CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Nitisinone (MDK-NITISINONE)

(MendeliKABS Inc.)

Indication: for the treatment of HT-1 in combination with dietary restriction of tyrosine and phenylalanine

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	April 2018
Report Length:	22 Pages

CADTH

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

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

CADTH

Table of Contents

Tables

Figure

CADTH

Abbreviations

AE	adverse event
CDR	CADTH Common Drug Review
CHB	chronic hepatitis B
CUA	cost-utility analysis
HT-1	hereditary tyrosinemia type 1
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-year

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Nitisinone (MDK-Nitisinone) capsules, 2 mg, 5 mg, 10 mg, 20 mg
Study Question	What is the cost-effectiveness of nitisinone (MDK) with dietary restriction compared with dietary restriction alone for the treatment of hereditary tyrosinemia type1?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with HT-1 in Quebec
Treatment	Nitisinone plus dietary restriction (not defined)
Outcome	QALYs
Comparator	Dietary restriction alone (not defined)
Perspective	Public health care system (Ministry of Health of Quebec used as proxy)
Time Horizon	Six years
Results for Base Case	ICUR: $63,823 per QALY
Key Limitations	• The manufacturer's model is unconventional in nature and does not adhere to best practices. Progression of the condition is driven by assumption and whether the patient receives nitisinone, not based on health states and/or events. • Mortality, adverse event probabilities and risk of complications such as transplant or HCC were not incorporated in a way that could be explored, nor aligned with the clinical data. • The manufacturer's choice of a six-year time horizon does not adequately reflect the lifetime duration of the condition, nor the need for continued therapy, e.g., nitisinone, anti-rejection therapies after liver transplant, or nutritional supplements required to maintain a tyrosine- and phenylalanine-restricted diet. Nitisinone is dosed based on patient weight, therefore the annual cost of treatment increases with age (through adulthood). • Utility values were based on a Canadian survey of adults in various disease stages of CHB infection as measured by the HUI-3. The applicability of utilities from adults with a different condition is uncertain. Sensitivity analyses exploring utility weights from other liver conditions (such as CHC) or using other measurements were not conducted. • The manufacturer uses aggregate cost data, making it difficult to examine resource use separately which impedes validation. • The manufacturer's model is inflexible due to the model structure, source data, and the use of hard coding.
CDR Estimate	An estimate of the cost-effectiveness of MDK-Nitisinone could not be determined due to the substantial limitations with the submitted economic evaluation.

CDR = CADTH Common Drug Review; CHB = chronic hepatitis B; CHC = chronic hepatitis C; HCC = hepatocellular carcinoma; HT-1 = hereditary tyrosinemia type 1; HUI-3 = Health Utilities Index Mark 3; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Drug	Nitisinone (MDK-Nitisinone)
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, 10 mg, and 20 mg capsules
NOC Date	September 20, 2016
Manufacturer	MendeliKABS Inc.

Executive Summary

Background

Nitisinone (MDK-Nitisinone) is an inhibitor of the tyrosine catabolic pathway and is indicated for 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. The submitted price of nitisinone is based on dose: 2 mg ($14.78), 5 mg ($34.18), 10 mg ($64.70) and 20 mg ($128.10).[2,3] The recommended initial daily dose of nitisinone is 1 mg/kg body weight divided into two doses administered orally. The dosage of nitisinone should be increased to 1.5 mg/kg/day in patients whose plasma and urine succinylacetone are still detectable one month after starting treatment; a maximum of 2 mg/kg/day may be needed based on evaluation of all biochemical parameters. If the biochemical response is satisfactory, dosage should be adjusted only according to body weight gain.[1]

The manufacturer submitted a cost-utility analysis (CUA) that compared the costs and quality of life associated with nitisinone plus dietary restriction with dietary restriction alone in infants less than 30 days of age over a six-year time horizon, from a public health care system perspective (Quebec used as proxy). The manufacturer did not apply a discount rate to costs and benefits in the CUA.[4] The manufacturer also presented a supplementary cost-consequence analysis, based on a 2010 master's thesis (and subsequent publication) evaluating the costs associated with nitisinone for the treatment of HT-1.[4-6] Nutritional therapeutic products containing amino acid supplements free of tyrosine and phenylalanine are reimbursed in some jurisdictions but not included as comparators.[4,7]

The CUA incorporated three states: receiving nitisinone treatment, not receiving nitisinone treatment (before liver transplant), and not receiving nitisinone treatment (after liver transplant). All patients in the no nitisinone groups transitioned from the pre-liver transplant to post–liver transplant state at age 2. Patients in the nitisinone treatment state did not transition to another state, and no mortality was applied to either group (Figure 1). The manufacturer stated that efficacy data were based on Larochelle et al.[8] Utilities were applied to the duration of time in each state, and disutilities for adverse events (AEs) or health states related to AEs were not incorporated. Utilities were derived from a quality of life study in adult patients (average age: 54 years) with chronic hepatitis B.[9] Costs were derived in aggregate form from the cost-consequence study,[6] and inflated to 2016 dollars using the Quebec Consumer Price Index for Health and Personal Care.[4] A discount rate of 3% was

applied to drug costs and 5% to physician and hospital fees within the cost-consequence analysis.[6]

The manufacturer reported that nitisinone in addition to dietary restriction was associated with an additional 1.36 quality-adjusted life-years and an additional $86,799 compared with dietary restriction alone over the six-year time horizon, resulting in an incremental cost-utility ratio of $63,823 per quality-adjusted life-year. No probabilistic or scenario analyses were undertaken.

During the submission process, the 20 mg strength of MDK-Nitisinone was approved by Health Canada and added to the review. The manufacturer indicated that the pharmacoeconomic evaluation and the cost-utility addendum of MDK-Nitisinone was not updated to include this new capsule strength due to the price of the 20 mg capsule relative to the 10 mg capsule.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations, resulting in CDR questioning the validity of the submitted model, which did not allow for any reanalyses based on more reasonable assumptions or sources of information.

The manufacturer did not incorporate health state transitions or event probabilities in its CUA, but instead simply multiplied the time spent in a state by the assumed utility value. This does not adequately capture the potential movements between relevant health states by patients. Patients were assigned health states based on treatment choice, rather than on clinical state. The manufacturer indicated that data from Larochelle et al. were used to inform treatment efficacy, yet model assumptions do not align with the clinical data; for example, mortality, complications associated with liver transplant, and the uncertainty associated with finding a suitable donor were not considered. AE probabilities and risks of complications such as hepatocellular carcinoma or liver transplant were not appropriately incorporated. A time horizon of six years was used despite the lifelong nature of HT-1 and the necessity of continuing nitisinone therapy, which underestimates the costs associated with nitisinone therapy as it is dosed by weight and thus increases in cost per year. Utilities were derived from a different population (an adult population of chronic hepatitis B patients), which may not be generalizable to patients with HT-1. Costs were presented in aggregate form and hard-coded into the model, making it difficult to examine different resource use or identify double counting or errors. Additionally, costs and benefits were not discounted equally, nor at the rate recommended by CADTH in the Guidelines for Economic Evaluation.[10] Finally, the manufacturer did not conduct scenario or sensitivity analyses to test its assumptions, nor did it undertake its analyses probabilistically to test variability in the estimates.

CDR requested that the manufacturer provide a CUA that better aligned with the CADTH Economic Evaluation guidelines.[10] The manufacturer declined to do so.

Conclusions

The manufacturer's economic model was insufficient to adequately estimate the cost-effectiveness of its brand of nitisinone plus dietary restriction compared with dietary restriction alone in Canadian patients with HT-1. CDR was unable to conduct reanalyses to provide an estimated incremental cost-utility ratio.

Two other nitisinone products have recently been approved for use by Health Canada; one has recently been reviewed by CADTH, while the other is expected to be submitted to CADTH in the near future. MDK-Nitisinone received Health Canada approval based on the clinical studies for the reference product (Orfadin), and the results of a bioequivalence study demonstrating comparable pharmacokinetic profiles for MDK-Nitisinone and Orfadin in healthy volunteers. Given the clinical data indicate these treatments are comparable, whether MDK-Nitisinone delivers value for money will depend on its cost relative to the cost of other nitisinone products.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis (CUA) that compared the costs and quality of life associated with nitisinone plus dietary restriction with dietary restriction alone in infants under 30 days of age over a six-year time horizon, from a public health care system perspective (Quebec used as proxy). The manufacturer did not appear to apply a discount rate to costs or benefits in the submitted CUA.[4] The manufacturer also presented a supplementary cost-consequence analysis, based on a 2010 master's thesis evaluating the costs associated with nitisinone for the treatment of hereditary tyrosinemia type 1 (HT-1) and its subsequent publication.[4-6] Clinical effectiveness in the form of increased survival, increased survival without transplant, reduced neurological crises, and a reduction in tyrosinemia-related hospitalizations was reported based on a Quebec cohort study, Larochelle et al.[8]

The economic analysis incorporated three states: nitisinone treatment, no nitisinone treatment before liver transplant, and no nitisinone treatment after liver transplant. All patients in the no nitisinone groups transitioned from the pre- to post–liver transplant state at age 2. Patients in the nitisinone group did not transition to any other health state. No mortality rate was applied to either group (see Figure 1).[4]

Constant utilities were accrued during the course of each state, and adverse events (AEs) were not incorporated. Utilities were derived from a utility and quality of life study in adult patients (average age: 54 years) with chronic hepatitis B (CHB), with nitisinone plus treatment being assigned the non-cirrhotic CHB utility of 0.87, pre-transplant no nitisinone patients assigned the CHB with decompensated cirrhosis utility of 0.49, and post-transplant no nitisinone patients assigned the CHB post-transplant utility of 0.72.[9]

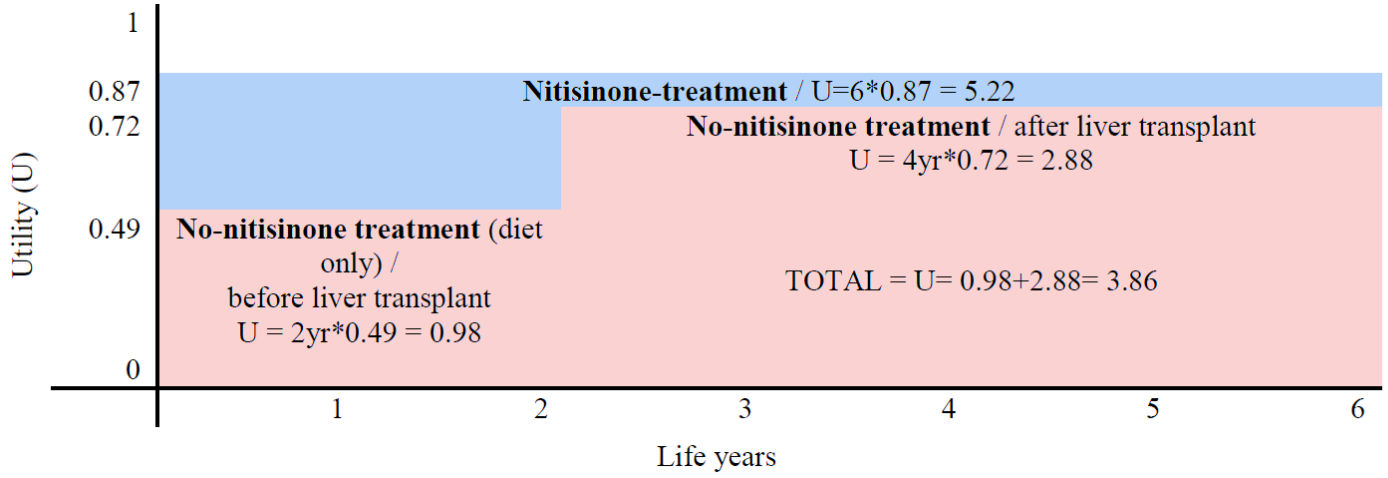
Costs were derived from the cost-consequence study,[6] and inflated to 2016 dollars using the Quebec Consumer Price Index for Health and Personal Care.[6] A discount of 3% was applied to drug costs and 5% for physician and hospital fees within the cost-consequence study, and appear to be captured in the values used by the manufacturer. Nutritional therapeutic products containing amino acid supplements free of tyrosine and phenylalanine are reimbursed in some jurisdictions but not included in the model.[4,7]

No sensitivity or scenario analyses were conducted.

Manufacturer's Base Case

The manufacturer presented a simple and deterministic base case, multiplying the number of years spent in each health state by the assigned utility of the state (see Figure 1).

Figure 1: Manufacturer's Model Structure



U = utility.
Source: Figure 1 of the Manufacturer's CUA Addendum, Pharmacoeconomic submission.[4]

Costs were calculated using annual health care resource costs and annual nitisinone costs per patient, multiplied by six (see Table 9 and Table 10).

The manufacturer reported the six-year cost of treatment with nitisinone in patients with HT-1 to be $215,151 per patient, which was $86,799 more than that of patients not receiving nitisinone ($128,352 per patient). Patients using nitisinone accumulated 5.22 quality-adjusted life-years (QALYs) over the six years, 1.36 more than those not receiving nitisinone. These findings result in an incremental cost-utility ratio (ICUR) of $63,823 per QALY (see Table 2).

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

	Total Costs ($)	Incremental Cost of Nitisinone ($)	Total QALYs	Incremental QALYs of Nitisinone	Incremental Cost per QALY ($)
No nitisinone	128,352	86,799	3.86	1.36	63,823
Nitisinone	215,151		5.22		

CUA = cost-utility analysis; QALY = quality-adjusted life-year.
Source: Table 3 of the Manufacturer's CUA Addendum, Pharmacoeconomic submission.[4]

Limitations of Manufacturer's Submission

- **Model structure does not adequately reflect the clinical condition, nor the clinical data**:
  - While the manufacturer's analysis includes both costs and utilities, and technically fulfills the broad criteria for a CUA, the model does not incorporate state transitions or event probabilities, and thus fails to align with customary methodology (e.g., a Markov model or decision tree) and is not consistent with the clinical data presented in Larochelle et al.[8]

- Modelled patients are assigned to either nitisinone treatment or no nitisinone treatment at birth, with 100% of patients in the no nitisinone treatment transferring from a before-liver-transplant to an after-liver-transplant state after two years. Health states are defined entirely by therapy received, with nitisinone therapy assigned the health state with the highest utility, no nitisinone pre-liver transplant the lowest, and no nitisinone post–liver transplant in between.[4] Health states should not be dependent on treatment allocation, but instead on possible clinical states, with treatment allocation then affecting the relative probability of a patient experiencing any given state and transitioning to others, including an absorbing state such as death.
- Mortality was not incorporated in the manufacturer's analysis, despite the high mortality rates associated with dietary-restriction-only HT-1, complications associated with organ transplant, and the uncertainty associated with finding a suitable donor. AE probabilities and risks of complications such as transplant or hepatocellular carcinoma were not incorporated in a disaggregated manner that could be explored, nor were event-associated disutilities. All in all, the manufacturer's model structure and assumptions do not align with the clinical data.
  - **Time horizon is not sufficient:** The manufacturer's choice of a six-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 liver transplant, 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. Additionally, as nitisinone is weight-based, the cost per year to treat each patient is expected to rise over time while still accruing similar QALYs, at least until adulthood is reached. This biases the results in favour of nitisinone.
  - **Generalizability of utility values is uncertain:** The manufacturer assumed a utility value of 0.87 in the nitisinone-treated state, while patients who were 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. These utility weights were derived from Woo et al.,[9] a Canadian survey of men (mean age: 54 years) in various disease stages of CHB infection as measured by the Health Utilities Index Mark 3. However, Woo et al. also reported utilities derived using the EuroQol 5-Dimensions generic health state preference instrument, which reported higher utilities of 0.92, 0.84, and 0.73 for non-cirrhotic CHB infection, post–liver transplant, and decompensated cirrhosis, respectively — the same health states used to correlated the Health Utilities Index Mark 3 results to the nitisinone treatment, post-transplant HT-1, and pre-transplant HT-1 health states in the manufacturer's model.[9] While acknowledging the uncertainty in modelling a pediatric population using adult utility data, the clinical expert consulted by CADTH Common Drug Review (CDR) considered chronic hepatitis C infection to be a more relevant proxy for patients with HT-1, as it is more likely to reflect disease progression and elevated risk of hepatocellular carcinoma. While CDR did not consider the model adequate to perform formal reanalysis, it did note that substituting the Woo et al. EuroQol 5-Dimensions–derived utilities[9] resulted in a near doubling of the ICUR, while using utilities derived in a CADTH therapeutic review of hepatitis C[11] approximately tripled it.

- **Aggregate costing:** The model uses aggregate costs derived from Simoncelli[5,6] and Simoncelli et al.,[5,6] making it difficult to examine resource use separately or detect double counting. Additionally, the model provided is non-transparent as to which resources were included in its final figures due to the hard coding of most entries. For example, the manufacturer reports the costs of hospitalization for no nitisinone treatment of $13,847 per patient per year, which leads to a total health care resource cost of $21,392 for the non-nitisinone group. However, this figure appears nowhere in the submitted model; the model instead reports a figure of $15,726 for discounted per-patient hospitalization costs inflated to 2016 dollars, while still reporting total health care resource costs of $21,392.
- **Discounting:** CADTH guidelines recommend that costs and outcomes be discounted at the same rate of 1.5%. The cost-consequence analysis[6] used as the basis for the manufacturer's model discounted "3% annually to 2008 for drug costs and 5% annually to 2008 for physicians and hospitals' fees." Exact methodology is unclear due to hard coding in the model. Additionally, QALYs have not been discounted despite the six-year time horizon, resulting in an underestimation of the ICUR.

CADTH Common Drug Review Reanalyses

The model provided by the manufacturer was insufficient to adequately estimate the cost-effectiveness of nitisinone in Canada. Due to the inadequacies of the submitted model highlighted in the limitations section above, CDR was unable to undertake reanalyses that would present a reasonable estimate of the cost-effectiveness of nitisinone.

The manufacturer was asked to provide a CUA that better aligned with the CADTH Economic Evaluation guidelines[10] but declined to do so.

Issues for Consideration

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 that may be associated with different costs due to the infrequency of their use.

Availability of other nitisinone products: MDK-Nitisinone received Health Canada approval based on the clinical studies for the reference product (Orfadin), and the results of a bioequivalence study demonstrating comparable pharmacokinetic profiles for MDK-Nitisinone and Orfadin in healthy volunteers. Other nitisinone products for the treatment of HT-1 have been approved by Health Canada, and are either under review by CADTH or expected to be reviewed by CADTH in the near future.

Unknown pricing agreements for comparators: The manufacturer based its assertion that its brand of nitisinone is 1.7 times less expensive than the original brand on the market on historical costs through Health Canada's Special Access Programme for marketed drugs for compassionate use from 1997 through 2008, financed by the Quebec Ministère de la Santé et des Services sociaux.[4] It is not known whether patient access schemes or discounts have been negotiated for the original branded product more recently.

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 experiencing fewer hospitalizations, neurological crises, liver transplants, and other complications, compared with best supportive care (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, which left patients concerned about the efficacy of the treatment they were receiving. While the patient group noted that although 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, rather than travelling — sometimes long distances — to hospitals.

Conclusions

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

Two other nitisinone products have recently been approved for use by Health Canada; one has recently been reviewed by CADTH, while the other is expected to be submitted to CADTH in the near future. MDK-Nitisinone received Health Canada approval based on the clinical studies for the reference product (Orfadin) and the results of a bioequivalence study demonstrating comparable pharmacokinetic profiles for MDK-Nitisinone and Orfadin in healthy volunteers. Given the clinical data indicate these treatments are comparable, whether MDK-Nitisinone delivers value for money will depend on its cost relative to the cost of other nitisinone products.

Appendix 1: Cost Comparison

The comparators presented in the Table 3 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 Table 3, and as such, may not represent the actual costs to public drug plans.

Table 3: CDR Cost Comparison for Hereditary Tyrosinemia Type-1

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Nitisinone (MDK-Nitisinone)	2 mg 5 mg 10 mg 20 mg	Capsule	14.7833[a] 34.1833[a] 64.7000[a] 128.1000[a]	1 mg/kg per day in two divided doses, may be increased to a maximum of 2 mg/kg per day	First year of life: $18,998[b] Second year: $27,540[b] Increases thereafter with weight. Cost per year for: 50 kg adult: $119,416 75 kg adult: $179,124
Nitisinone (Orfadin)	2 mg 5 mg 10 mg 20 mg	Capsule	Currently under review by CDR	1 mg/kg per day in two divided doses, may be increased to a maximum of 2 mg/kg per day	Not publicly available
Nitisinone (Nitisinone tablets)	2 mg 5 mg 10 mg	Tablet	Approved by Health Canada	1 mg/kg per day in two divided doses, may be increased to a maximum of 2 mg/kg per day	Not publicly available

CDR = CADTH Common Drug Review.
Note: The manufacturer cites prices for Orfadin brand capsules as follows: $25.00 for 2 mg, $57.00 for 5 mg, and $108.00 for 10 mg, but no source is provided.
[a] Manufacturer's submitted price.
[b] Derived using median weight by month of age; World Health Organization growth charts for Canada 0 to 24 months. Assumes treatment initiated at two weeks of age. Some daily doses are not equally divided.[12]

Appendix 2: Summary of Key Outcomes

Table 4: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is MDK-Nitisinone Relative to Dietary Restriction Alone?

Nitisinone Plus Diet vs. Diet alone	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	Unknown cost per QALY, manufacturer's submission inadequate for appropriate estimation or re-estimation by CDR					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

Appendix 3: Additional Information

Table 5: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	The manufacturer's model is unconventional in nature and does not adhere to best practices. Many outcomes of relevance not considered. Difficult to track calculations, sources not always referenced, and model is mostly hard-coded rather than calculated from existing inputs. Potential double counting could not be checked due to aggregate costing and hard-coded inputs.		
Was the material included (content) sufficient?			X
Comments	Model was not flexible, and did not allow CADTH to appropriately consider the cost-effectiveness of MDK-Nitisinone. CDR requested that the manufacturer provide a pharmacoeconomic submission that was better aligned with the CADTH Economic Evaluation guidelines; the manufacturer declined to do so.		
Was the submission well organized and was information easy to locate?			X
Comments	Sources and methods of calculation were often unclear, discrepancies between the different hard-coded inputs within the model in terms of disaggregated costs.		

CDR = CADTH Common Drug Review.

Table 6: 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

CDR = CADTH Common Drug Review.

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

The following Health Technology Assessment agencies have reviewed nitisinone (Orfadin) for treatment of patients with HT-1: Quebec's Institut national d'excellence en santé et en services sociaux (INESSS),[13] Australia's Pharmaceutical Benefits Advisory Committee (PBAC),[14,15] and France's Haute Autorité de Santé (HAS).[16] HAS and INESSS recommended that nitisinone should be listed for the indications and at the dosages requested. PBAC recommended that nitisinone not be listed on the basis of uncertain and unacceptably high cost-effectiveness.

No publicly available documentation was found to indicate these jurisdictions have evaluated MDK-Nitisinone.

Appendix 5: Reviewer Worksheets

Data sources used in the manufacturer's economic analysis can be found in Table 7.

Table 7: Data Sources

Data Input	Description of Data Source	Comment*
Efficacy	Drug efficacy from Larochelle et al. (2012) [8] as reported in Simoncelli et al. (2015),[6] in which 41 newborns who received nitisinone within the first month of life were followed for a mean of 6.2 years.	Newborns who are not identified and treated within 30 days will have more adverse outcomes than those used to inform the model, which limits generalizability in patients not treated within first 30 days.
Natural history	Natural History from Larochelle et al.[8] as reported in Simoncelli et al. (2015),[6] in which a historical cohort of patients with HT-1 who did not receive nitisinone were followed for a mean of 12.6 years. Despite a high mortality rate, particularly prior to transplant and associated with transplant reported by Simoncelli et al. (2015), the manufacturer did not incorporate mortality into their analysis.	Despite the high mortality rate prior to transplant and associated with transplant reported by Simoncelli et al.for patients with HT-1 on dietary restriction only, the manufacturer did not incorporate mortality into their analysis.
Utilities	From Woo et al. (2012)[9]	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 HUI-3. Feedback from the clinical expert consulted by CADTH suggested utility values for infection with chronic hepatitis C virus may 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	From Simoncelli et al. (2015),[6] included only in aggregate form in the manufacturer's model, incorporated into cost per patient-year of non-nitisinone medical and hospitalization costs.	This aggregated form does not allow for testing of alternate rates or scenarios to determine the robustness of results.
Mortality	Not incorporated.	May bias the results against nitisinone.
Costs and resource use		
Drug	Nitisinone based on manufacturer's submitted price. Price based on Orfadin cost divided by 1.7. Other drug costs, such as anti-rejection therapies, are only incorporated in aggregate form. Nutritional supplement costs were not incorporated.	A 2016 price per Orfadin brand capsule is listed in Table 35 of the manufacturer's submission; however the source of this value is unclear. Aggregate costing does not allow for scenario analysis exploration or detecting double counting or errors.
Administration	Pharmaceutical services defined as prescription drug fees from Simoncelli et al. (2015).[6]	Inclusion of markup and dispensing fees is not appropriate for a submission to CDR.
Events	Simoncelli et al. (2015)[6] for direct hospital and drug costs based on RAMQ (Rx, medical visits, surgeries, and procedures) and CHU-Justine as well as MED-ECHO (audiologists or genetic counsellors in hospitals or outpatient clinic); Quebec hospital association was used for ED visits.	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*
Health state	Based on treatment allocation.	Inappropriate. Should be based on possible outcomes of disease, with probabilities of entering, remaining, and/or exiting each state dependent on treatment allocation.

CDR = CADTH Common Drug Review; CHU-Justine = Centre hospitalier universitaire Sainte-Justine; ED = emergency department; HT-1 = hereditary tyrosinemia type 1; HUI-3 = Health Utilities Index Mark 3; MED-ECHO = Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière; RAMQ = Régie de l'assurance maladie du Québec.

Table 8: 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.
Health state definitions dependent on treatment.	Not appropriate. While treatment assignment will often increase or decrease a patient's likelihood of spending time in a given health state, it is inappropriate to define a health state by the treatment assigned.
As the early-nitisinone-treated group were followed for a mean of 6.2 years (compared with 19.2 years for the non-nitisinone group), a time horizon of 6 years was used.	A 6-year time horizon is not appropriate 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 likely biases the results in favour of nitisinone, as incremental costs can be expected to increase with patient weight over time, while incremental QALYs gained per year are likely to remain similar or decrease.
Mortality not included.	Inappropriate. When treated with dietary restriction alone, HT-1 is associated with high mortality rates.[17] Additionally, there is a significant risk of death associated with liver transplants.
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.
Clinical effectiveness is based on a single study from Quebec.	A systematic review of available studies is not reported. Concerns regarding the transferability of the Larochelle et al. (2012) cohort were raised with the clinical expert consulted by CADTH, who suggested patients outside of Quebec may be harder to identify due to lower prevalence and differences in screening programs across Canada as well as differences in natural history. Additionally, the assumptions in the model structure (e.g., no mortality in either treatment group, 100% of patients receiving a liver transplant after two years if treated with dietary restriction alone) are not aligned with the results of Larochelle et al. (2012).
A description of specific resources and units is not provided due to reliance on Simoncelli (2010) and 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 assumes all no nitisinone patients receive a liver transplant at age 2. As liver transplant is incorporated into the aggregate cost per patient-year of the no nitisinone group, it is not possible to test the effect of this assumption on costs.

HT-1 = hereditary tyrosinemia type 1; QALY = quality-adjusted life-year.

Manufacturer's Results

As noted in the main body of the report, costs were calculated using the total of average health care resource costs (Table 9) and average nitisinone costs per patient-year for each treatment group, multiplied by six (see Table 10).

Table 9: Manufacturer's Base Case Health Resource Costs, Excluding Nitisinone

Costs per Patient-Year	No Nitisinone ($)	Nitisinone ($)
Global hospitalization (including PICU)	13,847	757
Paramedical visits	105	5
Medical services	3,311	858
Pharmaceutical services	4,129	162
TOTAL	21,392	1,782

PICU = pediatric intensive care unit.
Source: Table 33 of the Manufacturer's cost-consequence analysis, Pharmacoeconomic submission.[4]

Table 10: Manufacturer's Base Case Total Costs

Treatment	Estimated Costs of Nitisinone	Other Health Care Resources	Total Costs per Patient-Year	Total Costs Over Six Years ($)
No nitisinone	0	21,392	21,392	128,352
Nitisinone	34,076	1,782	35,858	215,151

CUA = cost-utility analysis.
Source: Table 2 of the Manufacturer's CUA Addendum, Pharmacoeconomic submission.[4]

References

1. MDK-Nitisinone: 2 mg, 5 mg, 10 mg capsules [product monograph]. Saint-Hubert (QC): MendeliKABS Inc.; 2016 Sep 19.
2. CDR submission:MDK-nitisinone, 2 mg, 5 mg, 10 mg capsules. Company: MendeliKABS Inc. [**CONFIDENTIAL** manufacturer's submission]. Saint-Hubert (QC): MendeliKABS Inc.; 2017 Oct 12.
3. MendeliKABS Inc. response to January 9th, 2018 CDR request for additional information on SR0538 MDK-Nitisinone (2 mg, 5 mg, 10 mg and 20 mg capsules) CDR review **[CONFIDENTIAL** additional manufacturer's information]. St-Hubert (QC): MendeliKABS; 2018 Jan 11.
4. Pharmacoeconomic evaluation. In: CDR submission: MDK-nitisinone, 2 mg, 5 mg, 10 mg and 20 mg capsules. Company: MendeliKABS Inc. [**CONFIDENTIAL** manufacturer's submission]. Saint-Hubert (QC): MendeliKABS; 2017 Oct 12.
5. Simoncelli M. Évaluation des coûts de traitement de la tryrosinemie de type I [Internet]. Montreal: Université de Montréal; 2010. [cited 2017 Dec 15]. Available from: https://papyrus.bib.umontreal.ca/xmlui/bitstream/handle/1866/4815/Simoncelli_Marieve_2010_memoire.pdf?sequence=2&isAllowed=y Master's thesis.
6. Simoncelli M, Samson J, Bussieres JF, Lacroix J, Dorais M, Battista R, et al. Cost-consequence analysis of nitisinone for treatment of tyrosinemia type I. Can J Hosp Pharm [Internet]. 2015 May [cited 2017 Nov 20];68(3):210-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4485508
7. Inherited Metabolic Disease (IMD) Program. List of disorders, covered drugs, supplements and specialty foods: effective March, 2016 [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2016. [cited 2017 Dec 18]. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/funded_drug/pdf/list_food.pdf
8. Larochelle J, Alvarez F, Bussieres JF, Chevalier I, Dallaire L, Dubois J, et al. Effect of nitisinone (NTBC) treatment on the clinical course of hepatorenal tyrosinemia in Quebec. Mol Genet Metab. 2012 Sep;107(1-2):49-54.
9. Woo G, Tomlinson G, Yim C, Lilly L, Therapondos G, Wong DK, et al. Health state utilities and quality of life in patients with hepatitis B. Can J Gastroenterol [Internet]. 2012 Jul [cited 2017 Nov 20];26(7):445-51. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3395446
10. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 4th ed. Ottawa: CADTH; 2017. [cited 2018 Jan 2]. Available from: https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf
11. Drugs for chronic hepatitis C infection: cost-effectiveness analysis [Internet]. Ottawa: CADTH; 2016 Jan. [cited 2017 Nov 23]. (CADTH Therapeutic review; vol. 3, no. 1c). Available from: https://www.cadth.ca/sites/default/files/pdf/TR0008_Cost-Effectiveness_Report.pdf
12. WHO growth charts set 1 [Internet]. Toronto: Dietitians of Canada; 2014 Mar. [cited 2017 Dec 18]. Available from: https://www.dietitians.ca/dietitians-views/prenatal-and-infant/who-growth-charts/who-growth-charts-set-1.aspx
13. Institut national d'excellence en santé, et en services sociaux (INESSS). Orfadin^{MC} - Tyrosinémie héréditaire de type 1: 2 mg, 5 mg, 10 mg et 20 mg capsules [Internet]. Québec (QC): INESSS; 2017 Aug. [cited 2017 Nov 21]. Available from: http://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Aout_2017/Orfadin_2017_08.pdf
14. Pharmaceutical Benefit Advisory Committee. Public summary document: Nitisinone, 2 mg, 5 mg, 10 mg capsule, Orfadin® [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2014 Nov. [cited 2017 Nov 21]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2014-11/files/nitisinone-psd-11-2014.pdf
15. Pharmaceutical Benefit Advisory Committee. Public summary document: Nitisinone, 2 mg, 5 mg, 10 mg capsule, Orfadin® [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2015 Jul. [cited 2017 Nov 21]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-07/files/nitisinone-psd-july-2015.pdf
16. Transparency Committee. Orfadin 2 mg, 5 mg, 10 mg, capsules [Internet]. Saint-Denis (FR): Haute Autorité de Santé; 2007 Jun 20. [cited 2017 Nov 21]. Available from: https://www.has-sante.fr/portail/upload/docs/application/pdf/2010-11/orfadin_ct_4515.pdf
17. Van Spronsen FJ, Thomasse Y, Smit GP, Leonard JV, Clayton PT, Fidler V, et al. Hereditary tyrosinemia type I: a new clinical classification with difference in prognosis on dietary treatment. Hepatology. 1994 Nov;20(5):1187-91.