CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

GLUCAGON NASAL POWDER (BAQSIMI)

(Eli Lilly Canada Inc.)

Indication: For the treatment of severe hypoglycemic reactions which may occur in the management of insulin treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates.

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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.

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

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Abbreviations

CDR	CADTH Common Drug Review
CUA	cost-utility analysis
ED	emergency department
EMS	emergency medical service
HC	Health Canada
ICUR	incremental cost-utility ratio
IM	intramuscular
QALM	quality-adjusted life-minute
QALY	quality-adjusted life-year
SH	severe hypoglycemia
WTP	willingness to pay

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Glucagon nasal powder (Baqsimi)
Study question	What is the cost-effectiveness of nasal glucagon compared with IM glucagon when used by caregivers and acquaintances or bystanders in non-medical settings for the treatment of severe hypoglycemic events, when impaired consciousness precludes treatment with oral carbohydrates?
Type of economic evaluation	CUA
Target population	Insulin-treated patients with diabetes mellitus who experience SH reactions, when impaired consciousness precludes oral carbohydrates
Treatment	IN glucagon
Outcome	QALYs
Comparator	IM glucagon
Perspective	Canadian publicly funded health care payer
Time horizon	One year
Results for base case	IN glucagon dominated IM glucagon
Key limitations	CADTH identified several key limitations with the submitted analysis. • Since patients are dispensed treatment in advance of an event, it is possible that the drug will expire before needed. The sponsor did not capture patients who do not experience an SH event or use glucagon for an SH event prior to drug expiry. This may be a substantial proportion of patients. The reported SH risk in the literature ranges from 0.3% to 40.4%. According to the clinical expert consulted by CADTH, generally 1% to 5% of insulin-dependent patients with diabetes are expected to experience an SH event in a year, although observed SH rates may vary by population. • The submitted model did not consider that clinical management may intensify and caregiver education may increase in response to multiple SH events which may reduce SH risk and increase the caregivers' likelihood of attempting glucagon treatment and doing so successfully. This would reduce the cost-effectiveness of IN glucagon compared with IM glucagon. • The sponsor's assumption that bystanders to an SH event are twice as likely to attempt treatment with IN glucagon compared with IM glucagon was not supported by evidence. • The probability of a successful IM glucagon administration was based on a mannequin study that did not consider that administration of a partial dose of IM glucagon is also effective, potentially underestimating the probability of a successful IM glucagon administration and thus favouring IN glucagon. • The modelled relationship between successful glucagon treatment and a prevented EMS call, ED visit, and inpatient admission is uncertain as these health care resources may be accessed for multiple reasons independent of an unsuccessful glucagon treatment for an SH event. • The disutility associated with an intensive care unit admission was inappropriately used to model the QALY reduction associated with an inpatient admission. Disutility associated with an inpatient admission was inappropriately used to model the QALY reduction associated with an ED visit. The disutilities were also inappropriately applied over a year-long time horizon, longer than the 30 days used in the source study. • The cost of EMS is uncertain and may be overestimated as EMS responses that do not lead to patient transportations to the ED were not considered in the calculation of the cost.

CDR estimate	• CADTH addressed some of the limitations by incorporating the costs of patients who do not experience an SH event or do not have glucagon available during an SH event, and by appropriately applying disutilities. • In the CADTH base case, IN glucagon dominated IM glucagon, generating an additional 0.000011 QALYs (equivalent to six QALMs) at a reduced total cost ($123). • Considerable uncertainty remains given the structural and parametric limitations, especially regarding the modelling of SH risk, the impact of the IN formulation on the magnitude of the increased probability of glucagon treatment attempt and success, and the health utility gains attributable to a successful glucagon treatment. The above parametric assumptions were explored in sensitivity analyses where the ICUR ranged from indicating that IN glucagon is dominant to it having an ICUR of $314.2 million per QALY gained. The model is highly sensitive to changes in inputs and assumptions as the estimated incremental QALYs are small (ranging from less than one QALM to six QALMs in CADTH reanalyses). This small QALY benefit is in contrast to a more substantive difference in the drug acquisition costs with IM glucagon costing $93 per unit and IN glucagon costing $132 per unit. • Additionally, CADTH explored a scenario analysis where the annual SH risk was 3%, given feedback from the clinical expert consulted. Under this scenario, a price reduction of more than 9% would be required for IN glucagon to be cost-effective at a threshold of $50,000 per QALY gained.

CDR = CADTH Common Drug Review; CUA = cost-utility analysis; ED = emergency department; EMS = emergency medical service; ICUR = incremental cost-utility ratio; IM = intramuscular; IN = intranasal; QALM = quality-adjusted life-minute; QALY = quality-adjusted life-year; SH = severe hypoglycemia.

Drug	Glucagon nasal powder (Baqsimi)
Indication	For the treatment of severe hypoglycemic reactions which may occur in the management of insulin treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates
Reimbursement request	As per indication
Dosage form	Single use nasal dosing device containing 3 mg of glucagon powder
NOC date	September 25, 2019
Sponsor	Eli Lilly Canada Inc.

Executive Summary

Background

Glucagon nasal powder (Baqsimi) is indicated for the treatment of severe hypoglycemia (SH) reactions that may occur in the management of insulin-treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates. It is supplied as a single use nasal dosing device containing a 3 mg single dose at a price of $131.60. The recommended dose is one spray in either nostril.[1] According to the clinical expert consulted by CADTH, the treatment is prescribed to patients in preparation for an emergency involving the Health Canada (HC)-indicated SH event.

The sponsor submitted a cost-utility analysis (CUA) based on a decision tree comparing the availability of intranasal glucagon with intramuscular (IM) glucagon for a bystander who noticed a patient experiencing the HC-indicated SH event.[2] The sponsor modelled costs and health consequences arising from a single SH event managed with a single glucagon treatment over a one-year time horizon. The SH event was assumed to be witnessed by a bystander (either a caregiver or an acquaintance) who may decide to administer intranasal or IM glucagon in response. Whether glucagon treatment was attempted and was successful determined related events and health care resource use. A range of events of varying severity were captured, including potential resolution of an SH event without health care resource use; SH event resolution requiring emergency medical service (EMS), emergency department (ED) visit, or inpatient admission; and SH event follow-up care. A bystander with access to intranasal was assumed to be twice as likely to attempt administration of intranasal glucagon to the patient experiencing an SH event compared with attempting administration with IM glucagon. The probabilities of a successful full dose administration for intranasal and IM glucagon were based on the sponsor's treatment performance study of caregivers and other bystanders to a simulated SH event.[3] The efficacy of successfully administered intranasal and IM glucagon was assumed to be equivalent, based on the sponsor's claim that noninferior efficacy was demonstrated in the sponsor's IGBC and IGBB studies.[2,4,5] Other parameters were based on Canadian sources[6-11] and were assumed to be the same between the intranasal glucagon and IM glucagon. Mortality and adverse events were not modelled.

In the sponsor's base case, intranasal glucagon was associated with 0.001 incremental quality-adjusted life-years (QALYs) and cost savings of $382 compared with IM glucagon. At

a willingness-to-pay threshold of $50,000 per QALY, intranasal glucagon had a 67% probability of being cost-effective compared with IM glucagon.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several limitations with the sponsor's model.

The sponsor did not fully capture the costs and consequences of glucagon prescription in the proportion of the population that does not experience an SH event or the impact of an SH event where glucagon is not accessible. As emergency-use glucagon kits are prescribed in preparation for a potential future SH event, a proportion of the population who are dispensed glucagon may not use it before the drug expires either because an SH event did not occur or the kit was inaccessible during an SH event. The costs associated with this proportion of patients may be substantial as the reported SH risk in the literature ranges from 0.3%[12] to 40.4%.[13] According to the clinical expert consulted by CADTH, 1% to 5% of insulin-dependent patients with diabetes are expected to experience an SH event each year, and although observed SH rates may vary by population, the annual SH risk is not expected to be as high as 40.4%. Additionally, most SH events occur nocturnally[14] and patients may not always have the glucagon kit with them at the time of an SH event. Furthermore, the patient input received by CADTH indicated that patients usually leave the glucagon kit at home, and although the kit may be available in some school and work settings, administration of glucagon by a bystander may not be permitted. Collectively, the omission of these possibilities overestimate the health benefits and the avoided resource use associated with a glucagon prescription.

The submitted model structure also did not capture multiple SH incidences and the associated long-term potential changes in the management of the condition. According to the clinical expert consulted by CADTH, patients who experience an SH event are more likely to experience future SH events. Multiple events of SH occurring within a year can also be found in observational studies.[13,15] In these patients, diabetes may be managed more intensively and lead to a long-term reduction in SH risk and/or increase a caregiver's likelihood of attempting glucagon treatment and the probability of treatment success in a future SH event. Such changes may reduce the cost-effectiveness of intranasal glucagon compared with IM glucagon.

The impact of the route of administration on a bystander's probability of attempting glucagon treatment was uncertain. Although the sponsor listed potential reasons why bystanders may be more likely attempt treatment with intranasal glucagon compared with IM glucagon, they did not provide any specific evidence as to why the probability of a treatment attempt would be double for intranasal glucagon. Consequently, the magnitude of the improvement in the likelihood of a glucagon treatment attempt with intranasal glucagon compared to IM glucagon is unknown.

The impact of route of administration on the probability of successful glucagon administration was also uncertain. The sponsor based the probabilities of treatment success for intranasal and IM glucagon on a mannequin-based treatment performance study[3] that CADTH clinical reviewers concluded had uncertain generalizability to real-world conditions and users. The study also did not account for successful partial dose administration of IM glucagon. As the clinical expert consulted by CADTH indicated that less than a full dose injection of glucagon may also be effective at resolving an SH event, especially for pediatric patients who only require half of a dose,[16,17] a larger proportion of the IM glucagon

administrations could be successful if partial dose administration is considered. As such, the probability of successful IM glucagon treatment may be underestimated and thus favour intranasal glucagon in the analysis.

Furthermore, it is also uncertain how successful treatment impacts health care resource use. Although the sponsor's model structure links successful glucagon treatment to a prevented EMS call, ED visit (whether transported by EMS or by oneself), and inpatient admission, the strength of the correlation is unclear as the use of these additional health care resources may be due to a multitude of reasons (e.g., a motor vehicle accident caused by an SH event). The clinical expert consulted by CADTH also expressed uncertainty in the strength of the modelled relationship. In addition, the observational nature of data sources and their generalizability to the type of SH event specific to the HC-indicated population raises further uncertainty.

The sponsor inappropriately applied disutility values from a pediatric epilepsy modelling study.[18] The disutility value associated with an intensive care unit admission was used to model the QALY reduction associated with an inpatient admission, and the disutility value associated with an inpatient admission was used to model the QALY reduction associated with an ED visit. While the disutility values were only applied over a 30-day period in the source study,[18] the values were inappropriately applied over the one-year time horizon in the submitted model. These limitations increased the utility impact of hospital admissions and ED visits and favoured intranasal glucagon.

Finally, the cost of EMS may be overestimated and favour intranasal glucagon, as EMS responses that do not result in patient transportations were not considered in the calculation of the cost.

CADTH attempted to address some of the limitations by considering the costs and consequences of glucagon prescriptions in the patient population who do not experience an SH event or lack glucagon access during an SH event and appropriately applying disutility values associated with health care resource use.

Conclusions

In the CADTH base case, intranasal glucagon dominated IM glucagon as it was associated with an additional 0.000011 QALYs (equivalent to six QALMs) at a reduced cost. Considerable uncertainty remains in this analysis given the identified limitations with the model structure and parameters, especially regarding the modelling of SH risk, the impact of the intranasal formulation on the magnitude of increased glucagon treatment attempt and success, and the health utility gains attributable to a successful glucagon treatment.

The incremental cost-utility ratio (ICUR) ranged from intranasal glucagon being dominant to $314.2 million per QALY gained in the sensitivity analyses. As the estimated incremental QALY benefit in the CADTH reanalyses ranged from less than 0.000000 QALYs to 0.000011 QALYs (equivalent to from less than one QALM to six QALMs), the results of the analysis are highly sensitive to changes in model inputs and assumptions. This small QALY benefit associated with intranasal glucagon is in contrast to a more substantive difference in drug acquisition costs, with IM glucagon costing $93 per unit and intranasal glucagon costing $132 per unit.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a CUA comparing intranasal glucagon to IM glucagon for insulin-treated patients with diabetes mellitus who experience an SH event, when impaired consciousness precludes oral carbohydrates.[2] To capture the costs and consequences associated with this decision problem over the time horizon of one year, the sponsor used a decision tree to model a series of events that stem from a single SH event that was assumed to be witnessed by a bystander (either a caregiver or an acquaintance) who may decide to administer a single dose of intranasal or IM glucagon (Figure 1). Whether or not the glucagon treatment was attempted and whether or not it was successfully administered determined which modelled health care resource use events were triggered as the consequence. A range of events of varying severity were captured: potential resolution of an SH event without health care resource use; resolution via EMS, ED visit, or inpatient stay; and follow-up care.

A bystander witnessing an SH event with access to intranasal glucagon was assumed, without supportive clinical evidence, to be twice as likely to attempt administration of intranasal glucagon compared to IM glucagon. The probability of a successful administration for intranasal and IM glucagon was based on the sponsor's mannequin-based treatment performance study of caregivers and other bystanders witnessing a simulated SH event (see Yale et al. [2017][3] and similar studies reviewed in the accompanying CADTH clinical report).[3] The parameters of the probability of glucagon administration attempt and the probability of successful glucagon administration comprised key efficacy parameters in the model as the efficacies of the attempted and correctly administered intranasal and IM glucagon were assumed to be equivalent based on the sponsor's claim that noninferior efficacy was demonstrated in the sponsor's IGBC and IGBB trials.[2,4,5] Other patient flow parameters were based on Canadian prehospital and ED chart review studies and were assumed to be the same between the intranasal glucagon and IM glucagon branches of the decision tree.[9-11] Drug and health care resource use costs were based on Ontario provincial sources,[6-8] except for the EMS cost, which was derived from statistics based on the 2017 Toronto Paramedic Services report.[19] Mortality and adverse events were not modelled.

Sponsor's Base Case

The sponsor's base-case results are presented in Table 2. Intranasal glucagon was associated with 0.001 incremental QALYs and cost savings of $382, dominating IM glucagon in terms of cost-effectiveness. At a willingness-to-pay threshold of $50,000 per QALY, intranasal glucagon had a 67% probability of being cost-effective compared with IM glucagon.

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

Comparator	Total costs ($)	Incremental cost ($)	Total QALYs[a]	Incremental QALYs	Incremental cost per QALY ($)
IM glucagon	2,117		–0.004		
IN glucagon	1,735	–382	–0.003	0.001	Dominant

IM = intramuscular; IN = intranasal; QALY = quality-adjusted life-year.

[a] Reported total QALYs may be negative as the sponsor did not model base health utilities and the results only reflect health utility decrements.

Source: Sponsor's pharmacoeconomic submission.[2]

Summary of Sponsor's Sensitivity Analyses

The sponsor conducted sensitivity analyses for treatment attempt, treatment success, and health care resource use parameters. Cost-effectiveness results were not sensitive to the changes in these parameters as all of the sponsor's sensitivity analyses reported that intranasal glucagon dominated IM glucagon.

Limitations of Sponsor's Submission

The following limitations were identified with the sponsor's pharmacoeconomic submission.

- **Model structure does not fully capture the costs and consequences of glucagon prescription in the population that does not experience SH or in SH events where glucagon is not accessible:** An appropriate model structure for an economic evaluation should capture the relevant and meaningful aspects of the decision problem.[20] For emergency-use products such as intranasal and IM glucagon that are prescribed in preparation for an emergency situation, the cost of the prescription to the public health care payer when the emergency situation (i.e., SH event with impaired consciousness that precludes oral carbohydrate treatment) does not occur or does not allow the use of the product (e.g., SH event is not identified by any bystander or is identified but product is not accessible) should be captured. A wide range of estimated SH risk is reported in the literature, from 0.3% to 3.3% reported in trials for second-line therapies in type 2 diabetes[12] to 40.4% in a Canadian survey study,[13] highlighting the uncertainty associated with this parameter. According to the clinical expert consulted by CADTH, 1% to 5% of insulin-dependent patients with diabetes are expected to experience an SH event each year, and although observed SH rates may vary by population, annual SH risk is not expected to be as high as 40.4%. The majority of the SH events also occur nocturnally,[14] decreasing the probability that an SH event would be noticed by a bystander. The sponsor also effectively assumed that glucagon would be available in all SH events. If an SH event is noticed by the bystander, it is also unknown whether the bystander would be able to access a glucagon product as the clinical expert consulted by CADTH indicated that it is unlikely that the patient would always have the glucagon kit with them. The patient input received by CADTH also indicated that the majority of patients leave their glucagon kit at home, and although some may be available at school and work settings, bystanders in some settings may not be allowed to administer glucagon. Based on these considerations, the majority of patients who are dispensed glucagon are unlikely to be in the specific situation modelled by the sponsor. The sponsor's model inappropriately began at the moment of an indicated SH event, effectively assuming that all patients who are dispensed intranasal or IM glucagon experience the indicated SH event that would be noticed by bystanders who have access to the patient's prescribed glucagon. This

structure does not capture the full costs and consequences associated with glucagon prescription and favours intranasal glucagon. CADTH attempted to capture these additional costs in its reanalysis.

- **Model structure does not capture the patient experience of multiple SH events and long-term disease management process:** According to the clinical expert consulted by CADTH, patients who experience an SH event are more likely to experience further SH events. Results from observational studies report multiple annual incidences of SH in some patients.[13,15] The sponsor's model was unable to capture the costs and consequences of such frequent SH events. The model also did not capture the long-term clinical management that may follow frequent SH events. Diabetes in such patients may be managed more intensively via pharmacological, educational, and other interventions such as continuous glucose monitoring to reduce future SH risk and better prepare caregivers to respond to an SH event. The latter outcome may increase caregivers' likelihood of glucagon treatment attempts and glucagon treatment success regardless of the formulation of glucagon, potentially decreasing the differences in successful glucagon treatment between intranasal and IM glucagon. CADTH explored reduced differences in caregiver treatment attempts and treatment success probabilities between intranasal and IM glucagon as sensitivity analyses.
- **Uncertain impact on a bystander's probability of attempting glucagon treatment:** Although the sponsor listed potential reasons why bystanders may be more likely to attempt treatment with intranasal glucagon compared with IM glucagon, the specific size of the improvement (i.e., doubling of attempt) was not supported by any evidence. Consequently, it is unknown to what extent intranasal glucagon would improve the probability of successful glucagon treatment by increasing the probability of a treatment attempt.
- **Uncertain impact on the probability of a successful glucagon administration:** The sponsor's model relied on a mannequin-based treatment performance study[3] to inform the probability of a successful glucagon treatment. The study used an overly restrictive definition of treatment success as the definition only considered full dose injections as successes. The clinical expert consulted by CADTH indicated that less than a full dose of glucagon may also be effective at resolving an SH event, especially in the pediatric population who only require half of a dose based on the product monograph for the IM glucagon kit.[16,17] Furthermore, CADTH clinical reviewers concluded that although the evidence from mannequin-based studies suggests that successful administration of glucagon is more likely with intranasal delivery compared with IM delivery, generalizability to real-world conditions and users remains unclear. Collectively, these limitations may underestimate the probability of successful IM glucagon treatment and favour intranasal glucagon.
- **Uncertain impact of successful glucagon treatment on health care resource use:** The sponsor's model structure associated successful glucagon treatment with the prevention of health care resource use (i.e., EMS visits, ED visits, and inpatient admissions). However, as EMS visits, ED visits, and hospital admissions may be due to multifactorial reasons not exclusive to whether the HC-indicated SH event is successfully resolved (e.g., a motor vehicle accident caused by an SH event), it is unknown to what extent successful glucagon administration in the interval between an SH event and the arrival of EMS would impact further health care resource use. The clinical expert consulted by CADTH also expressed uncertainty regarding the proportion of patients who would avoid an EMS call, ED visit, or inpatient admission due to a successful glucagon administration. Furthermore, as the probability of an EMS call, ED visit, and hospital

admission were informed by observational studies that did not specifically study the population that experienced a HC-indicated SH event, it is uncertain whether the modelled probabilities reflect EMS calls, ED visits, and hospital admissions for the HC-indicated population.

- **Inappropriate application of disutility values associated with health care resource use:** The sponsor inappropriately applied disutility values cited in the Lee et al. (2013) study[18] that were associated with more intensive health care resource use. The disutility value associated with an intensive care unit admission was used to model the reduction in QALYs associated with an inpatient admission, and the disutility value associated with an inpatient admission was used to model the reduction in QALYs associated with an ED visit. Although the study applied the disutility values to a 30-day period,[18] the sponsor effectively applied the disutilities over the one-year time horizon. Collectively, these limitations increased the utility impact of hospital admissions and ED visits, favouring intranasal glucagon. Furthermore, the appropriateness of the sponsor's data source for disutility was also unknown due to the lack of information regarding the methodological validity of the proprietary disutility elicitation study that informed the disutility values in the Lee et al. (2013) study,[18] and the unknown generalizability of the disutility values elicited for pediatric epilepsy to the HC-indicated population (i.e., the treatment of severe hypoglycemic reactions in patients with insulin-treated diabetes mellitus).

- **Uncertain cost of EMS:** In the absence of accurate and detailed EMS costing information, the sponsor used an approach recommended in the CADTH costing guidance,[21] whereby the annual gross operating budget for a paramedic service was divided by the number of patients transported in the year. This estimate may overestimate the cost of EMS and favour intranasal glucagon, as not all EMS responses result in patient transportation to hospital. For example, in 2018, the Toronto Paramedic Service reported 234,610 patient transportations from 380,000 EMS responses.[22] As such, CADTH explored a scenario with a lower EMS cost in its reanalysis.

CADTH CDR Reanalyses

To address several of the identified limitations, CADTH conducted the following reanalyses:

1a. The decision tree structure was expanded to account for patients who are dispensed glucagon yet do not experience an SH event (Figure 2). The sponsor's base case compared intranasal glucagon with IM glucagon on the basis that an SH event had happened, whereas in practice, glucagon is prescribed in preparation for a potential future SH event.

As patients who are dispensed a glucagon kit but do not encounter an SH event will not benefit from the kit, CADTH incorporated SH incidence rates from a Canadian retrospective observational survey study provided by the sponsor[15] (Table 3).This study captured the long-term incidence of SH events in patients with type 1 diabetes (mean duration of insulin therapy was 22.5 years) and type 2 diabetes (mean duration of insulin therapy was 10.2 years).[15] CADTH weighted this incidence data based on the prevalence of type 1 (9% of Canadians with diabetes) and type 2 diabetes (90% of Canadians with diabetes) reported by the Public Health Agency of Canada[23] to estimate that approximately 67.1% of insulin-dependent patients would experience at least one SH event in the long-term, and that SH events would occur in these patients at an average rate of 0.88 events per 18 months. Expressed in annual terms, this is approximately equivalent to 38.4% of the indicated population experiencing an SH event annually.

The time horizon of the analysis was also increased to 18 months to reflect the room temperature shelf life of a glucagon kit.[17] As effectively assumed in the sponsor's base case, bystanders were assumed to have access to glucagon in all SH events.

1b. Analysis 1a was conducted with the consideration that bystanders to an SH event do not always have access to glucagon. Due to lack of information regarding this parameter, bystanders were assumed to have access to glucagon in 50% of SH events.

1c. Analysis 1a was conducted with the assumption that bystanders were assumed to have access to glucagon in 10% of SH events.

2a. Appropriate disutility values were incorporated from the Lee et al. (2013) study.[18] The disutility value associated with an ED visit was applied for a seizure (more than 10 minutes long or multiple seizures) that does not lead to a hospital admission. The disutility value associated with an inpatient admission was applied for a seizure that leads to a hospital admission (Table 4).

2b. Analysis 2a was conducted with the disutility values applied for only 30 days, instead of being applied for the entirety of the time horizon as was done in the sponsor's submission.

Table 3: Parameter Inputs for CADTH Reanalysis 1a, 1b, and 1c

Parameter	Parameter value for T1D	Value for T2D
(1) Proportion of patients with a specific type of DM	9.1% = 9%/(90% + 9%)[a]	90.9% = 90%/(90% + 9%)[a]
(2) Proportion of patients who have experienced an SH event	71.3% = 144/202[b]	25.6% = 34/133[b]
Weighted proportion of patients with DM who have experienced an SH event	29.7%[c]	
(3) Average number of SH events in patients who have had an SH event	12.7 SH events per patient[b]	8.1 SH events per patient[b]
(4) Mean duration of insulin therapy	22.5 years[b]	10.2 years[b]
(5) Estimated average SH incidence rate more than 18 months	0.85 SH events/18 months[d]	1.19 SH events/18 months[d]
Weighted average SH incidence rate in patients with DM more than 18 months	1.16 SH events/18 months [e]	

DM = diabetes mellitus; SH = severe hypoglycemia; T1D = type 1 diabetes; T2D = type 2 diabetes.

[a] Public Health Agency of Canada (2017).[23] Denominator was composed of the proportion of Canadians with DM who have T1D (90%) and T2D (9%).

[b] Leiter et al. (2005).[15]

[c] Calculated as the sum product of (1) and (2).

[d] Calculated as a quotient of (3) divided by (4).

[e] Calculated as the sum product of (1) and (5).

Table 4: Parameter Inputs for CADTH Reanalysis 2a and 2b

Parameter	Sponsor's base case mean disutility (standard error)	CADTH reanalysis 2a and 2b mean disutility (standard error)
Disutility associated with an SH event that led to an ED visit	–0.0044 (0.00022)	–0.0014 (0.00007)
Disutility associated with an SH event that lead to inpatient admission	–0.0057 (0.00029)	–0.0044 (0.00022)

ED = emergency department; SH = severe hypoglycemia.

Source: Lee et al. (2013).[18]

In the CADTH base-case analysis, which incorporated reanalyses 1b and 2b, intranasal glucagon dominated IM glucagon as it was associated with 0.000011 incremental QALYs (approximately equivalent to six QALMs) and cost savings of $123 (Table 5).

Table 5: CADTH Reanalysis (Intranasal Glucagon Versus IM Glucagon)

	Analysis	Comparator	Cost ($)	QALYs[a]	QALMs[a]	ICUR ($ per QALY)
	Sponsor's base case	IN glucagon	1,735	–0.003072	–1,611	–
		IM glucagon	2,117	–0.003821	–2,004	–
		Incremental	–382	*0.000749*	393	IN glucagon dominant
1a	Cost of glucagon prescription in patients who do not experience an SH event during an SH event were incorporated	IN glucagon	893	–0.001463	–768	–
		IM glucagon	1,052	–0.001815	–952	–
		Incremental	*–160*	*0.000352*	184	IN glucagon dominant
1b	1a + glucagon is accessible to a bystander in 50% of SH events	IN glucagon	879	–0.001433	–751	–
		IM glucagon	1,008	–0.001722	–903	–
		Incremental	*–129*	*0.000289*	152	IN glucagon dominant
1c	1a + glucagon is accessible to a bystander in 10% of SH events	IN glucagon	865	–0.001409	–739	–
		IM glucagon	957	–0.001636	–858	–
		Incremental	*–92*	*0.000227*	119	IN glucagon dominant
2a	Appropriate disutility application based on Lee et al. (2013)[18]	IN glucagon	1,731	–0.001579	–828	–
		IM glucagon	2,119	–0.001922	–1,008	–
		Incremental	*–388*	*0.000343*	180	IN glucagon dominant
2b	2a + appropriate disutility application to one-month period, based on Lee et al. (2013)[18]	IN glucagon	1,736	–0.000132	–69	–
		IM glucagon	2,112	–0.000160	–84	–
		Incremental	*–375*	*0.000028*	15	IN glucagon dominant
	1b + 2b	**IN glucagon**	**879**	**–0.000061**	**–32**	**–**
		IM glucagon	**1,003**	**–0.000072**	**–38**	**–**
		Incremental	***–123***	***0.000011***	**6**	**IN glucagon dominant**

ICUR = incremental cost-utility ratio; IM = intramuscular; IN = intranasal; QALM = quality-adjusted life-minute; QALY = quality-adjusted life-year; SH = severe hypoglycemia.

[a] Reported QALYs or QALMs may be negative as the sponsor did not model base health utilities and the results only reflect health utility decrements.

Due to the uncertainties associated with some model parameters, the following sensitivity analyses were conducted:

S1. Given the uncertainty regarding the incidence of SH events in the literature (0.3% to 3.3% reported in trials for second-line therapies in type 2 diabetes,[12] and up to 40.4% in a Canadian survey study of patients with type 1 and type 2 diabetes[13]), CADTH conducted additional analyses exploring lower annual risks of SH. According to the clinical expert consulted by CADTH, the observed SH rates may vary by patient population and is generally estimated to be between 1% and 5%, but not as high as 40.4%.

S1a. An annual SH risk of 5% was assumed.

S1b. An annual SH risk of 4% was assumed.

S1c. An annual SH risk of 3% was assumed.

S1d. An annual SH risk of 2% was assumed.

S1e. An annual SH risk of 1% was assumed.

S2. Sensitivity analyses below were based on the base case annual SH incidence of approximately 38.4%:

S2a. The probability of attempting glucagon administration for intranasal glucagon was assumed to be 1.5 times compared with IM glucagon, based on the opinion of a clinical expert consulted by CADTH. Sensitivity analysis was used to explore this parameter as the expert expressed some uncertainty regarding this estimate.

S2b. The probability of attempting glucagon administration for intranasal glucagon was assumed to be the same as IM glucagon.

S2c. All caregivers attending to an SH event (caregivers are assumed to be 68% of bystanders) were assumed to have the probability of successful IM glucagon administration that is equal to the probability for intranasal glucagon. This was based on the assumption that caregivers may be appropriately trained and/or experienced (especially if this is not their first SH event), leading them to have a higher probability of a successful glucagon administration than the 13% as modelled by the sponsor. The improvement of intranasal glucagon on the probability of successful glucagon administration was preserved for the 32% of the bystander population who were acquaintances.

S2d. The probability of successful IM glucagon administration was assumed to be equal to that associated with intranasal glucagon for all bystanders.

S2e. Analysis S2c (all caregivers have the same probability of successful glucagon administration) + analysis S2a (the probability of glucagon treatment attempt with intranasal glucagon is 1.5 times the probability associated with IM glucagon).

S2f. Analysis S2c (all caregivers have the same probability of successful glucagon administration) + analysis S2b (intranasal glucagon and IM glucagon have the same probability of glucagon treatment attempt).

S2g. To explore the uncertain impact of health care resource use on quality of life, disutility values associated with an EMS visit, ED visit, and an inpatient admission were made equivalent to the disutility value of an SH event without an EMS or hospital visit.

S2h. A lower EMS cost estimate derived from the 2018 Toronto Paramedic Service report[22] was used ($566.97 compared to $948.26 in the base case). The gross operating budget ($215,449,500) was divided by the number of EMS responses (380,000) instead of the number of patient transportations.

S3a-h. Analyses S2a to S2h were repeated with the assumption of 5% annual SH risk.

S4a-h. Analyses S2a to S2h were repeated with the assumption of 3% annual SH risk, which is the average of the 1% to 5% annual SH risk estimated by the clinical expert consulted by CADTH.

Although intranasal glucagon was dominant over IM glucagon in some scenarios, the cost-effectiveness results were sensitive to changes in the assumed SH risk and the assumed benefit of intranasal glucagon in terms of increased probability of glucagon treatment attempt, probability of treatment success, and attributable health utility gains (Table 11). The ICUR ranged from intranasal glucagon being dominant up to approximately $54.6 million per QALY gained depending on the assumed SH risk, and concurrently revising other uncertain parameters further increased the ICUR up to approximately $314.2 million per QALY gained. This wide range of cost-effectiveness results can be attributed to the relatively small incremental health benefit reported in the analyses, which ranged from less than 0.000000 QALYs to 0.000011 QALYs (equivalent to less than one QALM to six QALMs) and made the ICUR sensitive to small changes in incremental costs and health benefits. At an annual SH risk of 3%, the average of the 1% to 5% annual SH risk estimated by the clinical expert consulted by CADTH, a price reduction of more than 9% would be required for intranasal glucagon to be cost-effective at a cost-effectiveness threshold of $50,000 per QALY gained (Table 12).

Issues for Consideration

- It is uncertain whether the smaller size of intranasal glucagon compared with IM glucagon would increase the portability of glucagon for patients and improve glucagon availability for a bystander during an SH event.
- Patients may obtain multiple glucagon kits to increase the availability of glucagon in the event of an SH episode. This was not considered in the economic analysis.
- The confidential nature of the negotiated effective price for pharmaceuticals means that the CDR is unable to assess the impact of potentially lower prices of comparators on the results. Thus, it is unknown if the reduced effective price of comparators would lead to differing conclusions than the current analysis based on list prices.

Patient Input

Input was received from the Type 1 Together patient group and Diabetes Canada. Both organizations conducted online surveys of Canadians with type 1 diabetes and their family members. Of the survey participants, 25% reported previous glucagon use. Among survey participants who completed the survey section regarding glucagon use for SH, 23% reported satisfaction with IM glucagon, and 19% reported dissatisfaction. Participants emphasized affordability, usability, and portability of glucagon kits as key considerations, and reported a preference for a pre-mixed or an inhaled glucagon that may increase other's willingness to administer treatment. This preference and the finding that 12% of participants consider glucagon preparation to be stressful or confusing support the assumption in the sponsor's pharmacoeconomic submission that intranasal glucagon would increase the likelihood of a bystander attempting glucagon treatment.

On the other hand, portability was an aspect that was not considered in the sponsor's pharmacoeconomic submission. Issues related to portability, such as inconvenient size of the IM glucagon kit and storing the drug at a stable temperature were reported. Participants reported that the glucagon kits were often left at home, although some patients had glucagon at school and at work settings. Of note, the Type 1 Together patient group reported that 68% of children attend a school in Canada that does not receive support for glucagon injections from school staff, and that the school staff are often forbidden from administering glucagon.

Conclusions

In the CADTH base case intranasal glucagon dominated IM glucagon as it was associated with an additional 0.000011 QALYs (equivalent to six QALMs) at a reduced cost. Considerable uncertainty remains in this analysis given the identified limitations with the model structure and parameters, especially regarding the modelling of SH risk, the impact of the intranasal formulation on the magnitude of increased glucagon treatment attempt and success, and the health utility gains attributable to successful glucagon treatment.

The ICUR ranged from intranasal glucagon being dominant to $314.2 million per QALY gained in the sensitivity analyses. As the estimated incremental health benefit in the CADTH reanalyses ranged from less than 0.000000 QALYs to 0.000011 QALYs (equivalent to from less than one QALM to six QALMs), the results of the analysis are highly sensitive to changes in model inputs and assumptions. This small QALY benefit is in contrast to a more substantive difference in drug acquisition costs with IM glucagon costing $93 per unit and intranasal glucagon costing $132 per unit.

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 sponsor 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 Table of Drugs for Severe Hypoglycemia in an Insulin-Treated Patient With Diabetes Mellitus When Impaired Consciousness Precludes Oral Carbohydrates[a]

Drug/ comparator	Strength	Dosage form	Price ($)	Recommended dose	Average treatment cost ($)
In a person without IV access					
Glucagon (BAQSIMI)	**3 mg (Single use)**	**Nasal powder for IN administration**	**131.6000[b]**	**3 mg IN**	**132**
(GlucaGen, generic)	1 mg (Single use)	Lyophilized powder for injection	92.6000	1 mg IM	93
In a person with IV access					
Dextrose (D50W)	D50W (50 mL, 1,000 mL, 1,250 mL, 2,000 mL IV solution)	IV fluid and nutrient replenisher	0.0700 per mL[c] 0.0109 per mL[d] 0.0700 per mL[d] 0.0085 per mL[d]	10 to 25 g (20 to 50 mL of D50W) of glucose should be given IV over 1 to 3 minutes[a]	4

CDR = CADTH Common Drug Review; D50W = dextrose 50% in water; IM = intramuscular; IN = intranasal.

Note: All prices do not include costs of product dispensing, dose preparation, or administration. The calculated doses are based on the product monograph where available. When multiple formulations were available, the least expensive type was used to calculate costs. All injected comparators are assumed to be used as single use vials with leftover product being wasted.

[a] 2018 Diabetes Canada Clinical Practice Guidelines.[24]

[b] Sponsor submitted price.[25]

[c] Association québécoise des pharmaciens propriétaires price based on IQVIA DeltaPA database (August 2019).[26]

[d] Wholesale acquisition price based on IQVIA DeltaPA database (August 2019).[26]

Appendix 2: Additional Information

Table 7: Submission Quality

	Yes/ good	Somewhat/ average	No/ poor
Are the methods and analysis clear and transparent?		X	
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?			X
Comments Reviewer to provide comments if checking “poor”	Submitted model structure did not substantially capture the costs and consequences associated with the decision problem as it did not consider patients who have never experienced an SH event prior to drug expiry, or those who do not have access to glucagon during an SH event.		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

SH = severe hypoglycemia.

Table 8: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CDR
☐ Adaptation of global model/Canadian model done by the sponsor
☒ Adaptation of global model/Canadian model done by a private consultant contracted by the sponsor
☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the sponsor
☐ 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.

CADTH

Appendix 3: Summary of Other Health Technology Assessment Reviews of Drug

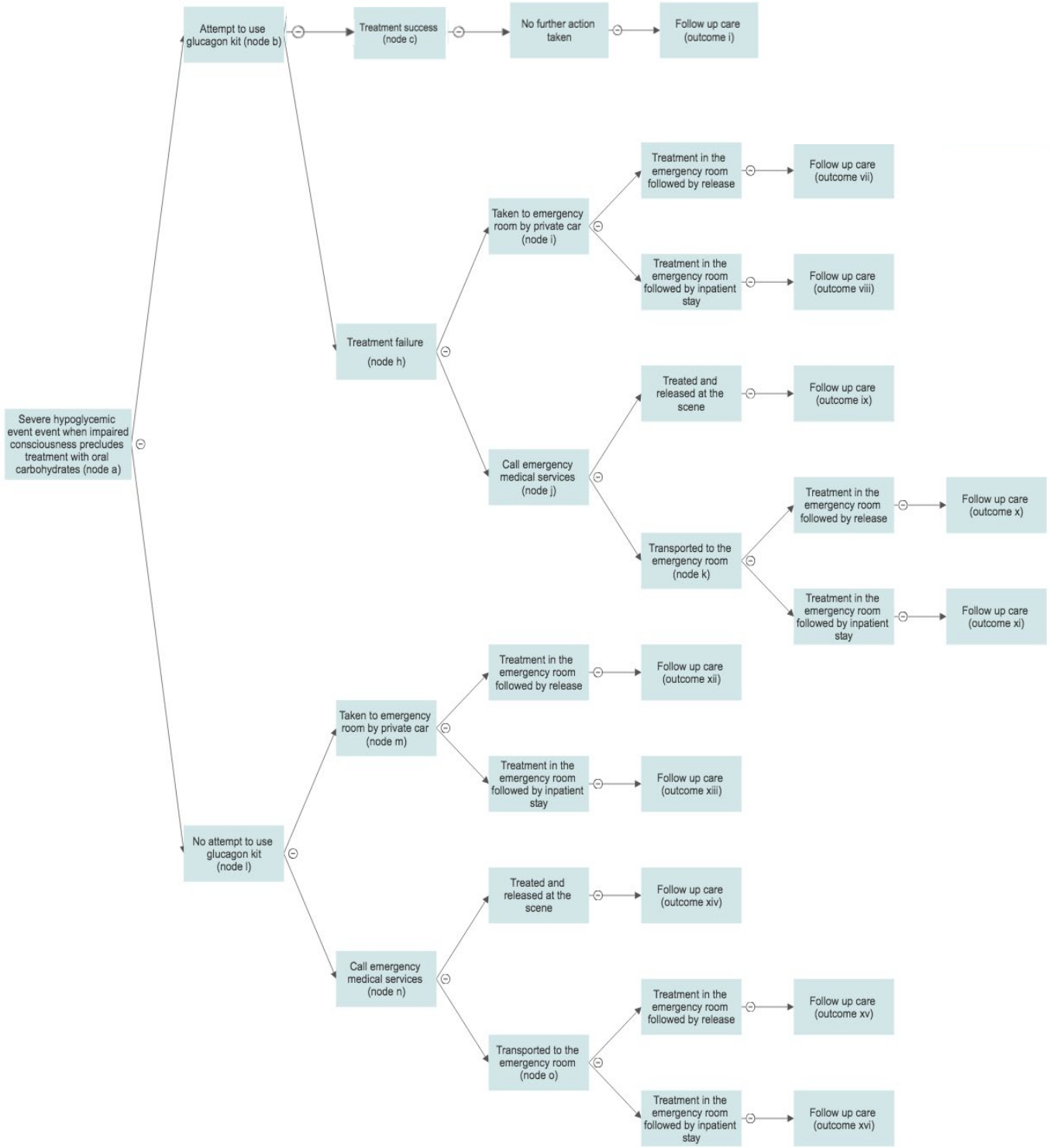
No other health technology agencies have reviewed glucagon nasal powder for the requested CDR indication.

Appendix 4: Reviewer Worksheets

Sponsor's Model Structure

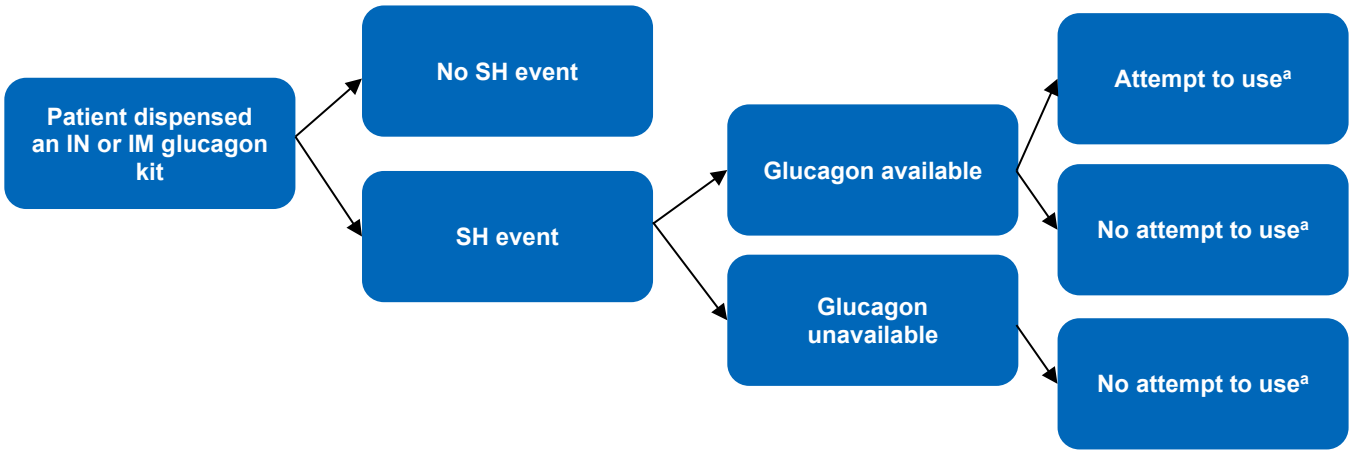
The sponsor submitted a CUA comparing intranasal glucagon to IM glucagon for insulin-treated patients with diabetes mellitus who experience an SH event, when impaired consciousness precludes oral carbohydrates.[2] To capture the costs and consequences associated with this decision problem over the time horizon of one year, the sponsor used a decision tree to model a series of events that stem from a single SH event that was assumed to be witnessed by a bystander (either a caregiver or an acquaintance) who may decide to administer a single dose of intranasal or IM glucagon (Figure 1). Whether the glucagon treatment was attempted and was successful determined which modelled health care resource use events were triggered as a consequence. A range of events of varying severity were captured, including potential resolution of an SH event without health care resource use, resolution via EMS visit, ED visit, or inpatient stay, and follow-up care.

Figure 1: Decision Tree Diagram of the Sponsor's Model



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

Figure 2: Expanded Decision Tree in CADTH Reanalysis



IM = intramuscular; IN = intranasal; SH = severe hypoglycemia.

[a] Further branches in the decision tree beyond these nodes are identical to the sponsor's pharmacoeconomic submission.[2]

Table 9: Data Sources

Data input	Description of data source	Comment
Baseline characteristics	NA; sponsor did not use patient baseline characteristic inputs	NA
Efficacy	IN glucagon was assumed to be equally efficacious as IM glucagon.	See Table 10
	Bystanders to an SH event were assumed to be twice as likely to attempt to use glucagon when IN glucagon is available compared to when IM glucagon is available.	See Table 10
	The proportion of bystanders to an SH event attempting glucagon treatment was based on the sponsor's CRASH web survey study.[25]	Acceptable. However, there is some uncertainty regarding this parameter estimate as the survey participants [redacted]. It is also unclear how the study's exclusion of patients [redacted] would impact the parameter estimate.
	The difference in the probability of a successful glucagon administration between the IN and IM formulations of glucagon was informed by the sponsor's Yale et al. (2017) study.[3]	Inappropriate. Yale et al. (2017) defined only a full dose injection as a successful treatment with IM glucagon.[3] However, according to the clinical expert consulted by CADTH, less than a full dose injection of glucagon may also be effective, especially for pediatric patients who only require half of a dose based on the IM glucagon product monograph.[16,17] Therefore, a more

Data input	Description of data source	Comment
		appropriate definition of a successful glucagon injection would also include successful partial dose injections. The use of the more restrictive definition of successful treatment favoured IN glucagon. CADTH clinical reviewers also noted uncertain generalizability due to the limitations in the ability of simulated scenarios to mimic real-world conditions, and the fact that study participants who were caregivers or patients with diabetes did not own a glucagon device or never had one, in contrast to the HC-indicated population who are likely to own one.
Natural history	The probability that patients who do not successfully receive glucagon treatment by a bystander would be privately transported to an ED was based on a 2015 Canadian ED chart review study.[11]	Uncertain. The input data are based on the proportion of patients with an SH event who were reported to have independently travelled to an ED in the Rowe et al. (2015) study.[2,11] This proportion is based on a denominator that represents a different population (i.e., patients with SH who visited ED) compared to those who are reflected in the probability (i.e., patients with SH with impaired consciousness that preclude oral carbohydrate treatment, who did not receive a successful glucagon treatment from a bystander). Additionally, the sponsor's approach did not replicate the proportion of patients observed in the Rowe et al. (2015) study as was seemingly intended. As the sponsor's decision tree also modelled additional paths for patients to be transported to the ED via EMS, the overall proportion of modelled patients who visit the ED in the model were lower than observed in the Rowe et al. (2015) study. Although this may favour IN glucagon because the model assumes that more patients could be diverted from the ED, the direction of bias is uncertain as it is unknown how the population in the Rowe et al. (2015) study is related to the HC-indicated population for IN glucagon.
	The probability of an EMS visit leading to an ED visit, and the probability of an ED visit leading to a hospital admission were based on a 2018 Canadian review of paramedic and ED records.[10]	Acceptable.
Utilities	Mean disutilities associated with SH event resolution without health care resource use, SH event involving EMS, SH event involving ED visit, and SH event involving inpatient admission were approximated by pediatric epilepsy-related disutilities	Inappropriate. The sponsor inappropriately applied the disutility value associated with an admission to intensive care unit to model the reduction in QALYs associated with an inpatient admission, and also inappropriately applied the disutility value associated with an

Data input	Description of data source	Comment
	reported in the Lee et al. (2013) cost-effectiveness analysis.[18]	inpatient admission to model the reduction in QALYs associated with an ED visit. Although the Lee et al. (2013) study applied the disutility values to a 30-day period,[18] the sponsor effectively applied the disutilities over the one-year time horizon. Furthermore, the methodological validity of the disutility values is unknown as the full methodology behind the disutilities, including the study country and the method of elicitation, is proprietary information that was not reported in the Lee et al. (2013) study.[18] The disutilities also reflect a pediatric population and their generalizability to the HC-indicated population is unknown. CADTH explored the uncertainty associated with health care resource use-dependent disutility values in a sensitivity analysis.
Adverse events	Adverse events were not modelled	NA
Mortality	Mortality was not modelled	NA
Resource use and costs		
Drug	Cost for IN glucagon was based on sponsor's submission.[25] Cost of IM glucagon kit was based on costs of Glucagen[17] and glucagon[16] from the Ontario Drug Benefit formulary[7] weighted by market share data from IQVIA reported by the sponsor.[2]	Appropriate. Appropriate.
Events	Resource use associated with follow-up care with a health care professional was based on reported referrals to endocrinologist, general internist, and primary care physician from the Rowe et al. study.[11] Physician unit costs were based on Ontario Schedule of Benefits,[8] and were inflated to 2019 Canadian dollars using the Canadian General Consumer Price Index.[27] The cost of EMS was derived from 2017 Toronto Paramedic Services Annual Report.[19]	Inappropriate. The sponsor selected only some of the reported referrals in the Rowe et al. (2015) study and excluded other referrals such as diabetes education, a relevant follow-up cost.[11] However, this selective costing does not impact the results of the pharmacoeconomic submission as the application of the follow-up costs did not differ between treatment arms by design. Appropriate. Acceptable. The sponsor's approach was based on CADTH costing guidelines.[21] However, this estimate is uncertain as the cost estimate approach divided the gross operating budget by number of patients transported. As not every EMS response results in patient transportation, this approach likely overestimates the cost of the

Data input	Description of data source	Comment
		average EMS response. In order to explore this uncertainty, CADTH conducted a scenario analysis with a lower cost estimate based on the annual number of EMS responses.
	The costs of an ED visit and an inpatient admission were based on the Ontario Case Costing Initiative database.[6]	Appropriate.

ED = emergency department; EMS = emergency medical service; HC = Health Canada; HRQoL = health-related quality of life; IM = intramuscular; IN = intranasal; NA = not applicable; QALY = quality-adjusted life-years; SH = severe hypoglycemia.

Table 10: Sponsor's Key Assumptions

Assumption	Comment
The sponsor's model structure comprehensively captured the experiences of the population of patients who are dispensed glucagon to use in a diabetic emergency.	Inappropriate. The sponsor's model effectively assumes that all patients who are dispensed an IN or IM glucagon kit will experience an SH event that will be noticed by a bystander who will have access to either IN or IM glucagon. This does not match the risk profile of insulin-dependent patients with diabetes and the model should incorporate SH risk to account for patients with glucagon who do not experience an SH event. Additionally the model should account for patients that have multiple SH events. The proportion of SH events that is noticed by a bystander should also be considered as this proportion would be lower than the proportion of patients who experience an SH event as most SH events occur nocturnally,[14] and the expert indicated that it is unknown whether most bystanders would be able to notice the SH event in such cases. Furthermore, the proportion of SH events noticed by a bystander with access to either IN or IM glucagon is likely to be even lower. The expert consulted by CADTH indicated that it is unknown whether the IN or IM glucagon kit would be accessible by the bystander. CADTH also received patient input that some schools do not allow staff to administer glucagon. Collectively these observations indicate that the population who could potentially benefit from IN glucagon is smaller than modelled in the sponsor's submission. The sponsor's model overestimated the proportion of patients who could be impacted by glucagon and favoured the IN glucagon kit.
Time horizon is one year.	Inappropriate. Although SH is an acute event, IM glucagon is expected to last approximately 18 months at room temperature.[17] As glucagon may potentially be used to treat an SH event at any point during this time frame before being replaced, the time horizon must be able to capture 18 months to more appropriately consider the costs and consequences of a glucagon kit prescription. Furthermore, as clinical management in response to SH (especially frequent SH) may alter SH risk and a caregiver's probability of glucagon treatment attempt and treatment success, a lifetime time horizon would be more appropriate.
IN glucagon and IM glucagon have the same efficacy in resolving an SH event.	Acceptable. The sponsor based this assumption on the sponsor's IGBC and IGBB trials.[2,4,5] CADTH clinical reviewers concluded that patients receiving IN glucagon have similar rates of treatment response compared to IM glucagon in the adult studies based on the definitions of response used in three noninferiority studies in adults (IGBC, IGBI, and IGBJ). Reviewers also noted that the pediatric trial (IGBB) was not designed to test noninferiority and therefore conclusions about the similarity of IN compared to IM administration are less certain in the pediatric population. The main limitation of the data from these trials is that none of the trials were conducted in patients with SH (they had induced hypoglycemia

Assumption	Comment
	instead) and therefore the relative efficacy of IN and IM glucagon in this context is uncertain.
Sponsor assumed that caregivers will be present for SH events occurring in private residences that are not one-person households, nursing homes, and for 50% of SH events occurring elsewhere.	Uncertain. It is challenging to validate this assumption given lack of informative literature.
Bystanders to an SH event are twice as likely to attempt to use glucagon when IN glucagon is available compared to when IM glucagon is available.	Uncertain. According to the clinical expert consulted by CADTH, caregivers such as a parent of a child may be determined to attempt glucagon treatment regardless of the route of administration. The expert expected that IN glucagon would encourage treatment more frequently in bystanders who were acquaintances. However, the size of the increased treatment attempt probability is unknown.
All additional patients who successfully receive SH treatment will consequently avoid an EMS visit, an ED visit, or an inpatient admission.	Uncertain. Given the following points, the Sinclair et al. (2018) study population may have been transported to ED or admitted as inpatients for reasons unrelated to whether the specific type of SH event indicated for IN glucagon was successfully treated: • a substantial proportion of the population observed in the Sinclair et al. (2018) study were fully conscious at baseline (i.e., Glasgow Coma Scale score of 15) • 24.5% of paramedic impressions of patients were associated with other concerns not relevant to hypoglycemia or were potentially associated with a seizure or alcohol complication • only 37.6% of patients had a diagnosis of hypoglycemia in the ED.[10] The clinical expert consulted by CADTH was also uncertain regarding the proportion of these patients who would avoid an EMS visit, an ED visit, or an inpatient admission.
Mortality or adverse events were not modelled.	Acceptable. According to the clinical expert consulted by CADTH, neither aspects are expected to differ between IM glucagon and IN glucagon.

ED = emergency department; EMS = emergency medical service; IM = intramuscular; IN = intranasal; SH = severe hypoglycemia.

CADTH CDR Reanalyses

CADTH conducted the following sensitivity analyses.

S1a. An annual SH risk of 5% was assumed.

S1b. An annual SH risk of 4% was assumed.

S1c. An annual SH risk of 3% was assumed.

S1d. An annual SH risk of 2% was assumed.

S1e. An annual SH risk of 1% was assumed.

S2. The following sensitivity analyses were based on the base case annual SH incidence of approximately 38.4%.

S2a. The probability of attempting glucagon administration for intranasal glucagon was assumed to be 1.5 times compared with IM glucagon based on the opinion of the clinical expert consulted by CADTH.

S2b. The probability of attempting glucagon administration for intranasal glucagon was assumed to be the same as IM glucagon.

S2c. All caregivers attending to an SH event (caregivers were assumed to be 68% of bystanders) were assumed to have the probability of successful IM glucagon

administration that is equal to the probability for intranasal glucagon. The impact of intranasal glucagon on the probability of successful glucagon administration was preserved for the 32% of the bystander population who was an acquaintance of the patient.

S2d. The probability of successful IM glucagon administration was assumed to be equal to that associated with intranasal glucagon for all bystanders.

S2e. Analysis S2c + analysis S2a.

S2f. Analysis S2c + analysis S2b.

S2g. Disutility values associated with an EMS visit, an ED visit, and an inpatient admission were made equivalent to the disutility value of an SH event without an EMS or hospital visit.

S2h. A lower EMS cost estimate derived from the 2018 Toronto Paramedic Service report[22] was used ($566.97 compared to $948.26 in the base case). The gross operating budget ($215,449,500) was divided by the number of EMS responses (380,000), instead of the number of patient transportations.

S3a-h. Analyses S2a to S2h were repeated with the assumption of 5% annual SH risk.

S4a-h. Analyses S2a to S2h were repeated with the assumption of 3% annual SH risk, which is the average of the 1% to 5% annual SH risk estimate provided by the clinical expert consulted by CADTH.

The results of these additional analyses are reported in Table 11.

Table 11: CADTH Sensitivity Analyses (Intranasal Glucagon vs. IM Glucagon)

	Analysis	Comparator	Cost ($)	QALYs	QALMs[a]	ICUR ($ per QALY)
S1a	5% annual SH risk	IIN Glucagon	305	–0.000014	–7	–
		IM Glucagon	306	–0.000017	–9	–
		Incremental	*–14*	*0.000003*	*1*	*IN glucagon dominant*
S1b	4% annual SH risk	IN Glucagon	271	–0.000011	–6	–
		IM Glucagon	264	–0.000013	–7	–
		Incremental	*7*	*0.000002*	*1*	*3,187,690*
S1c	3% annual SH risk	IN Glucagon	236	–0.000008	–4	–
		IM Glucagon	222	–0.000010	–5	–
		Incremental	*14*	*0.000002*	*1*	*8,433,616*
S1d	2% annual SH risk	IN Glucagon	201	–0.000006	–3	–
		IM Glucagon	180	–0.000007	–4	–
		Incremental	*21*	*0.000001*	*1*	*19,189,578*
S1e	1% annual SH risk	I˜ Glucagon	167	–0.000003	–2	–
		IM Glucagon	138	–0.000003	–2	–
		Incremental	*29*	*0.000001*	*0*	*54,607,896*
S2a	Probability of ˆ˜ glucagon attempt 1.5 times the probability of IM glucagon attempt	I˜ Glucagon	939	–0.000065	–34	–
		IM Glucagon	1,008	–0.000072	–38	–
		Incremental	*-69*	*0.000007*	*4*	*IN glucagon dominant*
S2b		IN Glucagon	986	–0.000069	–36	–

	Analysis	Comparator	Cost ($)	QALYs	QALMs[a]	ICUR ($ per QALY)
	Probability of IN glucagon attempt equivalent to the probability of IM glucagon attempt	IM Glucagon	1,006	–0.000072	–38	–
		Incremental	-20	*0.000004*	*2*	*IN glucagon dominant*
S2c	Probability of successful IN glucagon administration equivalent to the probability of successful IM glucagon administration for patients attended by caregivers	IN Glucagon	878	–0.000061	–32	–
		IM Glucagon	979	–0.000070	–37	–
		Incremental	–101	*0.000010*	*5*	*IN glucagon dominant*
S2d	Probability of successful IN glucagon administration equivalent to the probability of successful IM glucagon administration for all patients	IN Glucagon	880	–0.000061	–32	–
		IM Glucagon	957	–0.000069	–36	–
		Incremental	–76	*0.000008*	*4*	*IN glucagon dominant*
S2e	S2c + S2a	IN Glucagon	930	–0.000070	–34	–
		IM Glucagon	979	–0.000065	–37	–
		Incremental	–49	*0.000006*	*3*	*IN glucagon dominant*
S2f	S2c + S2b	IN Glucagon	1,000	–0.000069	–36	–
		IM Glucagon	969	–0.000070	–37	–
		Incremental	30	*0.000001*	*0*	58,432,086
S2g	Disutilities associated with EMS visit, ED visit, and inpatient admission equivalent to the disutility associated with seizure that do not involve EMS or hospital visit	IN Glucagon	874	–0.000011	–6	–
		IM Glucagon	1,002	–0.000011	–6	–
		Incremental	*-128*	*0.000001*	*0*	*IN glucagon dominant*
S2h	Lower EMS cost	IN Glucagon	764	–0.000061	–32	–
		IM Glucagon	860	–0.000072	–38	–
		Incremental	*–96*	*0.000011*	*6*	*IN glucagon dominant*
S3a	S2a + 5% annual SH risk	*IN Glucagon*	*319*	–0.000015	–8	–
		IM Glucagon	*307*	–0.000017	–9	–
		Incremental	*13*	*0.000002*	*1*	*7,407,593*
S3b	S2b + 5% annual SH risk	*IN Glucagon*	331	–0.000016	–8	–
		IM Glucagon	307	–0.000017	–9	–

	Analysis	Comparator	Cost ($)	QALYs	QALMs[a]	ICUR ($ per QALY)
		Incremental	*24*	*0.000001*	*0*	*30,921,472*
S3c	S2c + 5% annual SH risk	*IN Glucagon*	305	–0.000014	–7	–
		IM Glucagon	300	–0.000016	–9	–
		Incremental	*5*	*0.000002*	*1*	*2,318,654*
S3d	S2d + 5% annual SH risk	*IN Glucagon*	305	–0.000014	–7	–
		IM Glucagon	*296*	–0.000016	–8	–
		Incremental	*9*	*0.000002*	*1*	*4,577,604*
S3e	S2e + 5% annual SH risk	*IN Glucagon*	320	–0.000015	–8	–
		IM Glucagon	300	–0.000016	–9	–
		Incremental	*20*	*0.000001*	*1*	*16,905,733*
S3f	S2f + 5% annual SH risk	*IN Glucagon*	333	–0.000016	–8	–
		IM Glucagon	300	–0.000016	–9	–
		Incremental	*33*	*0.000000*	*0*	*130,642,273*
S3g	S2g + % annual SH risk	*IN Glucagon*	305	–0.000002	–1	–
		IM Glucagon	*308*	–0.000003	–1	–
		Incremental	*–4*	*0.000000*	*0*	*IN glucagon dominant*
S3h	S2h + 5% annual SH risk	*IN Glucagon*	279	–0.000014	–7	–
		IM Glucagon	*275*	–0.000017	–9	–
		Incremental	*3*	*0.000003*	*1*	*1,190,443*
S4a	S2a + 3% annual SH risk	*IN Glucagon*	244	–0.000009	–5	–
		IM Glucagon	223	–0.000010	–5	–
		Incremental	*21*	*0.000001*	*1*	*20,063,314*
S4b	S2b + 3% annual SH risk	*IN Glucagon*	253	–0.000010	–5	–
		IM Glucagon	*222*	–0.000010	–5	–
		Incremental	*31*	*0.000000*	*0*	*73,861,285*
S4c	S2c + 3% annual SH risk	*IN Glucagon*	237	–0.000009	–5	–
		IM Glucagon	219	–0.000010	–5	–
		Incremental	*18*	*0.000001*	*1*	*13,735,887*
S4d	S2d + 3% annual SH risk	*IN Glucagon*	236	–0.000008	–4	–
		IM Glucagon	216	–0.000010	–5	–
		Incremental	*19*	*0.000001*	*1*	*15,882,542*
S4e	S2e + 3% annual SH risk	*IN Glucagon*	244	–0.000009	–5	–
		IM Glucagon	218	–0.000010	–5	–
		Incremental	*26*	*0.000001*	*0*	*35,359,746*
S4f	S2f + 3% annual SH risk	*IN Glucagon*	253	–0.000010	–5	–
		IM Glucagon	*218*	–0.000010	–5	–
		Incremental	*35*	*0.000000*	*0*	*314,192,492*
S4g	S2g + 3% annual SH risk	*IN Glucagon*	237	–0.000001	–1	–
		IM Glucagon	*223*	–0.000002	–1	–
		Incremental	*14*	*0.000000*	*0*	*144,606,915*
S4h		*IN Glucagon*	219	–0.000009	–5	–

	Analysis	Comparator	Cost ($)	QALYs	QALMs[a]	ICUR ($ per QALY)
	S2h + 3% annual SH risk	*IM Glucagon*	202	–0.000010	–5	–
		Incremental	*17*	*0.000002*	*1*	*10,380,437*

ED = emergency department; EMS = emergency medical service; ICUR = incremental cost-utility ratio; IM = intramuscular; IN = intranasal; QALM = quality-adjusted life-minute; QALY = quality-adjusted life-year; SH = severe hypoglycemia; vs. = versus.

[a] QALMs were calculated as reported QALYs were unable to sufficiently capture the estimated health differences. Reported QALMs may be negative as the sponsor did not model base health utilities and the results only reflect health utility decrements.

Table 12: CDR Reanalysis Price Reduction Scenarios (Based on Analysis S1c)

ICURs of IN glucagon versus IM glucagon		
Price	**Base-case analysis submitted by sponsor**	**CADTH reanalysis S1c: 3% annual SH risk**
Submitted	IN Glucagon Dominant	8,433,616
5% reduction	IN Glucagon Dominant	4,074,195
6% reduction	IN Glucagon Dominant	3,146,754
7% reduction	IN Glucagon Dominant	2,970,617
8% reduction	IN Glucagon Dominant	2,621,902
9% reduction	IN Glucagon Dominant	983,801
10% reduction	IN Glucagon Dominant	**IN glucagon dominant**

ICUR = incremental cost-utility ratio; IM = intramuscular; IN = intranasal; SH = severe hypoglycemia.

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