INESSS
LE SAVOIR PREND FORME

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Continuous glucose monitoring system (Dexcom G6MC, Dexcom)

English summary

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

Direction des services de santé et de l'évaluation des technologies

Québec

SUMMARY

The Institut national d'excellence en santé et en services sociaux (INESSS) was mandated by the Bureau de l'innovation to assess the relevance of public coverage of the Dexcom G6® Mobile System, a continuous glucose monitoring (CGM) technology, for type 1 diabetics aged 2 years or older.

Evaluation process

A systematic literature review was conducted to identify the evidence relevant to the evaluation and to supplement the information submitted by the manufacturer. An advisory committee consisting of clinicians and patients was formed to gather experiential and contextual data to shed light on the potential benefits, the drawbacks, and the concerns associated with the use of the G6. Cost-effectiveness was evaluated using a model developed at INESSS and inspired by that developed by Health Quality Ontario (HQO). A budget impact analysis was also performed. All of the data gathered and generated by the project team were submitted to the Comité scientifique de l'évaluation des médicaments aux fins d'inscription (CSEMI) for the purpose of developing recommendations.

Health need

It is estimated that approximately 70% of type 1 diabetics (T1Ds) do not achieve HbA_{1c} (glycosylated hemoglobin) targets. Episodes of nocturnal or severe hypoglycemia are also a significant problem in these patients: adult T1D patients may experience an average of approximately one episode of symptomatic hypoglycemia (nighttime or daytime) per week and 0.2 to 3.2 episodes of severe hypoglycemia per year, 11% of which reportedly result in complications. Lastly, approximately 20% of the T1D population reportedly have hypoglycemia unawareness. The unmet needs specific to the pediatric population include the fact that young children are considered to be at higher risk for severe hypoglycemia, that the leading cause of mortality and morbidity in children and adolescents with T1D is related to the high frequency of diabetic ketoacidosis, and that hyperglycemia has a potential impact on cognitive development.

Description of the technology under consideration

The Dexcom G6® is a continuous interstitial glucose monitoring system. In Canada, its indication is approved for use in the management of diabetes in patients 2 years of age and older. Approval is granted for making treatment decisions in place of capillary blood glucose testing.

The Dexcom G6® is a modification of previous glucometers offered by Dexcom (G4 and G5). The G6 permits continuous, real-time, fingerstick-free glucose monitoring using a sensor inserted under the skin of the abdomen (or upper buttocks for ages 2 to 17 years) that remains in place for 10 days. The G6 requires no calibration. A reusable transmitter

sends data to the reading device once every 5 minutes. The device enables one to track blood glucose trends.

In the event of blood glucose deviations, configurable alerts and an integrated alarm warn the patient. The G6 also has an “Urgent Low Soon” alert that is activated when a value of ≤ 3.1 mmol/L is predicted by the device within the next 20 minutes. The G6 is considered reliable on the basis of a mean absolute relative difference (MARD) of approximately 9.6%.

Results

The scientific evidence is based on seven publications from three RCTs: DIAMOND [Beck *et al*., 2017a], GOLD [Lind *et al*., 2017] and HypoDE [Heinemann *et al*., 2018]. Given the rapid technological developments in this area, with a life cycle of approximately 3 years, most of the clinical data for evaluating the G6 were obtained with previous generations of Dexcom (G4 and G5). The duration of the interventions was 6 months in all three RCTs. These studies compared the efficacy and safety of Dexcom monitors with capillary blood glucose monitoring in T1D patients receiving intensive insulin therapy (multiple insulin injections, MIIs). The pivotal study DIAMOND, which was funded by the manufacturer, involved 158 T1D patients 25 years of age and older with suboptimal glycemic control. The GOLD crossover RCT [Lind *et al*., 2017] involved 161 adult T1D patients with an HbA_{1c} ≥ 7.5%. The total duration of this manufacturer-independent study was 69 weeks (2 x 26 weeks separated by a 17-week washout period). The HypoDE study [Heinemann *et al*., 2018], which was funded by the manufacturer, involved 149 T1D patients at high risk for severe hypoglycemia. The methodological limitations of these studies introduce a risk of bias that must be noted.

Glycosylated hemoglobin (HbA_{1c})

Dexcom use, compared to standard monitoring, significantly decreased HbA_{1c} in the T1D participants with suboptimal blood glucose management (-0.47% to -0.6%; moderate level of evidence) [Beck *et al*., 2017a; Lind *et al*., 2017] and who used the monitor more than 70% of the time [Lind *et al*. 2017]. The size of the decrease in HbA_{1c} in the DIAMOND study was proportional to its initial value [Billings *et al*., 2018]. No effect on HbA_{1c} was observed in T1Ds with well-controlled diabetes who were at high risk for severe hypoglycemia.

The health professionals consulted believe that Dexcom is effective in improving diabetes management in patients who have not achieved optimal control of their disease. According to these professionals, any improvement in HbA_{1c} levels would benefit patients. A decrease in HbA_{1c}, even a modest one, which would be accompanied by a reduction in the number of hypoglycemic events and in glycemic variability, is considered by the clinicians consulted to be an important clinical improvement that would have long-term benefits for the patient. The experts consulted are unequivocal about the relationship between the clinical efficacy of continuous glucose monitors and the extent to which they are used, highlighting the need for pre-use training.

Hypoglycemic events

Clinical studies show a significant reduction in daytime and nighttime non-severe hypoglycemic events in T1Ds who used the Dexcom, regardless of their initial blood glucose control status (low level of evidence) [Heinemann *et al*., 2018; Olafsdottir *et al*., 2018; Riddlesworth *et al*., 2017]. Only the patients at risk for severe hypoglycemia or who were unable to detect hypoglycemia benefited from the technology by way of a reduction in the number of severe events [Heinemann *et al*., 2018]. However, in this study, only severe events that did not require medical assistance were found to be significant.

The advantages of the Dexcom are perceived by the clinicians and patients consulted, particularly for its impact on the duration and severity of hypoglycemic events. In their opinion, the device reduces the intensity of hypoglycemic events without tipping the patient into hyperglycemia. During a hypoglycemic episode, Dexcom G5 users are able to react more quickly and are able to reduce the episode’s duration. Users also note a beneficial effect on the frequency of nighttime events, thanks to the alerts and alarms, and on their ability to detect the presence of previously undetected nocturnal events. Clinicians have also commented that the data provided by CGM devices gives them a better understanding of their patients' glycemic profile, which, in turn, enables them to adjust the treatment more proactively.

Safety

Rare mild adverse events consisting of mild skin irritation, erythema or edema at the sensor adhesion site were observed. No severe adverse effects or cases of ketoacidosis were reported in the studies.

Treatment satisfaction and quality of life

In general, the selected RCTs showed satisfaction with Dexcom use. However, no effect on health status as measured by the EQ-5D questionnaire was observed. Furthermore, in all three RCTs, Dexcom use was not shown to have a significant impact on the fear associated with hypoglycemic episodes as measured by the Hypoglycemia Fear Scale (HFS).

The Dexcom users consulted reported an improvement in their quality of life, especially in terms of reduced stress levels and improved quality of sleep. Possible uptake issues were raised with regard to the adolescent population. The main reasons for discontinuation are alert fatigue, sensor discomfort and sensor insertion/adhesion problems.

Pediatric population

The use of the Dexcom for the pediatric population was approved on the basis of reliability data. No pediatric studies were identified. Nonetheless, the diabetes clinicians consulted believe that the results obtained with this device in adult T1D populations can

be extrapolated to children. Nevertheless, the demonstration of a clinical gain in pediatric patients is based on very limited evidence.

Efficiency

To evaluate the efficiency of the Dexcom G6® System compared to capillary blood glucose monitoring, INESSS developed a semi-partitioned Markov model. Continuous glucose monitoring technologies are aimed at better diabetes management by the patient and therefore generate clinical benefits in terms of decreased HbA_{1c} levels and severe and non-severe hypoglycemic events. However, given the short duration of follow-up in the studies, there is considerable uncertainty as to whether the observed benefits are maintained over time. To quantify this uncertainty, a range of possible cost-utility ratio estimates were generated based on the duration of maintenance.

In one scenario, where the benefits are maintained over a lifetime time horizon, the incremental cost-utility ratio (ICUR) of the Dexcom G6® relative to capillary blood glucose monitoring is approximately $177,000/QALY (quality-adjusted life year). In this scenario, the results of the probabilistic analysis of the efficiency model indicate an 80% probability that the ICUR would range from $130,000/QALY to $229,000/QALY.

However, for the most optimistic ICUR value to be achieved, the benefits would have to be maintained for more than 20 years. On the other hand, the ICUR would be approximately $316,000/QALY if clinical benefits were not maintained beyond the first year.

Budget impact analysis

Coverage of the Dexcom G6® System for type 1 diabetics under 18 years of age could result in expenditures of approximately $7.6 million over 3 years for a population of approximately 850 individuals. When the market shares are varied by 15%, the results of the probabilistic budget impact analysis show that there is an 80% probability that expenditures would range between $6.3 million and $8.7 million. For adults, the expenditures would be approximately $61 million over 3 years for a population of approximately 9,100 individuals. The probabilistic budget impact analysis shows an 80% probability that the expenditures for adults with TD1 would range between $51 million and $71 million.

SUMMARY OF DELIBERATIONS

The members of the Comité scientifique de l'évaluation des médicaments aux fins d'inscription (CSEMI) unanimously recognize the incremental therapeutic value of the Dexcom G6® **for type 1 diabetics over 2 years of age** compared to capillary blood glucose self-monitoring. However, the cost-benefit ratio, which is subject to considerable uncertainty, was judged to be too high. In the interest of fairness, the Committee members felt that at the price submitted, public coverage of Dexcom G6® was not an equitable and reasonable option.

Reasons for the members' unanimous position

- More than 70% of T1D patients have suboptimal glycemic control.
- Non-severe and severe hypoglycemic episodes are a significant problem in T1D patients.
- The pediatric population is a population at risk for severe hypoglycemia and hyperglycemia.
- The members recognize, based on the clinical data and expert opinions, a clinically significant decrease in HbA_{1c} and both severe and non-severe hypoglycemic events with the use of the Dexcom G6® compared to capillary blood glucose self-monitoring.
- The members felt that a large proportion of T1D patients could potentially benefit from the use of Dexcom G6® for glucose self-monitoring. Despite optimal disease management, some T1D patients have inadequate glycemic control or are prone to frequent hypoglycemic episodes.
- Nevertheless, uncertainties remain regarding the long-term impact on the prevention of diabetic complications and its reproducibility in real-world settings:
    - Consistent use of the Dexcom G6® is necessary to ensure its clinical impact on diabetes management (more than 70% of the time).
    - Dexcom G6® use confers benefits to patients and clinicians, but the technology is intended for users who are willing to be actively involved in the management of their disease. Therefore, pre-use training on the Dexcom G6® and ongoing support from the diabetes team are essential for achieving meaningful results.
- The cost-benefit ratio, which is highly uncertain, was considered unacceptable by the Committee's members.
- The budget impact would be very significant.

At the proposed price, public coverage of the Dexcom G6® System does not constitute an equitable allocation of the public health care and social services system's resources.

INESSS's recommendation

The Institut national d'excellence en santé et en services sociaux recognizes the significant disease burden in patients with type 1 diabetes and the potential benefits of the Dexcom G6® System. The price proposed by the manufacturer does not make for an efficient option, and coverage would not be a fair, reasonable and equitable option. Consequently, INESSS recommends that the Dexcom G6® System not be covered under these conditions.

In the event of an agreement with the manufacturer, INESSS suggests the following payment indications for the Dexcom G6®:

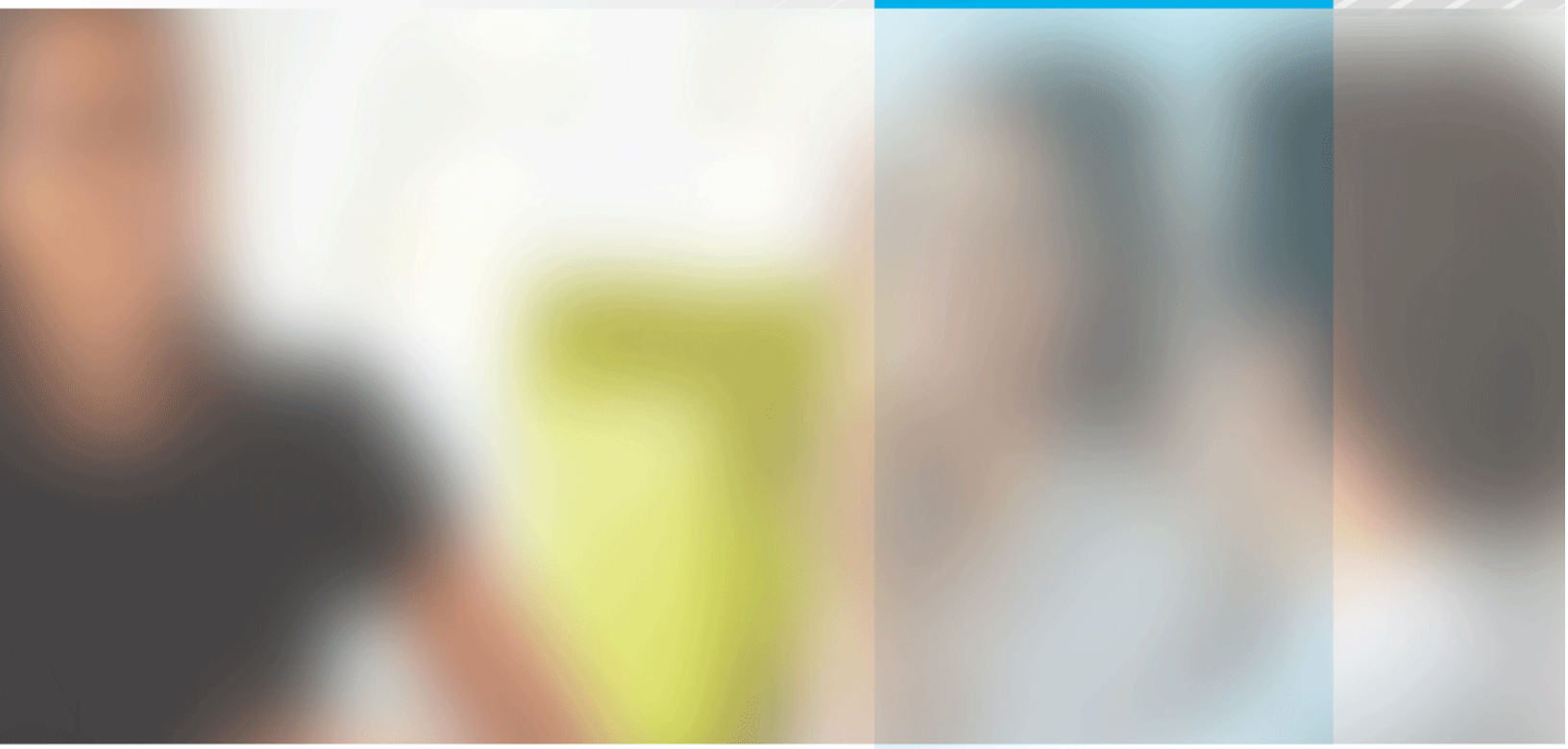
- Type 1 diabetics aged 2 years or older who meet one or more of the following criteria:
  - Inadequate glycemic control despite optimal management of the disease;
  - Frequent hypoglycemic episodes despite adherence to a blood glucose management plan;
  - The inability to recognize or report symptoms of hypoglycemia.

The initial request is authorized for a period of 6 months to assess the patient's ability to use the Dexcom G6® and to wear the sensor.

Requests to continue the treatment are authorized for up to 12 months if the patient demonstrates optimal use of the Dexcom G6®, i.e., at least 70% of the time.

Specific considerations regarding implementation

- Pre-use training on the Dexcom G6® to enable patients to become proficient in applying the sensor and to learn how to interpret and use the information it transmits.
- Ongoing support from the diabetes team.



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