A Review of the First Long-term Implantable Continuous Glucose Monitoring System Available in the United States

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Abstract

Background: Although real-time continuous glucose monitoring (rtCGM) has been shown to improve glycemic control in patients with type 1 diabetes mellitus and type 2 diabetes mellitus treated with insulin, rates of adoption have been low. A novel approach, with the use of a long-term implantable continuous glucose monitoring (LTI CGM) has the potential to overcome barriers to rtCGM. The purpose of this review is to provide a background on the first LTI CGM technology to be approved, along with a review of contraindications, interference, safety, accuracy, and efficacy. Considerations for patient selection are discussed based on the available evidence.

Methods: PubMed, EMBASE, and Cochrane Library were searched for keywords and subject headings to identify studies assessing LTI CGM.

Results: Seven studies were identified which assessed LTI CGM. Mean absolute relative difference is similar to available CGM devices. Rates of adverse events were low. Change in hemoglobin A1c with LTI CGM may be comparable to rtCGM.

Conclusions: Based on the available evidence, LTI CGM appears to be safe and accurate. Additional clinical trial investigation is warranted to evaluate the glycemic efficacy of LTI CGM.

Keywords

continuous glucose monitoring, diabetes, diabetes technology, implantable glucose sensor

Background

Continuous glucose monitoring (CGM) is an alternative to self-monitoring of blood glucose (SMBG) and allows patients with diabetes to react to glycemic patterns, which can inform meal intake, physical activity, carbohydrate counting, and medication adjustments.¹ As compared with SMBG, real-time CGM (rtCGM) and intermittent-scanned CGM (isCGM) technology have been shown to improve glycemic control in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).^{2–5} Although there are clinical benefits to rtCGM and isCGM, a common barrier is the need to frequently replace sensors every 6 to 10 (depending on the device) or 14 days, respectively. Moreover, up to 41% of patients in the T1D registry discontinued rtCGM use in the first year from discomfort, trouble inserting the sensor, poor sensor adherence to skin, cutaneous reactions, and interference with sports and physical activity.⁶

Eversense Long-term Implantable CGM

A novel long-term implantable (LTI) subcutaneous CGM device (Eversense CGM System; Senseonics, Inc., Germantown, MD, United States) was approved by the U.S. Food & Drug Administration (FDA) on June 6, 2019, and has been available in the European Union and European Economic Area since May 2016.⁷ The device is indicated in the United States for adults aged 18 years or older with

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diabetes. Historical data from the system can be used non-adjunctively to replace SMBG for making diabetes treatment decisions, although it requires two fingersticks daily with SMBG for calibration. The Eversense LTI CGM system contains an implantable fluorescence-based sensor, transmitter, and a mobile application (downloadable by smartphone or tablet).

Technology

Sensor

The sensor (3.5×18.3 mm) contains core electronics and optics, and is sealed in epoxy within a polymethyl methacrylate (PMMA) encasement. A 100- μ m-thick copolymer matrix is grafted to the outside of the PMMA encasement. This polymer is fluorescent and uses selective, fully reversible binding between glucose and a covalently attached molecular complex to sense changes in interstitial glucose. When glucose binds, there is an increase in fluorescent intensity, which is measured by the sensor's optical system. The sensor sends fluorescent measurements to the externally worn transmitter for calculation and storage of glucose values every five minutes via Bluetooth transmission.

Within the sensor is a silicone collar component containing 1.75 mg of dexamethasone, which is released at 3 μ g per day over the sensor's life to reduce tissue inflammation around the sensor. The sensor must be inserted by a health-care provider in-office and needs to be replaced every 90 days (Eversense; currently available in the United States) or up to 180 days (Eversense XL; not available in the United States). The sensor is also designed to provide an alert to the user when it needs to be replaced.

Transmitter

The transmitter (1.5×1.7 inches; 0.6 inches thick) is worn externally over the inserted sensor and uses Bluetooth low energy technology to wirelessly send interstitial glucose information to the mobile medical application (MMA) for display on a handheld device. The transmitter uses a rechargeable battery and can be charged with a supplied universal serial bus powered cradle. The transmitter is also capable of providing vibration signals to the user for the detection and prediction of episodes of hypo- or hyperglycemia, even if the MMA is not close by the user.

Mobile Medical Application

The MMA receives and displays calculated glucose information from the transmitter. Glycemic information available to display includes real-time glucose readings, glucose trend information, and glucose alerts.

Contraindications and Interference

The device should not be used if the patient is going to undergo magnetic resonance imaging (MRI) procedures, unless the MRI meets criteria including a static magnetic field of 1.5 or 3.0 T, the maximum spatial field gradient is 2000 G/cm, and the maximum whole body specific absorption rate is 4 W/kg.⁸ Additional contraindications include lithotripsy, diathermy, or electrocautery. Forty-one potentially interfering substances were evaluated in an in vitro study.⁹ Tests were performed at two glucose concentrations (77 and 321 mg/dL) except for sugar alcohols, which were tested at 54, 108, and 271 mg/dL.⁹ The results indicated that only two substances, mannitol, and tetracyclines, may interfere with glucose measurement with the LTI CGM system.⁹ Notably, neither acetaminophen nor ascorbic acid produced a sensor bias that exceeded International Standardization Organization (ISO) limits.⁹

Safety and Accuracy

The PRECISE trial evaluated the accuracy, longevity, and impact of the Eversense LTI CGM device for up to 180 days.¹⁰ This study was a prospective, multicenter trial in adults (≥ 18 years of age) with T1DM and T2DM conducted in Europe.¹⁰ Results demonstrated that the overall mean absolute relative difference (MARD) was 11.1% (95% CI: 10.5%-11.7%) for samples >75 mg/dL, and 84% of CGM values were within 15 mg/dL or 20% of the Yellow Springs Instruments (YSI) reference glucose values.¹⁰ Clarke Error Grid analysis showed 99.2% of samples to be within the clinically acceptable error zones A and B.¹⁰ While no serious device-related adverse events occurred, 14 device- or procedure-related nonsevere adverse events occurred ($n = 11$).¹⁰ Five cases of skin reactions were recorded.¹⁰ Two cases of incision skin infection occurred of which one required antibiotics.¹⁰ Although quality of life was unchanged at study conclusion, 84% of subjects stated that they would want to use the Eversense LTI CGM in the future and 90% felt that the system helped them minimize diabetes burden.¹⁰

The PRECISE II trial sought to assess the accuracy and safety of the Eversense LTI CGM device in adults (≥ 18 years of age) with T1DM and T2DM for up to 90 days.¹¹ This was a nonrandomized prospective blinded, single-arm multicenter study with 90 subjects conducted in the United States.¹¹ The overall MARD was 8.8% (95% CI: 8.1%-9.3%). Ninety-three percent of Eversense LTI CGM values were within ± 20 mg/dL or 20% of YSI reference glucose values.¹¹ Clarke Error Grid analysis showed 99.3% of samples to be within the clinically acceptable error zones A (92.8%) and B (6.5%).¹¹ During the study, 14 adverse events were noted and related to device insertion or removal.¹¹ Twelve of the events were classified as mild, and two were classified as moderate in severity.¹¹ There were

nine documented events of bruising, erythema, or pain/discomfort.¹¹ One serious adverse event was documented because the sensor could not be removed on first attempt.¹¹

In a third study (PRECISION), accuracy and safety of the Eversense LTI CGM device in adults (≥ 18 years of age) with T1DM and T2DM was further confirmed up to 90 days.¹² This was a nonrandomized, prospective multicenter study with 35 subjects conducted in the United States. Overall MARD was 9.6% (95% CI: 8.9%-10.4%).¹² The overall percentage of CGM values within 15/15% of YSI reference was 85%.¹² Notably, the Eversense LTI CGM system agreement within the hypoglycemic range was 92% between 40 and 60 mg/dL and 87% between 61 and 80 mg/dL with a corresponding MARD of 7.2 and 7.6 mg/dL, respectively.¹² There were a total of eight adverse events among five subjects either related or possibly related to the device or insertion/removal during the study.¹² Twenty percent of participants reported being unwilling to use the device again after the study.¹²

Although not approved in the United States, the Eversense XL LTI CGM system has a life span of 180 days as compared with 90 days with the original Eversense LTI CGM system. In a nonrandomized, nonblinded, prospective, single-center study in Canada of patients with T1DM (aged ≥ 12 years), the overall MARD for the Eversense XL LTI CGM was 9.4% (95% CI: 8.6%-10.5%).¹³ The Eversense LTI CGM system agreement at 15/15% ($n = 7,163$) through 60, 120, and 180 days was 82.9% (95% CI: 78.4%-86.1%), 83.6% (95% CI: 80.4%-85.7%), and 83.4% (95% CI: 79.7%-85.5%), respectively.¹³ The surveillance error grid analysis showed 98.4% of paired values to be within clinically acceptable error zones A and B.¹³ There was no insertion, removal, or device-related serious adverse events that occurred with the Eversense XL LTI CGM device.¹³ In this study, 82% of participants agreed or highly agreed that the Eversense XL LTI CGM was easy to use.¹³ No additional studies have been published to date including children or adolescents.

To date, only one study has investigated the accuracy of the Eversense LTI CGM device as compared with the Dexcom G5 rtCGM and the FreeStyle Libre Pro isCGM devices.¹⁴ In this study conducted under real-world conditions, the MARD compared with plasma glucose for the Eversense LTI CGM was 14.8%, Dexcom G5 rtCGM was 16.3%, and FreeStyle Libre Pro isCGM was 18% (Eversense vs FreeStyle Libre Pro, $P = .004$; other $P = \text{NS}$).¹⁴ Of note, this study was conducted in 23 subjects with T1DM who wore all three devices concomitantly. When taken together, the overall MARD from the PRECISE, PRECISE II, and PRECISION was 11.1% (95% CI: 10.5%-11.7%),¹⁰ 8.8% (95% CI: 8.1%-9.3%),¹¹ and 9.6% (95% CI: 8.9%-10.4%),¹² respectively. The overall MARD is comparable to that seen with several commonly used rtCGMs including the Dexcom G6 (9%),¹⁵ Medtronic Guardian Sensor 3 (9.1%),¹⁶ and Medtronic Guardian Connect (9.4%).¹⁶ MARD with the isCGM (FreeStyle Libre) has been reported to be between 11.4% and 13.2%.^{17,18}

Postmarketing data evaluating the Eversense LTI CGM among adults (≥ 18 years of age) with T1DM and T2DM ($n = 3023$) across 534 sites in Europe and South Africa demonstrated that the most frequently reported adverse events were related to sensor location site infection (0.96%; 2.46 events per 100 person-years), inability to remove the sensor upon first attempt (0.76%; 1.90 events per 100 person-years), and adhesive patch location site irritation (0.66%; 1.59 events per 100 person-years).¹⁹ Safety and accuracy data from the aforementioned studies are summarized in Table 1.

Glycemic Efficacy

The PRECISE study found a -0.35% decrease (95% CI: -0.55% , -0.21% ; $P < .001$) in hemoglobin A1c (HbA1c) at 180 days as compared with baseline HbA1c values.¹⁰ Aronson et al also found that HbA1c decreased at day 90 (-0.6%) and at day 180 (-0.2%) as compared with baseline HbA1c among adolescents. However, among adults in the study, HbA1c decreased (-0.1%) at day 90, but increased ($+0.1\%$) at 180 days.¹³ The changes in HbA1c with LTI CGM in these two studies are comparable to that seen with several studies of rtCGM and isCGM.^{2,20-22}

Using de-identified glucose data (Eversense LTI CGM) from the Eversense data management system, Sanchez et al found that the percentage of sensor glucose readings at <54 mg/dL was 1.2%, <70 mg/dL was 4.1%, time in normal glycemic range (70-180 mg/dL) was 62.3%, >180 -250 mg/dL was 21.9%, and > 250 mg/dL was 11.6% at 90 days.²³ The median transmitter wear time in this analysis utilizing post-marketing data was 83.6%.²³ This real-world analysis suggests that the Eversense LTI CGM may provide similar benefits to isCGM and conventional rtCGM, although additional comparative efficacy analysis is lacking at this time.²³ However, there are several ongoing clinical trials designed to further evaluate the glycemic efficacy of the Eversense LTI CGM (Table 2).²⁴

Conclusion and Patient Selection

Based on the available evidence, the Eversense LTI CGM appears to be safe and accurate. Additional clinical trial investigation is warranted to evaluate the glycemic efficacy of the Eversense LTI CGM, especially as compared with isCGM and rtCGM devices, which are widely used in clinical practice. Based on limited efficacy data, the Eversense LTI CGM may reduce HbA1c and improve time in glycemic range.^{10,13,23} At this time, there is insufficient evidence to support using LTI CGM use in children <12 years of age, pregnant women, or those planning to become pregnant.

Selection considerations for conventional rtCGM still apply to the Eversense LTI CGM. These include the use of multiple daily insulin injections or continuous subcutaneous insulin infusion, high glycemic variability and frequent, problematic hypoglycemia, and high likelihood of adherence and

Table 1. Summary of Studies Evaluating Safety, Accuracy, and Glycemic Efficacy of Long-term Implantable Continuous Glucose Monitoring.

Study (reference)	Study design	Population	Key outcome(s)
Kropff et al ¹⁰ [PRECISE]	Eversense LTI CGM (n = 71) nonrandomized, prospective, multicenter (n = 7 sites in Europe)	Adults (≥ 18 years of age) with T1DM and T2DM using insulin for 180 days	<ul style="list-style-type: none"> The MARD value against reference glucose values >75 mg/dL was 11.1% (95% CI: 10.5-11.7). Clarke Error Grid analysis showed 99.2% of samples in the clinically acceptable error zones A and B HbA1c improved in the study group from 7.54% at baseline to 7.19% at end of study [-0.35% (95% CI: -0.55%, -0.21%); $P < .001$] No device-related serious adverse events occurred during the study. Fourteen device or procedure-related nonsevere adverse events occurred (n = 11). Five cases of skin reactions were recorded. Two cases of incision site infection occurred Quality of life was unchanged from baseline to end of study, although there was a high device acceptance and reduction in self-perception of minimizing diabetes burden
Christiansen et al ¹¹ [PRECISE II]	Eversense LTI CGM (n = 90) nonrandomized, prospective, multicenter (n = 8 sites in United States)	Adults (≥ 18 years of age) with T1DM and T2DM for 90 days	<ul style="list-style-type: none"> The MARD value against reference glucose values was 8.8% (95% CI: 8.1%-9.3%). Ninety-three percent of CGM values were within 20/20% of reference values over the total glucose range of 40-400 mg/dL. Clarke Error Grid analysis showed 99.3% of samples in the clinically acceptable error zones A (92.8%) and B (6.5%) Ninety-one percent of sensors were functional through day 90 There were a total of 14 adverse events among seven participants (two moderate and 12 mild). Nine events were related to bruising, erythema, or pain/discomfort; eight of these events were considered mild in severity and one instance of arm pain was considered moderate. One serious adverse event occurred secondary to inability to remove the sensor
Christiansen et al ¹² [PRECISION]	Eversense LTI CGM (n = 35) nonrandomized, prospective, multicenter (n = 3 sites in the United States)	Adults (≥ 18 years of age) with T1DM and T2DM for 90 days	<ul style="list-style-type: none"> The MARD value against reference glucose values was 9.6% (95% CI: 8.9%-10.4%). For the hypoglycemic range, CGM system agreement within 40-60 and 61-80 mg/dL was 92% and 87% with corresponding mean absolute difference of 7.2 and 7.6 mg/dL, respectively There were a total of eight adverse events among five participants that were either related or possibly related to the device or insertion/removal procedures. No incision/removal-related infections occurred Plasma dexamethasone levels were undetectable (<0.05 ng/mL) for all participants before insertion. Through the 90-day study, no dexamethasone was detected in any subject after day 8 Twenty percent of participants were unwilling to use the device after the study was complete
Aronson et al ¹³	Eversense XL LTI CGM (n = 36; n = 30 aged 12-17 years) nonrandomized, prospective, single-center in Canada	Adolescents and adults (≥ 12 years of age) with T1DM for 180 days	<ul style="list-style-type: none"> The overall MARD was 9.4% (95% CI: 8.6%-10.5%). CGM system agreement at 15/15% through 60, 120, and 180 days was 82.9% (95% CI: 78.4%-86.1%), 83.6% (95% CI: 80.4%-85.7%), and 83.4% (95% CI: 79.7%-85.5%), respectively. Surveillance error grid analysis showed 98.4% of paired values in clinically acceptable error zones A and B In the adolescent group, HbA1c decreased from $8.1 \pm 1.5\%$ at baseline to $7.5 \pm 1.1\%$ at day 90 and to $7.9 \pm 1.4\%$ at day 180. In the adult group, HbA1c at baseline was $7.5 \pm 1.0\%$, decreased to $7.4 \pm 0.8\%$ at 90 days and increased to $7.6 \pm 0.9\%$ at 180 days No insertion/removal or device-related serious adverse events were reported A high percentage (82%) agreed or highly agreed that the Eversense LTI CGM was easy to use

(continued)

Table 1. (continued)

Study (reference)	Study design	Population	Key outcome(s)
Jafri et al ¹⁴	Eversense LTI CGM vs FreeStyle Libre Pro isCGM vs Dexcom G5 rtCGM (<i>n</i> = 23)	Adults (≥ 18 years of age) with T1DM enrolled in a bionic pancreas study for six weeks	<ul style="list-style-type: none"> The Eversense LTI CGM achieved the lowest MARD (14.8%) followed by Dexcom G5 rtCGM (16.3%) and FreeStyle Libre Pro isCGM (18.0%) Eversense LTI CGM vs FreeStyle Libre Pro isCGM: <i>P</i> = .004, other comparisons <i>P</i> = NS. In the two-way comparison, the MARD difference between the Eversense LTI CGM (15.1%) and the Dexcom G5 rtCGM (16.9%) was statistically significant (<i>P</i> = .008)
Deiss et al ¹⁵	Eversense LTI CGM (<i>n</i> = 3023) across 534 sites in Europe and South Africa	Adults (≥ 18 years of age) with T1DM and T2DM from the Postmarket Clinical Follow-up (PMCF) registry	<ul style="list-style-type: none"> The most frequently reported device-related adverse events were sensor location site infection (0.96%; 2.46 events per 100 person-years), inability to remove the sensor upon first attempt (0.76%; 1.90 events per 100 person-years), and adhesive patch location site irritation (0.66%; 1.59 events per 100 person-years) No serious adverse events were reported Complete sensor life was achieved by 91% of 90-day sensors and in 75% of 180-day sensors
Sanchez et al ¹⁶	Eversense LTI CGM (<i>n</i> = 205) among those who reached a 90-day wear period	De-identified glucose data from the Eversense data management system (<i>n</i> = 129 T1DM; <i>n</i> = 18 T2DM; <i>n</i> = 58 unreported)	<ul style="list-style-type: none"> The overall MARD was 11.2% (standard deviation: 11.3%) Time in glycemic range was 62.3% or 897.7 minutes (~15 hours) during the 24-hour time period and 61.8% for the nighttime There were ten (5%) patients who reported that they experienced transient skin irritation, redness, and/or swelling after sensor insertion or removal procedures, and four (2%) patients who reported mild infection at the insertion site (three which were treated with oral antibiotics)

Abbreviations: CGM, continuous glucose monitoring; HbA1c, hemoglobin A1c; isCGM, intermittent-scanned continuous glucose monitoring; LTI CGM, long-term implantable continuous glucose monitoring; rtCGM, real-time continuous glucose monitoring; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Table 2. Ongoing Clinical Trials to Evaluate Long-term Implantable Continuous Glucose Monitoring.

Study enrollment status	Study title	Intervention/treatment	Population	Key outcome(s)
Enrolling	Eversense and Dexcom G5 Comparison in Real Life: A Randomized Crossover Trial in Type 1 Diabetic Patients to Evaluate Differences in Accuracy, Efficacy and Quality of Life	Dexcom G5 rtCGM vs Eversense LTI CGM	Adults (≥ 18 years of age) with T1DM and HbA1c $< 10\%$ and body mass index $< 35\%$	Primary: Device accuracy, sensor accuracy (MARD) vs capillary blood glucose Secondary: Time spent in target glycemic range, change in HbA1c, sensor failure rate, adverse events, changes in quality of life, and changes in fear of hypoglycemia
Enrolling	An Investigator Initiated Pilot Study to Evaluate the Impact on Glucose Control and Safety of the Eversense Continuous Glucose Monitoring System in Children and Adolescents	Eversense XL LTI CGM	Children (aged 6 to < 18 years) with T1DM and HbA1c $< 11\%$ and pretreated with MDII or CSII for at least three months	Primary: Time in glycemic range Secondary: Time of hypoglycemia
Recruiting	A Post- Approval Study to Evaluate the Long-term Safety and Effectiveness of the Eversense Continuous Glucose Monitoring (CGM) System	Eversense LTI CGM	Adults (≥ 18 years of age) with T1DM or T2DM	Primary: Incidence of procedure-related adverse events, time in glycemic range

(continued)

Table 2. (continued)

Study enrollment status	Study title	Intervention/treatment	Population	Key outcome(s)
Recruiting	PROMISE Study: A Prospective, Multicenter Evaluation of Accuracy and Safety of an Implantable Continuous Glucose Sensor Lasting up to 180 days	Eversense XL LTI CGM	Adults (≥ 18 years of age) with T1DM or T2DM	Primary: Effectiveness measure (MARD), safety endpoint (incidence of device-related or sensor insertion/removal procedure-related serious adverse events)
Recruiting	Benefits of a Long Term Implantable Continuous Glucose Monitoring System for Adults With Diabetes - France Randomized Clinical Trial	Eversense XL LTI CGM	Adults (≥ 18 years of age) with T1DM or T2DM using MDII or CSII	Primary: Efficacy (percentage of HbA1c levels monitored, percentage of time spent in hypoglycemia) Secondary: Adverse events, time in glycemic range, hypoglycemia, mean sensor life, total time to wear transmitter, change in HbA1c, diabetes treatment satisfaction, quality of life, CGM satisfaction, and distress

Abbreviations: CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; HbA1c, hemoglobin A1c; LTI CGM, long-term implantable continuous glucose monitoring; MDII, multiple daily insulin injections; rtCGM, real-time continuous glucose monitoring; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

CGM sensor wear time. Cost must also be considered, and providers must be aware of criteria for CGM use, which varies, based on payer type. Additional characteristics to identify those most likely to benefit from the Eversense LTI CGM device are as follows: (1) patients who perceive frequent sensor replacement a burden,²⁵ (2) patients who would benefit from on-body vibration alerts,²⁵ (3) those with a history of skin problems or oversensitivity to adhesives such as isobornyl acrylate,^{25,26} (4) those with a need for transient removal of external devices such as those with a high level of physical activity,²⁵ (5) those physically handicapped (visual, hearing, dexterity),²⁵ or (6) those with a pain or needle phobia.²⁵

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