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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Nitisinone (Orfadin)

(Sobi Canada Inc.)

Indication: For the treatment of patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine

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

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Abbreviations

BSC	best supportive care
CDR	CADTH Common Drug Review
CHB	chronic hepatitis B
CHC	chronic hepatitis C
EQ-5D	EuroQol 5-Dimensions questionnaire
HCC	hepatocellular carcinoma
HT-1	hereditary tyrosinemia type 1
HUI3	Health Utility Index Mark 3
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-year

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Nitisinone (Orfadin) capsules; 2 mg, 5 mg, 10 mg, 20 mg
Study Question	What are the costs and health benefits of the use of nitisinone plus best supportive care (BSC) for the treatment of hereditary tyrosinemia type 1 (HT-1) in newborns who are identified and treated within one month of birth, either through a newborn screening program, or through physical examination, patient history, and specialized tests, including urine SA levels, from a health ministry perspective, compared with BSC?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Newborns identified with HT-1 at birth through screening and initiated treatment within 1 month of diagnosis
Treatment	Nitisinone 1 mg/kg body weight/day divided in 2 doses in combination with dietary restriction of tyrosine and phenylalanine via nutritional supplements (defined as BSC)
Outcome	Quality-adjusted life-years (QALYs)
Comparator	Dietary restriction of tyrosine and phenylalanine via nutritional supplements
Perspective	Canadian public health payer
Time Horizon	Lifetime (100 years)
Results for Base Case	ICUR = $322,850 per QALY (deterministic)
Key Limitations	• The manufacturer assumed all newborns will be identified and treated early (within 30 days), and that no treated patients would require liver transplant or die prematurely from disease. This assumption is questionable, given screening programs may not be present or may not identify 100% of infants. There are also documented cases of hepatocellular carcinoma in individuals receiving nitisinone. • The clinical data included in the model are from a relatively short-term study that may not capture long-term events in patients with HT-1. The results are contingent on continued benefit from treatment over an average lifetime of ~80 years. • The utility values used for patients receiving treatment with nitisinone are questionable as they are based on a survey of male adult patients with decompensated cirrhosis due to chronic hepatitis B infection. Appropriate justification for use of this input was not provided. The results of the model were highly sensitive to this input parameter. • The cost of diet was not included in the nitisinone group, and how it was considered in the BSC was not appropriately described or justified. • The results are sensitive to the dose of nitisinone. However, this was not appropriately considered probabilistically. CADTH was unable to test alternative dosing in the probabilistic analysis due to the model structure. • The manufacturer did not consider the potential for hepatocellular carcinoma and other relevant complications in patients with HT-1. This resulted in suboptimal methods being used to distinguish treatment effects within the model (e.g., different utility values within the same health state for treated and untreated patients).
CDR Estimate(s)	• CADTH's base case considered revised utility values, the inclusion of diet costs to both treatment arms, and the consideration of liver transplant for nitisinone patients. This resulted in an ICUR of $377,025 per QALY.

	• CADTH undertook scenario analyses considering alternate doses of nitisinone: at a dose of 0.8 mg/kg the ICUR was $303,706 per QALY; at a dose of 1.2 mg/kg, the ICUR was $453,064 per QALY. • These results apply only to patients treated within one month of birth. The ICUR is unknown in patients starting treatment at an older age. • The duration of treatment and clinical benefits (based on the estimated life expectancy of patients) of patients receiving nitisinone is uncertain due to the lack of long-term data in patients treated within one month of birth.

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; HT-1 = hereditary tyrosinemia type 1; QALY = quality-adjusted life-year; SA = succinylacetone.

Drug	Nitisinone (Orfadin)
Indication	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(s)	2 mg, 5 mg, 10 mg, and 20 mg capsules
NOC Date	December 13, 2016
Manufacturer	Sobi Canada Inc.

Executive Summary

Background

Nitisinone (Orfadin) is indicated for the treatment of patients with hereditary tyrosinemia type 1 (HT- 1) in combination with dietary restriction of tyrosine and phenylalanine.[1] Nitisinone is available as 2 mg, 5 mg, 10 mg, and 20 mg capsules for oral administration. The submitted price of nitisinone is based on dose: 2 mg ($22.50), 5 mg ($53.30), 10 mg ($100), and 20 mg ($193.33).[2] The recommended initial dosage in pediatric and adult populations is 1 mg/kg body weight daily divided in two doses administered orally.[1] If plasma or urine succinylacetone is still detectable one month after starting treatment, the dosage should be increased to 1.5 mg/kg daily to a maximum dosage of 2 mg/kg daily.[1] If the biochemical response is satisfactory, dosage should be adjusted only according to body weight gain.

Although nitisinone can be used in both pediatric and adult populations, the manufacturer's economic evaluation is based on a subset of the labelled indication: the treatment of newborns who are identified and treated within one month of birth, either through a newborn screening program or through physical examination, patient history, and specialized tests (including urine succinylacetone levels). The submitted cost-utility analysis compares costs and health benefits associated with nitisinone 1 mg/kg plus best supportive care (BSC; dietary restriction) versus BSC (dietary restriction) alone in the treatment of newborns at least one month old, from a health ministry perspective. The model is based on three health states: diagnosed with HT-1; liver transplant with associated tunnel states; and dead. The time horizon was a patient's lifetime (100 years), and future costs and benefits were discounted at 1.5% annually. Comparative treatment effect was based on assumptions regarding premature mortality taken from a study of a Quebec-based cohort (Larochelle et al.) of newborns followed for up to 14 years.[3] Utility values were derived from a cohort of men (average age 54 years) with decompensated cirrhosis resulting from chronic hepatitis B infection and measured with the Health Utility Index Mark 3 (HUI3) instrument.[4] Assumptions regarding resource use and costs were derived from a Quebec-based study of HT-1 patients as well as a British Columbia-based study of liver transplantation costs.[5,6]

In their deterministic base case, the manufacturer estimated that the addition of nitisinone to BSC (dietary restriction) versus BSC (dietary restriction) alone would produce an additional 33.21 quality-adjusted life-years (QALYs) for an additional $10,724,537 per person treated,

resulting in an incremental cost of $322,927 per QALY gained (probabilistic analysis, $320,985 per QALY).

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review identified several key limitations with the model submitted by the manufacturer.

First, the manufacturer's model structure may not appropriately represent the condition, as it does not consider the potential for hepatocellular carcinoma (HCC) and other relevant complications experienced by patients with HT-1. This was associated with suboptimal methods being used to distinguish treatment effect within the model. Specifically, in the health state "diagnosed with HT-1" the manufacturer used different utility values within the same health state for treated and untreated patients. This all-or-nothing approach does not characterize the natural history of disease or allow robust testing of differences between treatments, such as the effect of drug failure in nitisinone recipients or a cure in BSC recipients who have been transplanted. As such, it does not represent best practices in modelling.

Second, the population considered consists of patients identified and treated within a month of being born. This does not align with the Health Canada indication or listing request. Assessing this specific subpopulation does not allow for an estimate of the relative costs and health impact of patients who are identified later in life (i.e., in the absence of newborn screening programs) or who cannot initiate treatment within a month for other reasons. As such, the cost-effectiveness of initiating patients on nitisinone who are older than one month is not known.

Furthermore, the manufacturer's choice of inputs was associated with notable uncertainty. The utility values used for patients in the HT-1 health state and liver transplant were based on a survey of male adult chronic hepatitis B (CHB) patients with non-cirrhotic CHB, decompensated cirrhosis due to CHB, and post-transplant values from this patient population.[4] The choice of the instrument used to value these health states (HUI3 versus EuroQol 5 Dimensions [EQ-5D]), and the generalizability of the specific values chosen to the infantile HT-1 patient population is highly uncertain.

There is also limited information on the long-term effects of, and persistence/adherence to, treatment; the model assumes all nitisinone-treated patients continue to receive a 1 mg/kg dose, and have a normal life expectancy (~80 years). However, long-term data to support these assertions are lacking. Additionally, there is considerable uncertainty regarding the rate of liver transplantation in nitisinone recipients as well as differences in outcomes between those receiving nitisinone and those receiving BSC.

CADTH noted that the cost of diet was not included in the nitisinone group, and how it was considered in the BSC was not appropriately described or justified. However, this parameter had only a small impact on the overall results.

Last, the model was inflexible and did not allow for CADTH to undertake relevant reanalyses. For example, sensitivity and scenario analyses to examine the effect of liver transplant in nitisinone recipients and the impact of different dosing regimens required changes to the original model. Relevant outpatient costs were not considered by the manufacturer and sensitivity of the results to changes in resource use or alternate liver transplant outcomes based on treatment also could not be tested.

CADTH undertook reanalyses that: included 100% of the diet costs for both treatment arms (BSC [dietary restrictions] and nitisinone plus BSC [dietary restrictions]) throughout the time horizon; considered utilities from chronic hepatitis C virus infection (which were assumed to be more generalizable to patients with HT-1); and assumed that a small proportion of nitisinone-treated patients (0.16% per year) will develop HCC and require liver transplantation. This resulted in an incremental cost-utility ratio (ICUR) of $377,025 per QALY for nitisinone plus BSC (dietary restrictions) compared with BSC (dietary restrictions) alone (probabilistic analysis). CADTH was unable to test several limitations within the CADTH base-case probabilistic analysis, such as nitisinone dose variation, alternate liver transplant assumptions, and additional resource costs. CADTH undertook scenario analyses testing the implication of different nitisinone doses. The model results were sensitive to nitisinone dose.

Conclusions

In patients with HT-1 identified and treated within 30 days of birth, CADTH reported an ICUR of $377,025 per QALY for nitisinone plus BSC compared with BSC alone, in a revised base case.

The difference in incremental cost is largely driven by the acquisition cost of nitisinone and duration of treatment (based on the estimated life expectancy of patients). Weight-based costs associated with nitisinone in particular were not fully accounted for in the probabilistic analysis; the actual ICUR for nitisinone plus BSC compared with BSC alone may be higher or lower depending on the mean dose required. The difference in incremental QALYs was driven by the predicted life expectancy of patients, as well as the related utility values. CADTH was unable to test several key identified limitations as a result of the model structure, and noted that the lack of long-term information on patients receiving nitisinone increased the uncertainty of the magnitude of the likely clinical benefit.

At the current price, the likelihood that the addition of nitisinone to BSC is cost-effective at a willingness-to-pay threshold of $200,000 per QALY was 0% when considering either the CADTH or manufacturer's base case. A price reduction of at least 74% (for all nitisinone strengths) would be required for nitisinone to achieve an ICUR of less than $100,000 per QALY, and at least 87% for the ICUR to be below $50,000 per QALY based on the CADTH base case.

CADTH notes that the results only apply to patients who are treated in the first month of life; the manufacturer did not model patients receiving treatment with nitisinone beyond one month of age. The ICUR for nitisinone plus BSC compared with BSC is unknown in the patient population treated after one month of age.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis that compared costs and health benefits with nitisinone 1 mg/kg plus best supportive care (BSC; dietary restriction) versus BSC alone, in newborns at least one month old, from a health ministry perspective. The base-case analysis used a lifetime horizon (100 years), and future costs and benefits discounted at 1.5% annually. The model used a one-year cycle, and included a half-cycle correction.

The economic evaluation was based on a state-transition, semi-Markov, cohort model that considers disease progression in patients newly diagnosed with hereditary tyrosinemia type 1 (HT-1) until an absorbing dead state. The model consists of three states: newly diagnosed HT-1, liver transplant, and dead. The liver transplant state is further modelled into three fixed, sequential (called "tunnel") states: first year post-transplant, second year post-transplant, and more than two years post-transplant (Figure 1). Baseline characteristics and efficacy were derived from a study of a Quebec-based cohort (Larochelle et al., the "Quebec" study)[3] of 78 newborns followed for up to 14 years. In this study, none of the 24 early nitisinone-treated patients (within first 30 days) died or progressed to liver transplant, whereas seven of the 27 patients receiving BSC alone died before seven years and the remaining received a liver transplant. An additional cohort of 26 patients included in the study who were treated after the first 30 days were not considered in the submitted economic evaluation.[3] Similarly, a single patient (n = 1) receiving BSC and liver transplantation and who experienced long-term survival was not considered in the economic evaluation.

Health-related quality of life was derived from a cohort of men (average age 54 years) with decompensated cirrhosis resulting from chronic hepatitis B (CHB) infection and measured with the Health Utility Index Mark 3 (HUI3) instrument. Patients with a diagnosis of HT-1 and who were treated with nitisinone were assumed to have higher values than untreated patients (0.87 versus 0.49). Liver transplant and post-transplant was assumed to increase utility scores in BSC patients (from 0.49 to 0.72).

Assumptions regarding resource use and costs were derived from a Quebec-based study of HT-1 patients as well as a British Columbia-based study of liver transplantation costs. The manufacturer stated that patients in the model receive a specially prescribed diet formula as BSC. The manufacturer noted that given the lack of information about the use of diet in the historical control data, it was assumed that patients consumed one protein supplement daily by the age of 5. Hospitalization costs were assumed to be lower per person-year for nitisinone recipients ($1,146 versus $19,671), with liver transplant costs ($133,551) and follow-up transplant costs (first year, $22,749; second and subsequent years, $11,374) attributed to BSC recipients. The manufacturer stated that "all costs were inflated to 2016 dollars using the health care consumer price index published by Statistics Canada."

Manufacturer's Base Case

The manufacturer presented a deterministic analysis as the base case. The addition of nitisinone to BSC (dietary restriction) versus BSC (dietary restriction) alone would produce

an additional 33.21 quality-adjusted life-years (QALYs) for an additional $10,724,537 per person treated (in 2016 dollars). This resulted in an incremental cost-utility ratio (ICUR) of $322,927 per additional QALY gained (Table 2; see *Appendix 5* for more details).

The probabilistic analysis (1,000 iterations) indicated that the chance of being cost-effective at $100,000 per QALY and $200,000 per QALY was 0% and the results were most sensitive to choice of utility value and time horizon. The results of the probabilistic analysis are presented in Table 2. The base-case results were stable using 1,000 iterations. The manufacturer indicated the results were most sensitive to the utility value chosen in addition to drug price. The probabilistic results considered uncertainty on a small number of inputs relating to cost (hospitalization, liver transplant, and diet), utility values (± 10%), and transplant probabilities (± 10%).

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost of Nitisinone ($)	Life-Years	Incremental Life-Years of Nitisinone	Total QALYs	Incremental QALYs of Nitisinone	Incremental Cost per QALY
Deterministic analysis							
BSC	260,660		13.87[a]		7.86		
Nitisinone + BSC	10,890,712	10,724,537	47.21[a]	33.34	41.07	33.21	**$322,927[b]**
Probabilistic analysis							
BSC	261,001		NR[c]	NR[c]	7.91		
Nitisinone + BSC	10,985,171	10,724,171	NR[c]	NR[c]	41.32	33.41	**$320,985[b]**

BSC = best supportive care; NR = not reported; QALY = quality-adjusted life-years.

[a] Discounted life-years and actual life-years (18.8 years for BSC and 82.3 years for nitisinone + BSC) were obtained from the economic model.[2]

[b] Manufacturer's model incorrectly calculated the cost of treatment (transcription error that resulted in slight overestimation of the cost of nitisinone – deterministic ICUR = $319,232 per QALY; probabilistic ICUR = $317,184 per QALY).

[c] Not calculable.

Source: Derived from Manufacturer's Pharmacoeconomic Submission.[2]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer indicated the model is most sensitive to health state utility values in nitisinone-treated individuals, ranging from $469,870 per QALY (0.65 instead of 0.87) to $272,559 per QALY (1.00 instead of 0.87). This is a variation of between 16% and 45% of the base-case ICUR. Varying utility values for BSC recipients alone or post-transplant were also associated with uncertainty, but less so. Other parameters were tested but led to less uncertainty, with the exception of varying the annual probability of post-transplant death in BSC recipients beyond 2 years (from $316,886 per QALY to $331,493 per QALY). The manufacturer also provided an analysis of the sensitivity of the results to time horizon, reporting an ICUR of $71,551 per QALY using an eight-year time frame. While the manufacturer appropriately noted that the "lifetime horizon should be treated with increased caution due to limited primary data and the uncertainty of extrapolating outcomes," this analysis was considered inappropriate based on best practices,[7,8] as the costs associated with nitisinone therapy due to extended survival are relevant to the cost-effectiveness of the decision problem. The results can only be considered relevant if there are likely to be no additional health system costs associated with ongoing treatment with nitisinone after eight years.

Limitations of Manufacturer's Submission

- **The model structure does not capture all relevant outcomes:** The model was overly simplistic and did not consider relevant events for HT-1 patients such as hepatocellular carcinoma (HCC), porphyric crises, other relevant disease complications, and adverse events. This would have better captured the impact of disease, instead of assuming a difference in utility values between the treatment and non-treatment groups for the same health state (as described in the limitation relating to model inputs and assumptions).
- **The modelled population did not align with the Health Canada indication and listing request:** The manufacturer's modelled population assumed all patients were identified and treated within one month of being born, meaning patients are normalized and do not experience physiological damage from tyrosinemia. Assessing this specific subpopulation does not allow for an estimate of the relative costs and health impact for patients who are identified more slowly (i.e., in the absence of newborn screening programs) or who cannot initiate treatment within one month for other reasons, and so may not capture all relevant patients. The cost-effectiveness of nitisinone initiated in patients starting beyond one month is not known, but the ICUR is likely to be higher in an older population at starting age given the higher costs associated with late-treated patients,[5] and the potential that early-treated patients receive more clinical benefits.[3]
- **Application of the cost of diet/BSC in the model:** Although the manufacturer stated that patients in both arms received diet, this was not the case. The cost of diet with nutritional supplements was included in the BSC group only. This underestimates the total cost of treatment with nitisinone. Additionally, the method used to determine the cost of diet is highly uncertain, as the manufacturer considered only 10% of the cost of diet in the first cycle, 50% by cycle 5, and 100% after that. Given the lack of justification provided for this analysis, CADTH considered 100% of the cost of diet for both treatment arms. This had a marginal impact on the manufacturer's base case.
- **Several model inputs and assumptions are associated with uncertainty:**
  - **Length of life in nitisinone recipients:** In addition to assuming no liver transplant or complications in nitisinone recipients, the model also assumes that patients that receive nitisinone within the first 30 days live a normal length of life (predicted in the manufacturer's model to be 82.25 years before discounting), and that lifespan is not shortened due to complications of illness or other factors. As nitisinone was only introduced in 1992, there is uncertainty surrounding the actual length of life in treated individuals and no long-term data support this assumption.
  - **Utility benefit for treatment:** The utilities identified in the report were derived from a publication by Woo et al.[4] that assumed the valued preference for a state of health achieved in nitisinone-treated HT-1 patients is 0.87, while patients in the HT-1 health state who are not treated with nitisinone were assigned a utility value of 0.49. Patients who underwent liver transplant were assigned a utility value of 0.72. The publication by Woo et al.[4] was a Canadian-based survey of men (mean age of 54 years) with various disease stages of CHB infection as measured by the HUI3. The use of the HUI-3 from this study is notable as it produced a much lower score than those derived in the same study by the EuroQol 5 Dimensions (EQ-5D) generic health state preference instrument. EQ-5D scores were 0.92, 0.84, and 0.73 for states of non-cirrhotic CHB infection, post-transplant, and decompensated cirrhosis, which were reported by the manufacturer to correlate with patients treated with nitisinone, post-transplant patients, and patients receiving BSC alone, respectively. No justification was provided for using values from the HUI3 instead of the EQ-5D values.

    While the inherent challenges in measuring these values in a pediatric population is recognized, along with the need for proxy values, feedback from the clinical expert consulted by CADTH suggested that utility values for infection with chronic hepatitis C virus would be a more appropriate proxy for patients with HT-1, and more likely to

reflect disease progression and elevated risk of progression to HCC. Many utility values for hepatitis C are available, but CADTH considered the values used in the Therapeutic Review of Hepatitis C treatments to be the most appropriate for consideration (see Appendix 5: CDR reanalyses for further information).[6,9,10]

- **Rate of liver transplant/surgery in recipients versus non-recipients:** The rates of transplant in HT-1 are assumed to be 0% based on the Quebec study (Larochelle et al.)[3] and could be an underestimate. Every patient not receiving nitisinone and who has not died is assumed to have a transplant by year 7 in the model. However, the clinical expert consulted by CADTH indicated that rates in nitisinone recipients could be higher over a lifetime. In the Quebec study, for example, seven of 26 patients (27%) who initiated treatment *after* 30 days (i.e., late treatment) due to being missed during screening or identified too late, received liver transplantation within the five-year follow-up, with two deaths after transplantation. This is not accounted for in the model. Furthermore, the NTBC study reported liver transplantations in 13% of nitisinone recipients.[11,12] The largest natural history study identified[13] described a 0.16% rate occurring after nitisinone release (six years).
- **Differential outcomes for liver procedures in treated and non-treated patients.** The clinical expert consulted by CADTH stated that if liver transplant occurred in nitisinone recipients, they would have better outcomes than for patients receiving BSC alone. In the Quebec study, two of the seven patients receiving transplant who received nitisinone therapy late died (1.1% of patients observed). In contrast, the model assumed a roughly 10% mortality rate for non-nitisinone recipients receiving a liver transplant and did not assume liver transplant in nitisinone recipients. If it is assumed that some nitisinone recipients will receive liver transplant as seen in patients treated late (due to being missed during screening or not screened as per Larochelle et al.), then differential morbidity and mortality assumptions would also need to be applied. The model was not flexible enough to test this assumption.

- **The model did not appropriately test uncertainty, and was not sufficiently flexible to allow CADTH to appropriately test relevant parameters in the analyses:**
  - **Sensitivity of results to weight-based dosing:** Although the recommended dose is 1 mg/kg, the product monograph has provisions for 1.5 mg/kg and 2 mg/kg doses, depending on the response to treatment. In the overview of the Clinical Study Report, it is reported that the majority (77%, 224 of 291) of patients in the Quebec study received a nitisinone dose of ≥ 0.8 and < 1.2 mg/kg body weight. The model was not developed to test these dose ranges or the higher doses of 1.5 mg/kg and 2 mg/kg, and was not tested in sensitivity analyses by the manufacturer. Other studies of patients using nitisinone have reported 1.2 mg/kg average doses in treated cohorts (e.g., Zeybek et al.[14]) and dose variance should have been incorporated into the probabilistic model.
  - **Rates of liver transplantation and outcomes:** Despite considerable uncertainty regarding the need for liver transplantation and the potential for different outcomes between nitisinone and BSC recipients, sensitivity of the ICUR to these assumptions could not be tested using the submitted model. The model was altered to test assumptions regarding increased rate of transplantation in nitisinone recipients.
  - **Outpatient costs for monitoring were not included:** It is unclear whether outpatient costs, including eye exams, drug-level monitoring, dietitian visits, diagnostic imaging, and other relevant laboratory tests were not included. In the nitisinone studies, the most commonly reported adverse events were eye-related and required annual slit-lamp examination of the eyes before initiation of nitisinone treatment and also during treatment. Other assumptions not included were the need for serum tyrosine and/or blood/urine succinylacetone levels (more frequent early on, three per year for the first year, and one per year once dosing is stabilized). This may require sending samples abroad. Dietitian visits may be required for some patients. Monitoring for the development of HCC was also identified, as it required magnetic resonance imaging

(MRI) in addition to general anesthesia and associated costs for patients less than 5 years old. Beyond that age, ultrasound or MRI may be used alternately every six months (one per year for each). In addition to liver imaging, liver function tests and serum alpha-fetoprotein tests must also be administered. Platelets and white blood cells must also be monitored. The only costs captured in the model were hospitalization costs (assumed to be lower per person-year for nitisinone recipients) and aggregated costs after liver transplant (only attributed to BSC recipients). Drug costs for pharmaceuticals and devices were included and assumed to differ between treatment based on real-world data from patients in Quebec.[5]

CADTH Common Drug Review Reanalyses

In the CADTH base case, the following were considered:

- Utilities from chronic hepatitis C were deemed more relevant to patients with HT-1.[6,9,10]
- A small proportion (0.16% per year) of patients will develop HCC and require transplantation.[13]
- 100% of the reported diet costs are applied to both the nitisinone plus BSC (dietary restriction) and the BSC (dietary restriction) alone treatment groups.

The CADTH reanalysis resulted in an ICUR of $377,025 per QALY, based on an additional cost of $10.64 million and an additional 28.23 QALYs over a patient's lifetime, for patients treated with nitisinone plus BSC (dietary restriction) compared with BSC (dietary restriction) alone (Table 3).

Table 3: Summary of CDR Reanalysis Base Case

	Description	Incremental Cost of Nitisinone + BSC vs. BSC Alone	Incremental QALYs of Nitisinone + BSC vs. BSC Alone	ICUR	Variance[a]
	Manufacturer's submitted base case	**$10,724,171**	**33.41**	**$320,985**	**NA**
	Manufacturer's base case correcting for calculation error	**$10,507,695**	**33.08**	**$317,662**	**NA**
	CADTH reanalyses				
1	Revised diet costs across both treatments	$10,753,232	33.17	$324,196	+2.1%
2	Utility values – CHC instead of CHB	$10,507,560	28.05	$374,646	+17.9%
3	Rate of liver transplant for nitisinone – 0.16%	$10,400,000	33.08	$314,377	–1.0%
4	**CADTH base case (1, 2, and 3)**	**$10,643,298**	**28.23**	**$377,025**	**+18.7%**

BSC = best supportive care; CDR = CADTH Common Drug Review; CHB = chronic hepatitis B; CHC = chronic hepatitis C; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Versus manufacturer's base case with corrections by CADTH.

Additional scenario analyses were performed to demonstrate the sensitivity of the findings to dose, alternative utility values, alternative transplant rates, and alternative costs.

CADTH considered the following scenario analyses on the CADTH base case to address uncertainty within the identified limitations:

A. **Utility benefit:** Using utilities derived from the EQ-5D from Woo et al.[4] (CHB) reduced the ICUR from the CADTH Common Drug Review (CDR) base case, but were still above the manufacturer's base case.

B. **Dose:** Varying the dose between 0.8 mg/kg and 1.2 mg/kg has a corresponding effect on the ICUR (–19% to +20%). Doses of 1.5 mg/kg and 2 mg/kg increase the ICUR by 49% and 98% respectively.

C. **Rates of liver transplant:** CADTH noted that the rate of liver transplant in all nitisinone recipients (identified either early or late) in the study of Larochelle et al.[3] is seven of 50 (14%). In the NTBC study, this rate is 13% in nitisinone-treated patients.[11,12] Estimates assuming 10% and 20% risk of liver transplant in nitisinone recipients were also conducted to reflect a plausible range around these data.

Table 4: Summary of CDR Scenario Analyses

	Description	Incremental Cost (Discounted)	Incremental QALYs (Discounted)	ICUR	Variance (Notes)
	CDR base case	**$10,643,298**	**28.23**	**$377,025**	**NA**
A	**Utility values**				
Ai	EQ-5D instead of HUI3	$10,643,699	32.13	$331,302	–12.1%
B	**Nitisinone dose**				
Bi	0.8 mg/kg	$8,528,115	28.08	$303,706	–19.4%
Bii	1.2 mg/kg	$12,714,193	28.06	$453,064	+20.2%
Biii	1.5 mg/kg	$15,834,462	28.13	$562,724	+49.3%
Biv	2.0 mg/kg	$20,947,180	28.13	$744,713	+97.5%
C	**Rate of liver transplant**				
Ci	10%	$9,746,619	28.32	$344,173	–8.7%
Cii	20%	$8,738,030	28.51	$306,444	–18.7%

CDR = CADTH Common Drug Review; EQ-5D = EuroQoL 5-Dimensions questionnaire; HUI 3 = Health State Utility Index Mark 3; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

CADTH undertook a price-reduction analysis using both the manufacturer and CADTH base-case analyses. Using the CADTH base-case analysis, a price reduction across all capsule strengths of about 74% was required for nitisinone plus BSC to achieve $100,000 per QALY compared with BSC alone. A price reduction of 87% was required to achieve $50,000 per QALY compared with BSC alone. The reanalysis did not further test assumptions regarding specific price reductions for specific strengths. Assumptions regarding price reduction assumed a percentage reduction that applied equally to all strengths. The model predicts the 2 mg and 20 mg strengths will be used most often. For example, the relative proportion of 2 mg and 20 mg capsules required until a patient reaches 75 kg (i.e., a 75 mg dose) is 46% and 33%, respectively. This means different discounts applied by strength could lead to more favourable ICURs than discounts applied across all strengths. The model did not often consider that the dose needs to be split evenly throughout the day, which may underestimate the proportion of lower-strength capsules.

Table 5: CDR Reanalysis Price Reduction Scenarios

ICURs of Submitted Drug Versus Comparator		
Price	**Base-case analysis submitted by manufacturer**	**Reanalysis by CADTH**
Submitted	**$320,985/QALY**	**$377,025/QALY**
10% reduction	$290,012/QALY	$340,154/QALY
20% reduction	$257,098/QALY	$303,257/QALY
30% reduction	$224,183/QALY	$265,643/QALY
40% reduction	$191,268/QALY	$228,137/QALY
50% reduction	$158,353/QALY	$189,523/QALY
60% reduction	$125,438/QALY	$152,527/QALY
70% reduction	$92,524/QALY	$114,713/QALY
74% reduction		**$99,377/QALY**
80% reduction	$59,609/QALY	$77,026/QALY
87% reduction		**$50,346/QALY**
90% reduction	$26,694/QALY	$39,197/QALY

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Issues for Consideration

Testing uncertainty regarding rates of liver transplantation in nitisinone recipients revealed the ICUR was not highly sensitive to rates of liver transplant. However, the ICUR did go down with higher rates of transplant (See Section: *CADTH Common Drug Review Reanalyses*). This is because liver transplant in the model is associated with lower utility values post-transplant in nitisinone recipients. Moreover, no additional mortality risk is assumed for nitisinone plus BSC patients post-transplant, while additional mortality risk is assumed for BSC patients. This raises an issue of equity, as the drug may seem more attractive from a cost-effectiveness perspective, but at the cost of more associated morbidity and a reduced number of healthy years of life in nitisinone recipients.

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 the vast majority of patients within the first month of life for the submitted analyses and CADTH reanalyses to apply.

Other products for the treatment of HT-1 have been approved by Health Canada. They are either under review by CADTH, or expected to be reviewed by CADTH in the near future.

A societal perspective that includes lost productivity due to premature mortality was not addressed in the model but may have been of interest, and could have been provided as a supplemental analysis.

An oral suspension formulation (4 mg/mL) was approved during the course of the CDR review, but this formulation is not assessed in the current review.

Patient Input

Input was received from the Canadian Liver Foundation and the Canadian Organization for Rare Disorders. According to the input, most patients are currently receiving the drug under review or have used it previously. Respondents stated that starting nitisinone treatment immediately at diagnosis is a requisite part of therapy, and saw the treatment as "life-saving." Patients reported fewer hospitalizations, neurological crises, liver transplants, and other complications, compared with BSC (diet), without serious side effects from the treatment. Neurological crises and other complications, such as tumours, were not considered in the submitted economic model. The administration of nitisinone to infants was reported to be challenging for caregivers.

One patient group noted frustration when an uncommunicated switch from one manufacturer of nitisinone to another was implemented in Canada, leaving patients concerned about the efficacy of the treatment they were receiving. While the patient group noted that there was some contentment in accessing nitisinone through the Health Canada Special Access Programme from hospital pharmacies, being able to directly access their medication through the public drug plans and local pharmacies would be welcomed.

Conclusions

In patients with HT-1 identified and treated within 30 days of birth, CADTH reported an ICUR of $377,025 per QALY for nitisinone plus BSC compared with BSC alone, in a revised base case.

The difference in incremental cost is largely driven by the acquisition cost of nitisinone and duration of treatment (based on the assumed life expectancy of patients). Weight-based costs associated with nitisinone in particular were not fully accounted for in the probabilistic analysis; the actual ICUR for nitisinone plus BSC compared with BSC alone may be higher or lower depending on the mean dose required. The difference in incremental QALYs was driven by the predicted life expectancy of patients, as well as the related utility values. CADTH was unable to test several key identified limitations as a result of the model structure, and noted the lack of long-term information on patients receiving nitisinone increased the uncertainty of the magnitude of the likely clinical benefit.

At the current price, the likelihood that the addition of nitisinone to BSC is cost-effective at a willingness-to-pay threshold of $200,000 per QALY was 0% in both the CADTH and manufacturer's base case. A price reduction of at least 74% (for all nitisinone strengths) would be required for nitisinone to achieve an ICUR less than $100,000 per QALY, and at least 87% for an ICUR below $50,000 per QALY based on the CADTH base case.

CADTH notes that the results only apply to patients who are treated in the first month of life; the manufacturer did not model patients receiving treatment with nitisinone beyond one month of age. The ICUR for nitisinone plus BSC compared with BSC is unknown in the patient population treated after one month of age.

Appendix 1: Cost Comparison

The comparators presented in Table 6 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 6: CDR Cost Comparison for Treatments for HT-1

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Dose	Average Daily Drug Cost	Average Annual Drug Cost ($)
Nitisinone	2 mg 5 mg 10 mg 20 mg	Capsule	22.5000[a] 53.3333[a] 100.0000[a] 193.3333[a]	1 mg/kg body weight divided in 2 doses[b] (Maximum dose of 2 mg/kg)[b]	20 kg patient: $193.33 50 kg patient: $486.67 75 kg patient: $733.33	20 kg patient: $70,614 50 kg patient: $177,755 75 kg patient: $267,850

CDR = CADTH Common Drug Review.
[a] Manufacturer submitted price.
[b] Nitisinone (Orfadin) product monograph.[1]
Note: The product monograph indicates that the dose is to be divided evenly. The assumption was made that in patients under 10 years of age, they will likely still receive treatment as an oral liquid (capsule can be opened and product dissolved in water/formula); therefore, a single 20 mg capsule may still be appropriate.
Note: An oral suspension formulation (4 mg/mL) was approved during the course of the CDR review. However, this formulation is not assessed in the current review.

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes & Quality of Life, How Attractive is Nitisinone + BSC Relative to BSC Alone?

Nitisinone + BSC vs. BSC	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					
Incremental CE ratio or net benefit calculation	**CADTH base case: $377,025 per QALY**					

BSC = best supportive care; CE = cost-effectiveness; QALY = quality-adjusted life-year.

Appendix 3: Additional Information

Table 8: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	Transcription errors in model. Lack of justification of methods used for use of parameters, and calculations used in the model.		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

Table 9: 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)

	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		

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

The following health technology assessment agencies have reviewed nitisinone (Orfadin) for treatment of patients with hereditary tyrosinemia type 1: Quebec's Institut national d'excellence en santé et en services sociaux (INESSS),[15] Australia's Pharmaceutical Benefits Advisory Committee (PBAC),[16,17] and France's Haute Autorité de Santé (HAS).[18]

HAS recommended that nitisinone should be included on the list of medicines approved for hospital use and various public services for the indications and at the dosages specified in the marketing authorization and noted the product had substantial actual benefit to patients. No cost information was provided.[18] The PBAC and INESSS reviews are presented in Table 10.

Table 10: Other HTA Findings

	PBAC (November 2014 and July 2015)[16,17]	INESSS (August 2017)[15]
Treatment	Nitisinone capsules (2 mg, 5 mg, 10 mg, 20 mg)	Nitisinone capsules (2 mg, 5 mg, 10 mg, 20 mg)
Price	Redacted.	Redacted.
Similarities with CDR submission	Both submissions were CUA for nitisinone + BSC (diet) vs. BSC alone, in patients with HT-1. Same health states and utility values appear to be used. 100% compliance assumed. Cost of ongoing follow-up post liver transplant and cost of adverse events not included.	Both submissions were CUAs for nitisinone + BSC (diet) vs. BSC alone, in patients with HT-1. Same health states and utility values appear to be used. However, results reported had a lower ICUR.
Differences with CDR submission	Economic evaluation based on NTBC study and study by van Spronsen et al. (1994). Data from Quebec study used for extrapolation and trial-based analysis. Submitted analyses undertaken on 3 patient populations based on age at onset: < 2 months, 2 to 6 months, and > 6 months.	INESSS considered an average daily dose of 1.75 mg/kg for patients ≤ 5 years, 1.25 mg/ kg for 6 to 12 years, and 0.75 mg/kg for ≥ 13 years. This increased the ICUR. Different doses of nitisinone were used in sensitivity analysis.
Manufacturer's results	Redacted. PBAC report noted base case ICUR > $200,000/QALY for all treatment scenarios.	Redacted.
Issues noted by the review group	Did not consider impact of neonatal screening in Australian setting — likely underestimates proportion of patients receiving treatment earlier, and false positives and false negatives have important clinical and cost impacts. Appropriate to consider shorter time horizon to align with long-term clinical experience with drug. Using data from Larochelle et al. for subgroup treated ≤ 1 month of age, ICUR $105,000 to $200,000/QALY. Using Larochelle et al. for an older population (treated after 1 month), ICUR > $200,000/QALY.	Some complications of HT-1 not considered in model, which underestimates costs and overestimates the years of life and years of life weighted by the quality of patients on BSC. This means the ICER could be higher.
Results of reanalyses by the review group	Using a shorter time horizon (22 years) resulted in a reduction in ICUR, but still > $200,000/QALY.	< $232,243/QALY

	PBAC (November 2014 and July 2015)[16,17]	INESSS (August 2017)[15]
Recommendation	**November 2014:** PBAC deferred recommendation due to lack of clarity on current and future screening practices for HT-1 and recommended stakeholder meeting to provide clarity on clinical effectiveness of nitisinone. **July 2015:** PBAC rejected request to list nitisinone on PBS for HT-1 on basis of uncertain and unacceptably high cost-effectiveness. No new information in submission discussed at July 2015 meeting.	List in combination with a restrictive diet of tyrosine and phenylalanine for treatment of patients with HT-1 contingent on price reduction.

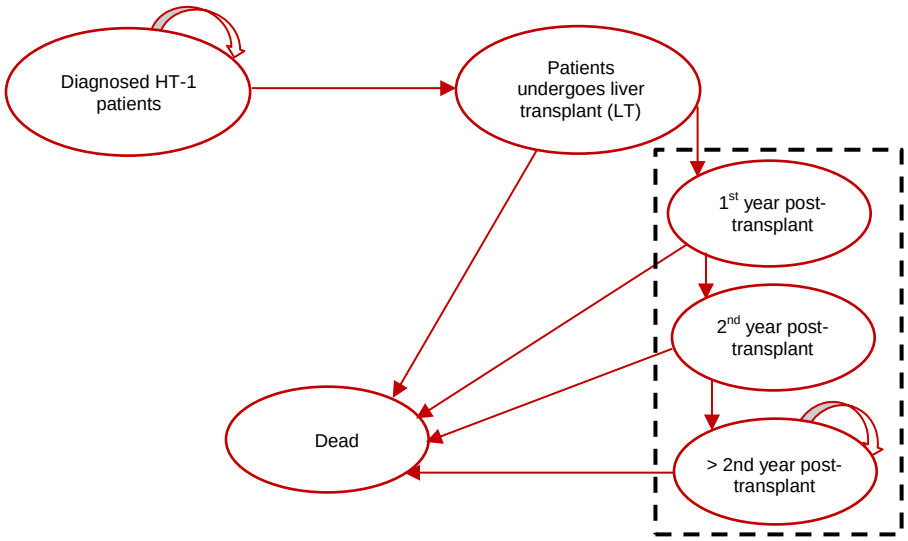
BSC = best supportive care; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; HTA = health technology assessment; HT-1 = hereditary tyrosinemia type 1; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; INESSS = Institut national d'excellence en santé et en services sociaux; QALY = qualify-adjusted life-year. PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer undertook a state-transition, semi-Markov, cohort model of disease progression in patients newly diagnosed with hereditary tyrosinemia type 1 (HT-1) until an absorbing dead state. The model consists of three states: newly diagnosed HT-1, liver transplant, and dead. The liver transplant state is further modelled into three fixed, sequential (called "tunnel") states: first year post-transplant, second year post-transplant, and more than two years post-transplant. A depiction of the model (adapted from the submission) is shown below (Figure 1).

Figure 1: Manufacturer's Model Structure



HT-1 = hereditary tyrosinemia type 1.
Source: Derived from Manufacturer's Pharmacoeconomic Submission.[2]

Although some details are provided regarding model validation, there is no mention of comparing the model to other published models (i.e., cross-validity testing). There is no description of techniques to validate the data serving as input into the model.

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Drug efficacy from Larochelle et al. (2012)[3] where 51 newborns (who fulfilled the manufacturer's target population) are followed for up to 14 years. An additional 26 patients who were treated after 1 month of age were also followed (late-treatment group).	The generalizability of this population needs to be considered. Newborns who are not identified and treated within 30 days will have more adverse outcomes than those used to inform the model. One patient in the Quebec cohort was transplanted, treated and not considered in the manufacturer's economic evaluation.
Natural history	From Larochelle et al. (2012)[3] where 51 newborns are followed for up to 14 years. Liver transplantation outcomes were calculated based on survival data obtained from the annual report of the Canadian Organ Replacement Register in 2015.	These data are described as "mainly" from Larochelle et al. (2012) although this is not qualified. It may relate to the omission of one patient in the not-treated arm who received transplant and remained alive.
Utilities	From Woo et al. (2012).[4]	This is from a study of ~50-year-old mostly males with various stages of chronic hepatitis B virus infection in the Toronto area. The authors use values obtained from the HUI3 but ignore EQ-5D. Feedback from the clinical expert consulted by CADTH suggested utility values for infection with chronic hepatitis C virus would be a more appropriate proxy for patients with HT-1, reflecting a more insidious progression and elevated risk of progression to hepatocellular carcinoma.
Adverse events	Not included in the model.	AEs identified in Larochelle et al. (2012) include ocular crystals, hypoglycemia, and asymptomatic ALT elevation. These AEs would require supportive care or dose adjustment which is not addressed in the model. This biases the results in favour of nitisinone. Data from the NTBC study could have been considered as well.[11,12]
Mortality	From disease, Larochelle et al. (2012)[3] where 9 of 28 patients died. From liver transplant: the Canadian Organ Replacement Register (2015)[2]	Assumes probability of death in nitisinone recipients is 0% and then according to natural life tables. From liver transplant state, assumes probability of death in first year would be similar to the 3-month survival rate.
Costs		
Drug	Nitisinone based on manufacturer submitted price. Diet costs based on nutritional supplement costs from RAMQ.	Does not use flat or linear pricing. RAMQ costs for nutritional supplementation may vary from other provinces.
Administration	Pharmaceutical services defined as prescription drug fees from Simoncelli et al. (2015).[5]	Markup and dispensing fees are not appropriate for economic evaluation according to CADTH guidance.
Event	Simoncelli et al. (2015)[5] for direct hospital and drug costs based on RAMQ (prescriptions, medical visits, surgeries, and procedures) and Centre hospitalier universitaire Sainte-Justine as well as MED-ECHO (audiologists or genetic	Costs from Simoncelli et al. (2015) reported in 2008 Canadian dollars with discounting at 3% annually for drugs and non-physician costs.

Data Input	Description of Data Source	Comment
	counsellors in hospitals or outpatient clinic); Quebec hospital association was used for emergency department visits.	
AEs	Not included.	As noted earlier, the exclusion of AEs was not appropriate.
Health state	Levy et al. (2009) for liver transplant costs.[19]	
Resource use	From Simoncelli, M., et al.,(2015).[5]	Resources are not explicitly modelled This is a Quebec-based costing study that considers hospitalization costs (assumed to be lower per person-year for nitisinone recipients: $1,146.47 vs. $19,670.54); LT costs ($133,550.66); and follow-up LT costs (first year, $22,748.92; second and subsequent years $11,374.46) only attributed to BSC recipients. No outpatient or monitoring costs were included.

AE = adverse event; ALT = alanine transaminase; EQ-5D = EuroQoL 5-Dimensions questionnaire; HUI3 = Human Utility Index Mark 3; LT = liver transplant; MED-ECHO = maintenance et exploitation des données pour l'étude de la clientèle hospitalière; RAMQ = Régie de l'assurance maladie du Québec.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
All patients are treated prior to 1 month of age.	May not be appropriate. While screening for HT-1 is used often in Quebec, it is uncertain as to how easily accessed this screening is across the rest of Canada. While screening may capture most cases, as highlighted in the Quebec study, there were still cases of late onset HT-1. These should have been considered in the economic model.
Nitisinone recipients never go on to liver transplant.	This assumes all patients are identified and initiated treatment within 30 days of birth. The Quebec study notes that some patients started treatment late due to being "missed" during screening. It also assumes that hepatocellular carcinoma does not develop in nitisinone recipients, although cases have been documented along with a theoretical basis for progression. This biases the results in favour of nitisinone.
The assumption of effectiveness is based on a single study from Quebec.	A systematic review of available studies is not reported. Concerns regarding the generalizability of the Larochelle et al. cohort were raised with the clinical expert consulted by CADTH, who suggested patients may be harder to identify due to lower prevalence and the lack of screening programs Canada-wide as well as differences in natural history outside of Quebec.
A description of specific resources and units is not provided due to reliance on Simoncelli et al. (2015).	The aggregate costs used make it difficult to examine different resource-use scenarios or detect double counting.
Probability of liver transplant.	The model did not readily allow testing of differences in LT probability in nitisinone and BSC recipients. However, sensitivity analyses were conducted manually. Furthermore, mortality associated with liver transplant was assumed to be ~5% in BSC patients, while assumed to be 0% in nitisinone + BSC patients.
The manufacturer used 0% and 5% for the sensitivity analysis to discount rate.	CADTH Guidelines suggest 0 and 3%. 5% is only to be used if being compared with an historical analysis.
The analysis states "Since no Quebec HT-1 patient has lived longer than 8 years without either nitisinone or a liver transplant, the model also allows for consideration of an 8-year time horizon."	An 8-year time horizon is not appropriate[7,8] or in line with CADTH Guidelines ("When modelling chronic conditions, or when the interventions have differential effects on mortality, a lifetime horizon is most appropriate.") This is because the costs associated with nitisinone therapy as a result of a decision to fund therapy are borne by the payer and must be compared with the benefits seen by the patient.

BSC = best supportive care; HT-1 = hereditary tyrosinemia type 1; LT = liver transplant.

Manufacturer's Results

The manufacturer's main results have been presented in the main body of the report. CADTH noted that the total costs of general hospitalization per person-year in 2016 were estimated at $1,146 and $19,671 for nitisinone and best supportive care (BSC), respectively. The annual cost of nitisinone ranged from $16,250 in an infant to more than $300,000.

CADTH Common Drug Review Reanalyses

Utility benefit: The utilities identified in the report come from a publication by Woo et al. that assumes the valued preference for a state of health achieved in nitisinone-treated HT-1 patients is 0.87, while post-transplant and untreated health states were assigned utility values of 0.72 and 0.49, respectively. CADTH used utilities derived from chronic hepatitis C (CHC) patients, based on an earlier Therapeutic Review in this area.[9] These values were: 0.80 for HT-1 diagnosis and treatment with nitisinone plus BSC, corresponding with CHC infection and viral clearance; 0.75 for post-transplant and liver transplant state, corresponding with the post-transplant state in CHC-infected patients; and 0.65 for patients diagnosed with HT-1 but on BSC only, corresponding with decompensated cirrhosis in CHC-infected patients. Utility values were altered.

Rates of liver transplant: Six-year rates of liver transplant of 0.16 %[13] were converted to an annual probability as per Briggs et al. by first converting to an annual rate (LN(1 – 0.0016)/6) and then to an annual probability (1 – EXP(–[annual rate]). This probability (0.000266845) was then applied to column C of the "Nitsinone+Diet" tab of the Excel sheet. It was assumed the annual probability would extend beyond six years and over a patients' lifetime. This incremental cost-effectiveness ratio reflects a small reduction in quality-adjusted life-years (QALYs) gained (0.20) and costs ($112,160). Although ratios drop with increase liver transplants, so do QALY gains. The relationship between drug costs and magnitude of QALY benefits is shown below. Additional analyses were undertaken using 10% and 20% rates of liver transplant. However, these were tested over the first 10 years in the model. The same calculation method was used as noted above.

In each of these scenarios, the life expectancy of patients in the nitisinone-treated group was ~80 years.

Table 13: Detailed CDR Reanalyses

Parameter Tested	Treatment	Total Costs ($)	Incremental Cost of Nitisinone ($)	Total QALYs	Incremental QALYs of Nitisinone	Incremental Cost per QALY
CADTH base case	BSC	273,791		9.53		
	Nitisinone + BSC	10,917,089	10,643,298	37.76	28.23	377,025
Scenario analyses on CADTH base case						
Utilities: EQ-5D from Woo et al.	BSC	273,289		11.17		
	Nitisinone + BSC	10,916,988	10,643,699	43.30	32.13	331,302
Dose 0.8 mg/kg	BSC	273,038		9.51		
	Nitisinone + BSC	8,801,153	8,528,115	37.59	28.08	303,706
Dose 1.2 mg/kg	BSC	273,657		9.51		
	Nitisinone + BSC	12,987,850	10,643,298	37.57	28.06	453,064
Dose 2.0 mg/kg	BSC	272,568		9.50		
	Nitisinone + BSC	21,219,748	20,947,180	37.63	28.13	744,713
10% risk of LT over 10 years for NTBC	BSC	273,547		9.49		
	Nitisinone + BSC	10,020,166	9,746,619	37.81	28.32	344,173
20% risk of LT over 10 years for NTBC	BSC	273,353		9.52		
	Nitisinone + BSC	9,011,383	8,738,030	38.04	28.51	306,444

BSC = best supportive care; EQ-5D = EuroQoL 5-Dimensions questionnaire; LT = liver transplant; QALY = quality-adjusted life-year.

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