CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

GLUCAGON NASAL POWDER (BAQSIMI — ELI LILLY CANADA INC)
Indication: For the treatment of severe hypoglycemia (SH) reactions which may occur in the management of insulin treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that glucagon nasal powder should be reimbursed for the treatment of severe hypoglycemia (SH) reactions which may occur in the management of insulin treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrate, only if the following conditions are met:

Conditions for Reimbursement

Initiation criteria
1. Patient is receiving insulin and is at high risk for SH

Renewal criteria
1. Patient continues to use insulin and remains at high risk for SH

Pricing conditions
1. Price not to exceed drug plan cost for the least expensive intramuscular (IM) glucagon product

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Reasons for the Recommendation

1. In two cross-over non-inferiority randomized controlled trials (RCTs) in adults with type 1 diabetes mellitus (T1DM): Studies IGBC and IGBI; and in one cross-over non-inferiority RCT with a mixture of patients with of T1DM or type 2 diabetes mellitus (T2DM): Study IGBJ; patients had hypoglycemia experimentally induced with insulin. Intranasal glucagon was non-inferior to IM glucagon with respect to the percentage of patients achieving treatment success. Treatment success was defined as an increase in plasma glucose to ≥ 3.9 mmol/L or an increase of ≥1.1 mmol/L from its lowest point within 30 minutes of the glucagon dose, with no additional actions required. In a similarly designed cross-over RCT in children 4 to 17 years of age (Study IGBB), all patients achieved treatment success (an increase in plasma glucose of at least 1.4mmol/L within 20 minutes following induction of hypoglycemia) regardless of being treated with IM or intranasal glucagon. Hence there was no evidence to suggest intranasal glucagon was more effective than IM glucagon.

2. At the sponsor-submitted price of $131.60, the 3 mg single-use nasal spray device was more costly than the 1 mg single-use IM injection with a list price of $92.60. The CADTH base case analysis found that intranasal glucagon was associated with 0.000011 additional quality-adjusted life-years (QALYs). This is equivalent to 6 quality-adjusted life-minutes [QALMs]) and a cost reduction of $123 compared with IM glucagon in insulin treated patients with diabetes mellitus. There were, however, limitations with the analysis that added considerable uncertainty to the small health benefit such as; the incidence of SH, the magnitude of increase in successful glucagon treatment attempts afforded by the intranasal device, and the costs and disutility associated with potentially avoided healthcare resource use.

3. The cost-effectiveness of intranasal glucagon is improved in patients with a high risk of SH. The clinical expert consulted by CADTH expected the annual risk of SH to range from 1% to 5% which corresponds to incremental cost-effectiveness ratios (ICERs) of $54.6 million to intranasal glucagon being dominant compared with IM glucagon. The specific annual risk of SH in different diabetic populations is uncertain.

Implementation Considerations

- The committee recommends that drug plans implement containment policies to mitigate inappropriate use and/or wastage, due to expiry, of intranasal glucagon.
- The committee considered that insulin-treated patients who are at high risk of SH may be identified by diabetes care teams or clinicians that are experienced in managing patients with diabetes.

Discussion Points

- The committee noted that while intranasal glucagon demonstrated non-inferiority to IM glucagon based on serum glucose response at 30 minutes, intranasal glucagon was associated with a longer time to successful response in studies IGBC and IGBI, and worse hypoglycemia symptom scores at some time points after glucagon administration in studies IGBC and IGBJ. The committee noted however, that the trials were not reflective of the real world given that glucagon was administered by trained healthcare professionals, and the primary outcome did not allow for other interventions during the recovery period (e.g., oral carbohydrates). The committee considered that the potential higher probability of an administration attempt by caregivers with intranasal glucagon compared with IM glucagon in a real world setting may lead to different results than obtained in the clinical trials.
- The committee recognized input from patients and caregivers regarding the disadvantages of injectable glucagon kits, including the difficulties and uncertainty in preparing and administering the product under stressful conditions The committee considered that a more user-friendly mode of delivery for glucagon is desirable, and that compared with IM administration, intranasal glucagon may be more likely to be attempted by lay-people, given that in the two mannequin studies, participants expressed a preference for using intranasal glucagon over injectable glucagon.
- The committee discussed that, compared with IM glucagon, the greater portability and less complex mode of delivery offered by intranasal glucagon may result in increased uptake by patients and caregivers; the potential for product wastage and/or misuse in situations where oral carbohydrates would be more appropriate was noted.
- The committee noted that adequate training should be given to the patient's parents, caregivers or close acquaintances in the administration of glucagon nasal powder. In addition, patients at risk of SH should be assessed and counselled about hypoglycemic awareness and the many potential strategies to reduce risk rather than relying solely on glucagon to treat episodes.

Background

Glucagon powder for intranasal administration (Baqsimi) has a Health Canada indication for the treatment of SH reactions which may occur in the management of insulin treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates. Glucagon is a peptide hormone that activates hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. It is supplied as a powder in a single use nasal delivery device and the Health Canada–approved dose is 3 mg administered as one actuation of the intranasal device into one nostril. The dose does not need to be inhaled.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH reviewers: a systematic review that included four randomized controlled trials (RCTs) of glucagon nasal powder in episodes of induced hypoglycemia, two non-randomized trials in real-world episodes of hypoglycemia, two RCTs in simulated episodes of hypoglycemia in mannequins, and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with diabetes, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

The patient groups Type 1 Together and Diabetes Canada provided input for this submission. Patient perspectives were obtained from online surveys of patients with T1DM and caregivers of patients with T1DM. The following is a summary of key input from the perspective of the patient groups:

- Hypoglycemia is one of the most fearful and stressful aspects of managing T1DM. Negative impacts of hypoglycemia on patients include increased anxiety, fear of nocturnal hypoglycemia, complications of timing insulin dosing and self-blood glucose monitoring, and fear of being alone with no one to assist if needed. Caregivers and parents also expressed significant stresses experienced in the course of their responsibilities for caring for someone with diabetes.
- Many respondents were familiar with injectable glucagon and 1 in 4 had experience using an injectable glucagon kit, with approximately one fifth of those reporting that they were unsatisfied with the experience. Patients and caregivers cited limitations in affordability, usability, and portability of injectable glucagon. Respondents were concerned about the general reluctance of by-

standers to administer it, and also cited difficulties related to lack of support from school staff in administering glucagon injections to students.

- Some caregivers mentioned that preparing injectable glucagon in an urgent situation is stressful and there are significant feelings of uncertainty regarding preparing and properly administering the product. Anxiety was reported as high for parents whose young children have experienced SH.
- Respondents said that they would like to see an alternative product to IM glucagon that is easy and quick to administer, has a small chance of error, and would result in a fast recovery from hypoglycemia.

Clinical Trials

The systematic review included four open-label, RCTs of patients with diabetes, two of which were pivotal trials: Studies IGBC (pivotal study, N = 77; T1DM), IGBI (N = 70; T1DM), IGBJ (N = 72; T1DM and T2DM) were performed in adults and Study IGBB (pivotal study; N = 48; T1DM) was performed in children aged 4 to 16 years. Hypoglycemia (not SH) was induced as part of the study procedures in the RCTs. Patients received a single 3 mg intranasal glucagon dose, and this was compared to a single 1 mg IM glucagon dose in crossover fashion.

Experimentally induced hypoglycemia was achieved via insulin infusion and monitored via a second catheter for blood sampling. Each glucagon dosing visit was conducted after an overnight fast of at least eight hours with a starting plasma glucose of at least 5.1 mmol/L. Hypoglycemia was induced by an intravenous infusion of regular insulin diluted in normal saline at an initial rate of 2 mU/kg/minute, which was adjusted at the investigator's discretion to reach the target nadir glucose level of less than 2.7 mmol/L. Glucagon was administered five minutes after the insulin infusion was stopped. The nadir was defined as the minimum plasma glucose at the time of or within 10 minutes following glucagon administration. In the pediatric study, the target nadir glucose level was less than 4.4 mmol/L and insulin could be administered through the patient's insulin pump, if available.

The RCTs were open-label, and this could have impacted assessment of subjective outcomes such as adverse events and the Edinburgh hypoglycemia scale score. In the pediatric trial, the primary outcome was not defined *a priori* and there was no formal sample size calculation performed. Plasma glucose measurements taken after administration of glucagon in Study IGBC were potentially biased as six patients (only one of whom was excluded from analysis) received oral carbohydrates following intranasal glucagon administration and no patients received oral carbohydrates following IM glucagon administration. However, the primary end point would not have been affected as it was assessed at an earlier time point.

Intranasal glucagon is indicated for treatment of SH reactions, but the included RCTs were not designed to study recovery from SH. The determination of hypoglycemia was based on glucose levels alone, rather than on symptoms of hypoglycemia. Real-world studies including the conditions specified in the indication (e.g. impaired consciousness) would be difficult to achieve; however, a major limitation of the studies remains since there were no controlled trials that tested the product under the conditions specified in the indication. Given the uniformity of the pharmacodynamic response to exogenous glucagon, the extrapolation of the results of the trials to SH is reasonable, but there remains uncertainty about the time to response relative to IM glucagon since this has not been directly quantified under severe hypoglycemic conditions.

According to the clinical expert, the populations enrolled in the clinical trials are reasonably similar to the Canadian patients who would be prescribed glucagon nasal powder. However, the trials lacked older (e.g. older than 65 years) populations who would be expected to have a longer duration of disease and a higher proportion of individuals with reduced awareness of hypoglycemia.

The primary outcome of the three adult trials was resolution of low glucose levels within a 30-minute interval. Clinicians and patients would expect a resolution of low glucose levels in less than 30 minutes given the serious sequelae that can result from SH that is not promptly and successfully treated.

In addition to the RCTs included in the systematic review, results from four other relevant studies were considered: Study B001 (N = 33 evaluable events in 14 pediatric patients with T1DM), Study B002 (N = 157 evaluable events in 69 adult patients with T1DM), Study IGBM (N = 32 caregiver participants; N = 33 acquaintance participants), and Study AMG111 (N = 16 caregiver participants;

N = 15 acquaintance participants). Studies IGBM and AMG111 compared use of intranasal glucagon and IM glucagon in randomized crossover fashion.

In the B001 and B002 studies, moderate hypoglycemic events in adults and children with diabetes (defined as the presence of neuroglycopenic symptoms and/or signs and low blood glucose) and SH events in adults (defined as clinical incapacitation of the patient) were treated using intranasal glucagon under real-world conditions. Limitations of these studies include the small sample size of events (particularly for SH events), the lack of a comparison with IM glucagon, and the possibility that caregivers and adult patients were more recently trained and therefore better prepared to treat hypoglycemia in the studies than they would be in real life.

The IGBM and AMG111 studies compared the usage of intranasal glucagon to IM glucagon in mannequins during simulated emergencies of SH and focused on the experience of caregiver and acquaintance (non-caregiver) participants. The results were subject to major limitations, particularly the small sample sizes and uncertainty in the generalizability of the simulated events to real-life hypoglycemic events.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following: treatment success/response, time to response, and symptoms of hypoglycemia (using the Edinburgh hypoglycemia scale). The Edinburgh hypoglycemia scale version used in the IGBI and IGBJ studies consisted of 13 symptoms, each rated on an ordinal scale of 1 (no symptom at all) to 7 (severe; hard to tolerate) and the scale version used in the IGBC study was not specified. The primary outcome in the adult trials was treatment success/response, defined as an increase in plasma glucose to 3.9 mmol/L or an increase of at least 1.1 mmol/L from nadir within 30 minutes of the glucagon dose, with no additional actions. A noninferiority margin of 10% was selected for the absolute difference of response rates between intranasal and IM glucagon, for all three adult trials.

The main outcome in the pediatric study, which was established post hoc, was an increase in plasma glucose of at least 1.4 mmol/L within 20 minutes following induction of hypoglycemia.

Quality of life and patient or caregiver satisfaction were not assessed in the included RCTs.

The primary outcome in the B001 and B002 studies was the proportion of hypoglycemic events with patients awakening or returning to normal status within 30 minutes following glucagon administration. The primary outcome in Study IGBM was the percentage of caregiver participants who successfully administered a complete dose of glucagon and completed all critical steps for administration. The same outcome was assessed for acquaintance participants. Time to complete administration, starting from when the glucagon device was found, and device preference were also assessed. Study AMG111 assessed similar outcomes, though there was no defined primary outcome.

Efficacy

The results of the primary outcome in all adult RCTs met the prespecified criteria for noninferiority since the upper boundary of the confidence intervals did not exceed 10% in any of the adult studies.

In Study IGBC, response criteria were met in 74/75 (99%) patients after receiving intranasal glucagon and in 75/75 (100%) patients after receiving IM glucagon (adjusted difference in proportion of 1.5%; one-sided 97.5% confidence interval [CI] of 4.3%). In Study IGBI, response criteria were met in 66/66 (100%) patients after receiving intranasal glucagon and in 66/66 (100%) patients after receiving IM glucagon (difference [95%CI]: 0.0% [-1.52% to 1.52%]). In Study IGBJ, response criteria were met in 68/68 (100%) patients after receiving intranasal glucagon and in 68/68 (100%) patients after receiving IM glucagon (difference [95%CI]: 0.0% [-1.47% to 1.47%]). In the pediatric study (IGBB), response criteria were met in 12/12 (100%) of patients after receiving intranasal glucagon and in 6/6 (100%) patients after receiving IM glucagon (no statistical testing results reported).

In Study IGBC, the mean time to treatment response was 16.2 minutes versus 12.2 minutes after intranasal glucagon versus and IM glucagon (difference of 4 minutes, variance not reported). In Study IGBI, the mean time to treatment response was 11.44 minutes (standard deviation [SD] of 3.01 minutes) after intranasal glucagon compared with 9.85 minutes (SD of 3.03 minutes) after IM glucagon (difference of 1.6 minutes, variance not reported). In Study IGBJ, the median time to treatment response was 10 minutes

(range of 5 of 25 minutes) after intranasal glucagon and 10 minutes (range of 10 to 20 minutes) after IM glucagon (*P* = 0.069 for the log rank test).

In Study IGBC, the Edinburgh Hypoglycemia Scale scores were numerically higher (worse) at 15, 30, 45 and 60 minutes (i.e., all time points) after glucagon was administered for the intranasal glucagon treatment compared with the IM glucagon treatment. In Study IGBI, the Edinburgh Hypoglycemia Scale scores were similar between intranasal glucagon and IM glucagon treatment at 15, 30, 45 and 60 minutes. In Study IGBJ, the score was higher (worse) for the intranasal glucagon treatment compared to the IM glucagon treatment at 15 minutes after the glucagon dose was administered and similar between treatments at later time points. Although the symptoms in the Edinburgh Hypoglycemia Scale have been shown to be specific to hypoglycemia, a minimally important difference for the Edinburgh Hypoglycemia Scale score was not identified.

The B001 and B002 studies reported a high rate of administration success in real-world episodes of hypoglycemia: 100% of moderate hypoglycemic events in pediatric patients and 96.2% of hypoglycemic events (including 12 SH events) in adult patients were successfully resolved within 30 minutes of administration.

The IGBM and AMG111 studies reported higher rates of successful administration with intranasal glucagon versus IM glucagon in simulated episodes of SH for both caregiver and acquaintance participants and that most participants administering the glucagon products to mannequins expressed a preference for using intranasal glucagon over injectable glucagon. Investigators also reported a shorter mean time to successful administration of intranasal glucagon compared to IM glucagon of between 30 seconds and two minutes faster.

Harms (Safety)

In the adult RCTs, the proportion of patients reporting at least one adverse event ranged from 19% to 57% after receiving either intranasal glucagon or IM glucagon. The proportions of patients reporting at least one adverse event were similar between treatments in each trial. The most frequently reported adverse events included nausea, vomiting, headache, nasal discomfort, nasal congestion, increased lacrimation, fatigue, nasopharyngitis and upper respiratory tract irritation. Oropharyngeal and eye symptoms occurred more frequently in patients after receiving intranasal glucagon, compared to IM glucagon, in Study IGBC. This included nasal discomfort (intranasal 10% vs IM 0%), nasal congestion (intranasal 8% vs IM 1%), lacrimation increased (intranasal 8% vs IM 1%), upper respiratory tract irritation (intranasal 19% vs IM 1%). In Study IGBI, nasal itching (49%) and sneezing (24%) occurred more frequently after treatment with intranasal glucagon compared to IM glucagon (0%).

In Study IGBJ, one patient with T2DM experienced a serious adverse event of positional vertigo that required hospitalization. The event occurred 36 days after receiving intranasal glucagon and approximately 28 days after receiving IM glucagon. In the pediatric study (IGBB), one patient experienced a serious adverse event of hypoglycemia during induction of hypoglycemia with insulin and made a full recovery after receiving oral carbohydrates.

There were two withdrawals due to adverse events of vomiting in the adult trials that occurred in relation to receiving intranasal glucagon.

Cost and Cost-Effectiveness

Intranasal glucagon is supplied as a single-use nasal spray device containing a 3 mg single dose at the sponsor's submitted price of $131.60. The recommended dose is one spray in either nostril.

The sponsor submitted a cost-utility analysis based on a decision-tree comparing the availability of intranasal glucagon with IM glucagon for bystander-administration of treatment for a patient experiencing an SH event. 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 who may decide to administer intranasal or IM glucagon to the patient. Whether or not glucagon treatment was attempted and was successful determined subsequent 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 in-patient admission; and, SH event follow-up care. A bystander with access to intranasal glucagon was assumed to be twice as likely to attempt administration of glucagon compared

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. The efficacy of successfully administered intranasal and IM glucagon were assumed to be equivalent, based on the sponsor's claim that non-inferior efficacy was demonstrated in the sponsor's IGBC and IGBB trials. Other parameters were based on Canadian sources and were assumed to be the same between 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 QALYs and cost savings of $382 compared with IM glucagon - intranasal glucagon was dominant. 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.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- Since patients are dispensed treatment in anticipation of a potential SH event, some glucagon preparations will expire before being needed. The sponsor did not capture patients who do not experience an SH event or do not use glucagon for an SH event before drug expiry. This may be a substantial proportion of patients.
- The sponsor did not consider that clinical management may intensify, and caregiver education may increase in response to patients experiencing frequent or multiple SH events. This would reduce the risk of SH and/or increase caregivers' likelihood of attempting glucagon treatment and doing so successfully.
- The sponsor's assumption that bystanders to an SH event are twice as likely to attempt treatment with intranasal glucagon compared with IM glucagon was not supported by evidence.
- The modelled relationship between successful glucagon treatment and a prevented EMS call, ED visit, and in-patient admission is uncertain as these health care resources may be accessed for multiple reasons independent of treatment success.
- The disutility associated with an intensive care unit admission was inappropriately applied to in-patient admissions for an SH event, while the disutility associated with an in-patient admission was inappropriately applied to 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 ED were not considered in the calculation of the cost.

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, intranasal glucagon was associated with an additional 0.000011 QALYs (equivalent to 6 QALMs) at a reduced total cost ($123) compared to IM glucagon.

Considerable uncertainty remains given the structural and parametric limitations of the pharmacoeconomic analysis, especially regarding the modelling of SH risk, the increased probability of glucagon treatment attempt and success associated with intranasal glucagon and the health utility gains attributable to a successful glucagon treatment. The above parametric assumptions were explored in sensitivity analyses where the cost effectiveness of intranasal glucagon ranged from being dominant to an ICER of over $314 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 1 QALM to 6 QALMs in CADTH reanalyses). This small QALY benefit is in contrast to a more substantive difference in the drug acquisition costs: injectable glucagon = $93 per unit, while intranasal glucagon = $132 per unit.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

December 11, 2019 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None