INESSS
LE SAVOIR PREND FORME

OCTOBER 2018

Flashglucose monitoring system (Freestyle Libre[MC], Abbott)

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

This is the English summary of the guidance entitled Système flash de surveillance du glucose (FreeStyle LibreMC, Abbott) published in October 2018.

The complete version of this guidance (in French) is available on the website of INESSS in the Publications section.

Membres de l'équipe de projet

Auteures principales
Nathalie Jobin, Ph. D.
Sylvie Arbour, Ph. D.

Collaborateurs internes
Sara Beha, M. Sc.
Marie-Ève Brouard, B.A., M.A.
Isabelle Ganache, Ph. D.
Mireille Goetghebeur, Ph. D.,
Karen Médina, M.D.
Olivier Demers-Payette, Ph. D.
Geneviève Plamondon, M.Sc.
Marie-Pascale Pomey, M.D., Ph. D.

Coordonnateurscientifique
Yannick Auclair, Ph. D.

Adjointe à la direction
Marième Simoncelli, B. Pharm, M. Sc.

Directrice
Michèle de Guise, M.D., FRCPC

Repérage d'information scientifique
Caroline Dion, M.B.S.I., *bibl. prof.*
Mathieu Plamondon, M.S.I.
Lysane St-Amour, M.B.S.I.
Julien Chevrier, M.S.I.
Flavie Jouandon, *tech. doc.*

Gestion de l'information
José Pérez, M.Sc.
Mike Benigeri, Ph. D.
Michèle Paré, M.Sc.

Soutien administratif
Christine Lemire

SUMMARY

The *Institut national d'excellence en santé et en services sociaux* (INESSS), at the request of the *ministère de la Santé et des Services sociaux* (MSSS), evaluated the relevance of reimbursing Freestyle Libre[MC] (Abbott) flash glucose monitoring systems (FGMS) under the prescription drug insurance plan (RGAM).

FGMS is a flash (or intermittent) real-time glucose level monitoring device. In Canada, its current indication is approved for measuring the glucose from interstitial fluids in adults of at least 18 years of age with at least two (2) years of experience in diabetes self-management.

Description of the technology under study

FGMS measures in real time the level of glucose without a single finger prick. A thin, flexible and sterile fiber, connected to a small disk held in place by medical adhesive, is inserted just under the skin. This sensor is designed for wear to the back of the upper arm for up to fourteen (14) days. The device collects glucose measurements from the interstitial fluid; the data is generated automatically every 15 minutes and has an 8-hour buffer memory.

Each scan of the reader over the sensor displays the value of interstitial glucose, 8 hours of glucose history and a trend arrow indicating if glucose is going up or down or changing slowly or rapidly. Treatment-related decisions must be made on the basis of real-time glucose values, orientation of the trend arrow, glucose history chart and glucose level readings.

The reader can store 90 days of data, including notes taken by the user (insulin, food intake, physical activity). The reader generates several reports: average glucose level over the past 7, 14, 30 and 90 days; day-to-day trends; number of hypoglycemia events; time spent in the glycemic target; and sensor use. The data can be downloaded in a computer with a specific software.

The manufacturer specifies that the sensor may display incorrect values if sugar levels fluctuate rapidly (this may occur after meals, insulin intake or physical activity) or in the presence of interfering substances (including ascorbic acid, or vitamin C, and medication with salicylic acid like Aspirin[MC]). It is mentioned that one should not rely solely on sensor readings if users perform activities where they can hurt themselves or hurt someone in the event of severe hypoglycemia (ex.: driving a motor vehicle).

Consequently, finger-stick testing with a capillary blood glucose reader remains necessary in certain situations:

- To confirm imminent hyperglycemia or hypoglycemia reported by FGMS readings;
- If symptoms are inconsistent with FGMS results.

Methods

Prior to delivering this notice, a systematic review of relevant literature was completed to identify evidence-based findings needed for assessing and completing the information provided by the manufacturer. Then, panels of patients (users and non-users of the technology in question) and clinicians with expertise in diabetes management were set up for gathering experiential and contextual data to help understand various viewpoints on FGMS; hence, criteria for diversifying the individuals to be consulted were defined and established for each panel to highlight potential advantages, disadvantages and concerns linked to FGMS use. Also, an economic evaluation and a budget impact analysis were conducted. All the data gathered and delivered by the project team was submitted to the Standing Scientific Committee on Entry on the List of Medications (CSEMI) for deliberation on therapeutic values of the FGMS prior to formulating recommendations.

Results

Evidence-based findings

While several studies were identified, available scientific evidence rests chiefly on two studies: IMPACT (Bolinder et al., 2016) and REPLACE (Haak et al., 2017). These two multicentre, non-blinded randomized clinical trials (RCT) were financed by the manufacturer, each involving a 6-month intervention period. The data was collected in the first and last fourteen (14) days of the study period and during which control group members were wearing a FGMS in hidden mode. These studies compared FGMS efficiency and safety to that of capillary blood sampling inpatients with type 1 (TD1) and type 2 (TD2) diabetes under insulin treatment. The IMPACT study involved the participation of 239 patients with DT1 and good blood glucose control; the primary variable was time spent in hypoglycemia. The REPLACE study involved the participation of 224 patients with TD2 diabetes and poor blood glucose control; the primary variable was glycated hemoglobin (HbA1c) level after 6 months. A risk of bias should be borne in mind given the methodological limitations of these studies.

Glycated hemoglobin (HbA1c)

A certain number of patients and clinicians consulted raised the fact that FGMS could have some effect on diabetes control: optimal frequency for self-monitoring of blood glucose, portrait of glycemic fluctuations for proactive treatment adjustment, and clearer understanding of positive effects of proper nutrition and life habits on blood glucose. In the IMPACT and REPLACE studies, however, these potential advantages do not translate into improvement of HbA1c values. The IMPACT study did not aim to demonstrate improvement in HbA1c, since the participants with DT1 were a priori patients with well controlled diabetes. The authors' hypothesis consisted in reducing the number of hypoglycemia events while maintaining HbA1c levels within the limits of normal values in patients. Conversely, the main outcome of interest in the REPLACE study was improving HbA1c values in patients with TD2 and poor diabetes control. In the overall, no improvement was observed in the group after six (6) months of using a FGMS.

Hypoglycemia

One potential benefit of using this device was raised in meetings with the patients and clinicians consulted: detection of daytime and nighttime hypoglycemia events. Documented information on glucose value excursions – which normally remain undetected – and data on upward or downward sugar level trends are elements of information considered to be of interest. However, FGMS overestimation of hypoglycemic events and necessity to validate with capillary blood glucose tests were matters raised by a few patients and clinicians; this would have led some patients to lose confidence in this device and others to develop anxiety.

The IMPACT and REPLACE studies report statistically significant reductions in duration and number of daytime and nighttime hypoglycemic events after using FGMS. Relative reductions of nearly 50% in time spent each day with glucose values inferior to 3,1 mmol/l were observed. These results translate after six months into an average daily reduction of about 50 minutes in patients with TD1 (IMPACT) and about 10 minutes in patients with TD2 (REPLACE). The IMPACT study reveals a significant increase in average daily time spent with glucose values within the desired target range (3.9 mmol/l to 10.0 mmol/l) – the equivalent of about 1 hour daily – after six (6) months. No differences were observed in the REPLACE study. It is difficult to evaluate the actual clinical effects of these results.

It is important to stress, however, that no significant differences were observed as regards severe hypoglycemic events – events requiring assistance from another person to treat and with proven clinical and economic effects. Severe hypoglycemic event is a parameter with a greater degree of objectivity and independent of FGMS. Since such events rarely occur, the size of the study populations was too small to observe any differences.

Safety

According to the individuals consulted, and while some users experienced adverse injection-site reactions (e.g. irritation), using FGMS is considered to be safe. The risk of erroneous readings leading to inadequate treatment decisions is real and was discussed by the panel participants. It is pointed out, however, that such risk may be lessened with validation of capillary blood glucose level, in case where symptoms not correlate with FGMS values. The panel participants put emphasis on the need to provide training to users and healthcare teams so as to ensure optimal FGMS use as part of diabetes treatment.

These findings are corroborated in the IMPACT and REPLACE studies. Except for those associated with injection-site reactions (erythema, pain, itching, bleeding, oedema, bruise, induration), undesirable events listed by both groups are similar.

Treatment satisfaction and quality of life

Consulted patients and clinicians recognize that pricking one’s finger less frequently for measuring capillary blood glucose levels can improve the quality of life of persons with diabetes. Easier glucose self-monitoring, greater flexibility and fewer constraints in terms

of participation in certain sports are among the elements mentioned. It seems, however, that not all patients enjoy these benefits, for some mentioned that FGMS could be more complicated to use. Certain patients and clinicians consulted also mentioned that FGMS could suit the specific needs of certain populations, including individuals with visual impairment (e.g.: the challenge of putting a drop of blood onto a small test strip; less finger sensitivity to read Braille) and persons whose professional occupations require tight blood glucose monitoring but have difficulty pricking the tip of their fingers as often as is desirable.

The IMPACT and REPLACE studies mention significant improvement in treatment satisfaction, but report no significant difference in other aspects of quality of life that were measured by three validated questionnaires: *Diabetes quality of life* (DQOL), *Diabetes Distress Scale* (DDS)and *Hypoglycemia Fear Survey* (HFS). These questionnaires reveal no significant impact on the following aspects: treatment effect, socio-professional apprehension, diabetes-related apprehension, hypoglycemia-related apprehension, emotional burden, interpersonal distress and lifestyle-related distress.

Long-term complications of diabetes and use of healthcare resources

The data available does not allow to evaluate the effect of FGMS in terms of long-term complications of diabetes and use of healthcare resources.

Efficiency

After deliberations, it was considered that too much uncertainty still existed in the evidence of efficiency to recognize the incremental therapeutic value of FGMS compared to capillary glycemia testing.

The INESSS therefore conducted a cost minimization study on four (4) target populations. The average annual cost of FGMS and capillary glycemia testing, per patient, was respectively estimated to:

- $2,717 and $803, for patients under insulin treatment (IT);
- $2,748 and $1,080 for patients with TD1 under intensive insulin treatment (TD1II);
- $2,717 and $895 for patients with TD2 under intensive insulin treatment (TD2II);
- $2,748 and $2,397 for patients under intensive insulin treatment (II) using more than 8 test strips daily.

It was found that, irrespective of the population under study, the cost of using FGMS is superior to the average cost of conducting capillary blood glucose testing; FGMS is therefore a nonefficient option. A probabilistic analysis conducted by the INESSS[1] reveals that FGMS has zero probability to be efficient for a population with TD2II and near-zero probability to be efficient for a population with TD1II and IT (0.15% and 0.3% respectively). However, it reports a 17% probability that FGMS is efficient for patients using at least 8 test strips daily.

[1] For more details, refer to Appendix H

Budget impact analysis

The probabilistic sensitivity analysis conducted on considered sub-populations reveals an 80% probability that additional costs incurred with the entry of FGMS on the RGAM list in the first three (3) years would vary as follows:

- $25 M to $37 M for patients with type 1 diabetes under intensive insulin therapy;
- $75 M to $109 M$ for patients with type 2 diabetes under intensive insulin therapy;
- $127 M to $187 M for all patients with diabetes under insulin therapy;
- -$0.007 M to $1.7 M for patients using more than 8 test strips daily.

Deliberation on all criteria laid down by law

The members of the *Comité scientifique de l'évaluation des médicaments aux fins d'inscription* (CSEMI) unanimously share the opinion to enter FreeStyle Libre[MC] on the RGAM list of medications for glycemia self-monitoring in patients under insulin treatment if a measure for easing the economic burden is implemented.

If no measure is implemented to reduce the economic burden, the members unanimously share the opinion to enter FreeStyle Libre[MC] on the list of exception drugs in accordance with the proposed recognized payment indication.

The Committee recommendation is formulated at the end of this notice and represents the position of the INESSS.

Reasons regarding the common position of the Committee members who exerted their voting right

- The consultations conducted with clinicians and patients highlighted many potential advantages of using FGMS, including lesser discomfort caused by finger pricking, professional and personal convenience and greater flexibility in illness management. It is also recognized that, by conducting capillary blood glucose testing, some patients, in particular those under intensive insulin treatment, conduct blood glucose self-monitoring deemed less than optimal if compared to current recommendations on good clinical practice.
- While clinical studies report statistically significant differences in terms of time spent in hypoglycemia and number of hypoglycemia events and time spent in the glycemic target, the degree of evidence is considered to be low and the actual clinical effect of the results observed are seen as highly uncertain.
- Compared to capillary blood glucose testing, no improvement in glycated hemoglobin rates (HbA1c) was observed in randomized clinical trials (RCT).
- The studies available do not allow to evaluate the effect on incidence of severe hypoglycemia events and the long-term effects on prevention of diabetes complications and use of healthcare resources.
- The positive effect of FGMS on the overall quality of life of patients is yet to be demonstrated.
- FGMS has a safety profile considered as acceptable. However, the frequency of injection-site reactions was mentioned and is a matter of concern.

- Given the limits of scientific proof available, the incremental therapeutic value of FGMS compared to that of capillary blood glucose testing was not recognized. Clearer demonstration of scientific proof is considered necessary.
- The members recognize that FGMS, like capillary blood glucose testing, could give patients greater autonomy in the management of their illness.
- Given the absence of recognized incremental therapeutic value compared to capillary blood glucose testing and its high cost, FGMS is not considered an efficient option.
- For patients under intensive insulin therapy whose diabetes is hard to control or patients who suffer frequent or severe hypoglycemia and require to measure their glycemia level at least 8 times daily, the incremental cost could be considered acceptable.
- The budget impact is very significant.

INESSS RECOMMENDATION

ENTRY – With condition

Recommendation

The *Institut national d'excellence en santé et en services sociaux* (INESSS), considering all the criteria laid down by law, recommends to the Minister of Health and Social Services to enter FreeStyle Libre^{MC} on the list of the prescription drug insurance plan (RGAM) for blood glucose self-monitoring for patients under insulin treatment, provided that the following condition is met.

Condition

Easing the economic burden

If the economic burden is not lessened, the INESSS recommends to enter FreeStyle Libre^{MC} on the list of exception drugs in accordance with the proposed recognized payment indication.

Recognized payment indication

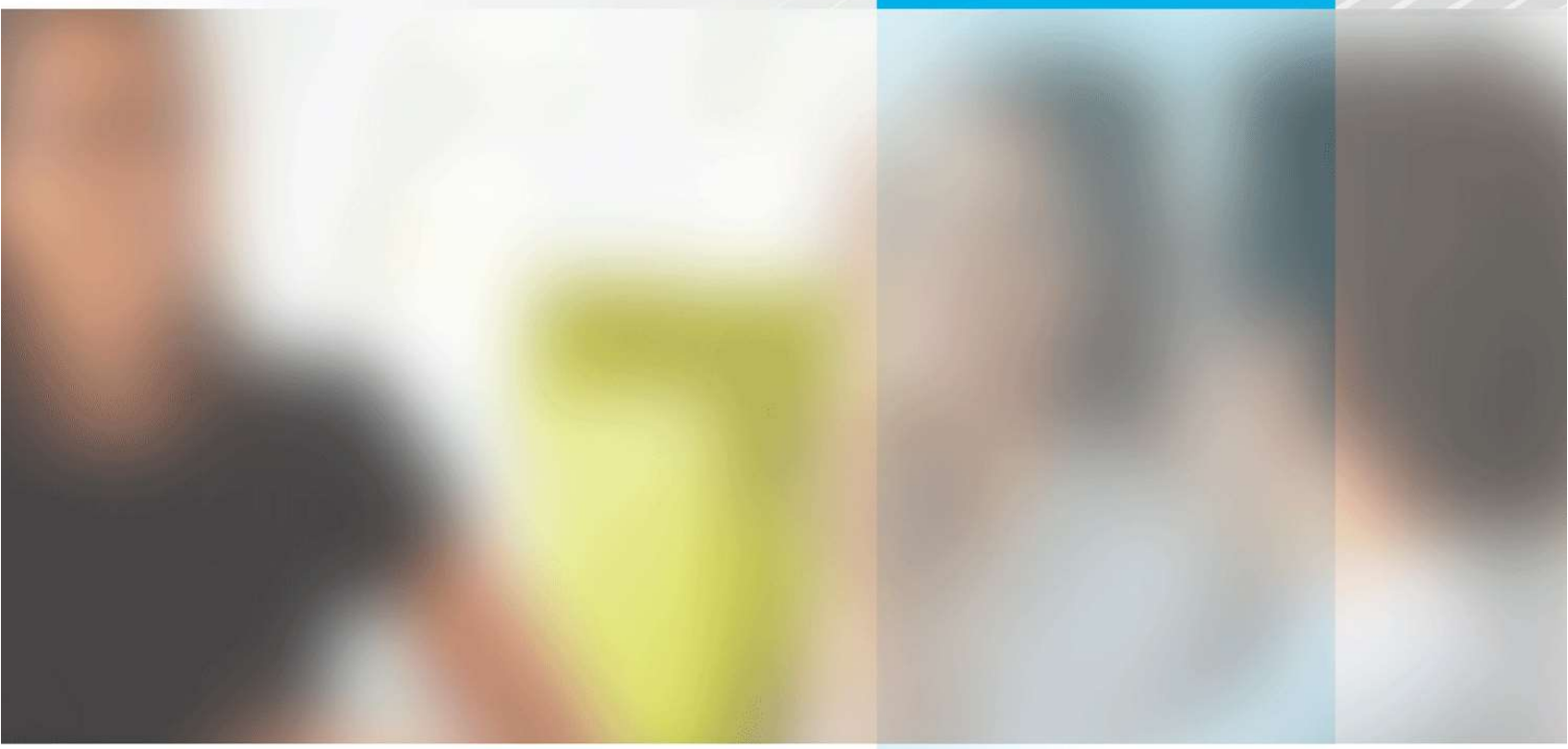
- Persons of minimum 18 years of age with at least two (2) years of experience in diabetes self-management who meet the following three (3) criteria:
    - Under intensive insulin treatment
    - Frequent or severe hypoglycemic events
    - Necessity for blood glucose self-monitoring at least 8 times daily

Initial request is authorized for three (3) months to evaluate patient capacity to use FreeStyle Libre^{MC} and wear the sensor.

Requests to pursue treatment authorized for maximum twelve (12) months if patients show a capacity to make an optimal use of Freestyle Libre^{MC}, i.e., at least 70% of the time.

Specific implementation-related consideration

Training so that patients can master sensor application and learn how to interpret and use the information provided by the device.



Siège social

2535, boulevard Laurier, 5e étage
Québec (Québec) G1V 4M3
418 643-1339

Bureau de Montréal

2021, avenue Union, 12e étage, bureau 1200
Montréal (Québec) H3A 2S9
514 873-2563
inesss.qc.ca

Institut national d'excellence en santé et en services sociaux
Québec