are illustrated in Figure 1.

### Figure 1: Manufacturer's Model Structure




Source: Manufacturer's pharmacoeconomic submission.[2]

Utility weights for each cycle-length health state and disutilities for transient states are detailed in Table 10.

## Table 10: Health State Utility Weights and Disutilities in Manufacturer's Model

| Health State | EQ-5D Utility Value Mean (95% CI) | Source |
|---|---|---|
| **HT-1** | 0.92 (0.91 to 0.94) | Woo et al.[20] |
| **HCC/cirrhosis** | 0.81 (0.67 to 0.94) | |
| **Post-LT** | 0.84 (0.77 to 0.91) | |
| **Death** | 0 | Definition |
| **Disutility Applied Per Transient Health State Event** | | |
| **Neurological crisis** | 0.018 | Tarride et al.[21] |
| **Liver failure** | 0.033 | Kantola et al.[22] |

CI = confidence interval; EQ-5D = EuroQol 5-Dimensions questionnaire; HCC = hepatocellular carcinoma; HT-1 = hepatorenal tyrosinemia type 1; LT = liver transplantation.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

## Table 11: Data Sources

| Data Input | Description of Data Source | Comment[a] |
|---|---|---|
| **Efficacy** | From early-treated cohort in Larochelle et al. (2012).[6] | Newborns who are not identified and treated within 30 days will have more adverse outcomes than those who receive early treatment as per the model. In the Quebec study, six patients born after nitisinone became available (one received a single week of nitisinone therapy and was considered untreated, five were late-treated) were not identified due to screening failure or because they were born outside Quebec. Due to lower HT-1 prevalence rates in other Canadian jurisdictions, patients outside Quebec may be less likely to be screened at birth. |
| **Natural history** | From the dietary-restriction alone cohort in Larochelle et al. (2012).[6] | Transitions through the model are based exactly on the number and timing of events observed in the diet-alone cohort, including the risk of death due to liver transplant. |
| **Utilities** | From Woo et al. (2012).[11] | EQ-5D results were used in the base case, with HUI3 values considered in a sensitivity analysis. The clinical expert consulted by CADTH suggested utility values for infection with CHC virus would be a more appropriate proxy for patients with HT-1, reflecting a more insidious progression and elevated risk of HCC. |
| **Resource use** | HT-1 monitoring tests as in Larochelle.[6]<br><br>Immunosuppression post-LT from Moini et al. (2015).[8] | Appropriate. |
| **AEs** | Not included. | AEs identified in Larochelle[6] included ocular crystals (resolved with diet restriction), asymptomatic fasting ketotic hypoglycemia, and asymptomatic elevations of ALT level over 60 IU/L after three or more months of treatment. Patients experiencing these AEs would require further monitoring, which would accrue costs, and may require supportive care or dose adjustment. |
| **Mortality** | From Larochelle.[6] | Patients could only die while in LF, LT, and NEC health states. All-cause mortality was not incorporated. |
| **Costs** | | |
| **Drug** | Nitisinone dosed at 1 mg/kg/day in the main analysis and based on | The pricing of Nitisinone Tablets is not flat or linear. Cost and treatment paradigms for immunosuppressive therapy may vary between |

| Data Input | Description of Data Source | Comment[a] |
|---|---|---|
| | average weights for each year from WHO growth charts.<br><br>Costs of Nitisinone Tablets were provided by the manufacturer. Cost of immunosuppressive therapy post-LT from the ODB formulary.<br><br>Diet supplementation not included. | jurisdictions. Cost of supplementation likely to differ between treatment arms. |
| **Administration** | Costs of monitoring HT-1 progression and nitisinone plasmatic levels from Ontario Schedule of Benefits for Laboratory Services[23] and Schedule of Benefits for Physicians Services.[24] | Appropriate. |
| **Event/health state** | LF, LT, and NEC from the Ontario Case Costing Initiative[25] and the Schedule of Benefits for Physician Services.[24]<br><br>HCC/cirrhosis costs from a Canadian cost study on CHB.[7] | Appropriate, although the costs associated with liver transplantation are substantially lower than those reported in a British Columbia–based study.[26] |
| **AEs** | Not included. | May be inappropriate, see earlier row. |

AE = adverse event; ALT = alanine transaminase; CHB = chronic hepatitis B; CHC = chronic hepatitis C; EQ-5D = EuroQol 5-Dimensions questionnaire; LF = liver failure; LT = liver transplantation; HCC = hepatocellular carcinoma; HT-1 = hepatorenal tyrosinemia type 1; HUI3 = Health Utilities Index Mark 3; NEC = neurological crises; ODB = Ontario Drug Benefit; WHO = World Health Organization.

## Table 12: Manufacturer's Key Assumptions

| Assumption | Comment |
|---|---|
| Nitisinone Tablets is clinically equivalent to nitisinone capsules reported in the literature. | Appropriate; Nitisinone Tablets met all bioequivalence requirements to be declared equivalent to the reference product, Orfadin, based on Health Canada guidelines.[27] See CDR Clinical Report, Appendix 5. |
| All nitisinone patients treated immediately upon birth. | May not be appropriate. While near-universal screening for HT-1 is used in Quebec, it is uncertain whether newborns in all other Canadian jurisdictions have access to HT-1 screening programs at birth. Additionally, some patients may immigrate to Canada having not been screened at birth. Six patients eventually treated in Larochelle were not detected by screening due to birth outside of Quebec or screening failure.[6] |
| Nitisinone patients never receive liver transplants. | This assumes all patients are identified and initiate treatment at birth. Of the six patients in Larochelle not detected by newborn screening, four needed liver transplants.[6] This biases the results in favour of nitisinone. |
| Effectiveness and transitions are based on a single study from Quebec. | Concerns regarding the generalizability of the Larochelle[6] cohort were raised by the clinical expert consulted by CDR, who suggested patients may be harder to identify due to lower HT-1 prevalence outside Quebec and lack of screening programs in some jurisdictions. Additionally, in replicating the exact outcomes of patients in the Larochelle study rather than modelling transition probability rates, the manufacturer's model lacks flexibility in exploring alternate efficacy assumptions, such as small risks of progression to HCC or LF, even with nitisinone treatment. This methodology also lacks a distribution for transition probabilities, reducing variation within the probabilistic model. |
| Cost of dietary supplementation assumed equal and not included. | Inappropriate. The overall cost of diet supplementation is likely to be greater in the nitisinone arm, given that patients receiving nitisinone remain in the HT-1 state for the duration of the model, thereby continuing to use diet supplementation. Patients in the diet-alone group |

| Assumption | Comment |
|---|---|
| | either die or undergo liver transplantation and are considered cured, eliminating or reducing the cost of restricting their diet. This may bias the ICUR slightly in favour of nitisinone, although this is unlikely to be significant, given the magnitude of the cost of nitisinone therapy relative to the cost of dietary restriction supplements. |
| All-cause mortality excluded. | This may slightly bias results in favour of nitisinone, however, patients are more likely to die of HT-1–related causes than unrelated causes within the 20-year time horizon and, thus, it is unlikely to significantly impact results. Patients who survive the initial liver transplant health state are also assumed to experience no subsequent mortality; this likely biases results in favour of dietary restriction alone. The exclusion of all-cause mortality precludes the ability to extend the time horizon to the lifetime of the patient. |
| No disutility or duration for liver transplant. | Organ transplant is a major surgical procedure. It is likely that patients undergoing transplantation would experience a reduced quality of life while recovering; thus, the exclusion of this factor may slightly bias the ICUR in favour of dietary supplementation alone. However, given the short-term nature of the issue and the already low health state of patients requiring transplantation, it is unlikely to make a significant difference. |
| Neurological seizures assumed to have a 28-day duration for the purposes of disutility. | The manufacturer cites Larochelle as the source of their assumption that the NEC health state lasts 4 weeks; Larochelle does not appear to report this. However, the model allowed the parameter to be changed to 1-, 2-, or 3-week durations for the disutility, which had little impact on the ICUR. The cost of hospitalization associated with NEC was taken from the Ontario Case Costing Analysis Tool for 2015-2016, code E802. |

CDR = CADTH Common Drug Review; LF = liver failure; HCC = hepatocellular carcinoma; HT-1 = hepatorenal tyrosinemia type 1; ICUR = incremental cost-utility ratio; NEC = neurological crises.

## Manufacturer's Results

The manufacturer's base-case analysis was presented as both deterministic and probabilistic results from a health care payer perspective (Table 13). The probabilistic analysis of the addition of nitisinone to diet restriction alone produced an additional 6.47 quality-adjusted life-years (QALYs) for an additional cost of $896,823 per person, resulting in an incremental cost-utility ratio (ICUR) of $138,658 per QALY (reporting corrected to probabilistic means rather than medians).

Treatment costs were not reported as components for the probabilistic analysis; however, the deterministic analysis reported a breakdown of discounted costs for drug acquisition, monitoring, liver failure, neurologic crises, hepatocellular carcinoma or cirrhosis (HCC/cirrhosis), and liver transplantation and immunosuppressive treatments for each treatment group, as outlined in Table 13.

## Table 13: Manufacturer's Base-Case Results, Including Cost Breakdowns

| Item | Nitisinone | Diet Restriction Alone | Incremental |
|---|---|---|---|
| **Deterministic Analysis** | | | |
| Drug cost ($) | 1,033,373 | 0 | 1,033,373 |
| Monitoring ($) | 15,899 | 1,647 | 14,253 |
| Liver failure ($) | 0 | 2,306 | −2,306 |
| Neurologic crisis ($) | 0 | 36,447 | −36,447 |
| HCC/cirrhosis ($) | 0 | 6,613 | −6,613 |
| Liver transplantation and immunosuppressive treatments ($) | 0 | 105,369 | −105,369 |
| **Total costs ($)** | 1,049,273 | 152,382 | **896,891** |
| Total QALYs | 16.032 | 9.565 | **6.47** |
| **Deterministic ICUR** | | | **$138,689/QALY** |
| **Probabilistic Analysis** | | | |
| Total costs ($) | **1,049,273** | **152,381** | **896,891** |
| Total QALYs | **16.035** | **9.567** | **6.47** |
| **Probabilistic ICUR** | | | **$138,658/QALY** |

HCC = hepatocellular carcinoma; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Manufacturer-reported ICUR based on median probabilistic costs and QALYs: incremental cost of $897,212 and incremental QALYs of 6.46 for an ICUR of $138,871.

Source: Adapted from manufacturer's model.[2] All results include a 1.5% discount on costs and QALYs beyond the first year.

The manufacturer also conducted deterministic sensitivity analyses, varying: weights of children based on the 25$^{th}$ and 75$^{th}$ percentiles of the World Health Organization (WHO) growth charts, the proportion of male children, utilities for health states, disutilities for transient health states, costs of transient health state events, and costs of monitoring and maintenance in health states. Altering the assumed mean body weight of the cohort, as well as the utility associated with the post–liver transplantation state, had the biggest effect on the ICUR.

Additionally, the manufacturer's model was capable of alternate scenarios that were not reported, such as rounding doses to the superior tablet strength rather than the inferior, and changing the daily dose from 1 mg/kg to 0.6 mg/kg or 2 mg/kg daily.

The manufacturer also presented an analysis using a societal perspective, incorporating productivity loss of parents due to hospitalizations as well as due to parental grief at the loss of a child. These results were similar to those of the health care payer perspective, producing an additional 6.47 QALYs at an additional cost of $886,468, resulting in an ICUR of $137,057 per QALY.

## CADTH Common Drug Review Reanalyses

Given the chronic nature of HT-1, the CADTH Common Drug Review (CDR) considered that a lifetime time horizon would be more appropriate for capturing all clinical outcomes and costs associated with nitisinone therapy. However, as nitisinone was only introduced in 1992, there is uncertainty in the actual length and quality of life that HT-1 patients will experience on nitisinone therapy. Additionally, the manufacturer did not incorporate all-

cause mortality into its model, precluding the ability to extend the analysis to the lifetime of a patient.

CDR was unable to conduct reanalyses exploring the possibility of patients treated with nitisinone eventually suffering HCC or liver failure, due to the inflexibility of health state transitions as modelled.

CDR noted that the manufacturer's model is distinctly different from the model submitted by the manufacturer of Orfadin, another nitisinone product. The CADTH Canadian Drug Expert Committee (CDEC) recommended that the price of Orfadin be reduced by at least 74%.[3] While the current submission has some strengths when compared with the Orfadin model (e.g., health states defined by health status rather than by treatment assignment, inclusion of HCC as an event of interest), it does not model the entirety of a patient's lifetime which, in a chronic condition like HT-1 involving continuous treatment started soon after birth, is the relevant time horizon. As the ICUR associated with adding Nitisinone Tablets to dietary restriction increases as the time horizon does ($4,303 per QALY for CDR's reanalysis over a five-year time horizon and $66,410 per QALY over a 10-year time horizon, compared with $149,197 per QALY over 20 years), it is likely that Nitisinone Tablets would appear less cost-effective over a lifetime time horizon.

At the submitted price, Nitisinone Tablets are less expensive than those submitted for the other two nitisinone products; however, its cost would still need to be reduced by 45 to 55% to be equivalent to the 74% price reduction recommended by CDEC for the reimbursement of Orfadin (Table 4).

### CDR Scenario Analyses

While not reported in the manufacturer's sensitivity analyses, the model was capable of rounding nitisinone dosing up to the nearest 1 mg (as opposed to down as used in the base case), as well as reporting results using doses of 0.6 mg/kg/day and 2 mg/kg/day as opposed to 1 mg/kg/day. Additionally, CDR tested the assumption used by INESSS in their assessment of Nitisinone Tablets,[19] namely, that nitisinone dosing would vary by age. The effects of these scenarios on the ICUR are reported in Table 14.

## Table 14: CDR Reanalyses Exploring Alternate Scenarios

| Description | Incremental Cost ($) | Incremental QALYs | ICUR ($) |
|---|---|---|---|
| CDR reference case | 955,483 | 6.404 | 149,197 |
| Daily nitisinone dose rounded to superior unit rather than inferior | 1,046,263 | 6.399 | 163,493 |
| 0.6 mg/kg nitisinone per day | 584,058 | 6.401 | 91,240 |
| 2.0 mg/kg nitisinone per day | 1,984,776 | 6.407 | 309,803 |
| Dosing as per INESSS:[19]<br>1.75 mg/kg/day age 0–5<br>1.25 mg/kg/day age 6–12<br>0.75 mg/kg/day age 13+ | 998,178 | 6.402 | 155,906 |

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; INESSS = Institut national d'excellence en santé et en services sociaux; QALY = quality-adjusted life-year.

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