Healthy Blue

Medical Policy

Subject:	Implantable Interstitial Glucose Sensors		
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Description/Scope

This document addresses the use of implantable interstitial glucose sensors (for example, the Eversense™ Continuous Glucose Monitoring System [Senseonics, Germantown, MD]). Such devices have been proposed as an alternative method of continuous interstitial glucose monitoring. These devices are inserted subcutaneously into the upper arm for up to 90 days and then removed or replaced.

For more information regarding interstitial glucose monitoring, please see:

- CG-DME-42 Non-implantable Insulin Infusion and Blood Glucose Monitoring Devices

Position Statement

Investigational and Not Medically Necessary:

Use of implantable interstitial glucose sensors is considered **investigational and not medically necessary** for all indications.

Rationale

The U.S. Food and Drug Administration (FDA) approved the Eversense continuous interstitial glucose monitoring (CGM) system on June 21, 2018 for continually measuring glucose levels in adults 18 years and older with diabetes for up to 90 days. Additional approval for use up to 180 days was granted on September 30, 2020,

The available published evidence addressing the use of these devices is limited. Kropff (2017) reported the results of the PRECISE trial, a prospective pivotal trial involving 71 subjects with type 1 diabetes. Subjects had the Eversense device implanted for 180 days and used the device continuously throughout the study period. Additionally, subjects underwent five 24-hour and three 8-hour in-clinic device performance assessments, as well as baseline and 2-week post-explantation visits. At the implantation visit, one device was implanted into both upper arms of the subjects. Subjects were allowed to choose the location and sensor to be used as the primary study sensor. A transmitter was then worn over the primary sensor and calibrated twice daily with blood glucose testing. The secondary sensor was used during the eight performance evaluations. Overall, 6 subjects withdrew from the trial and an additional 6 had electronic or mechanical failure of their devices. Data for these subjects was censored. An additional 5 subjects required replacement of faulty sensors within 3 months. Both subjects and investigators were blinded to the CIGM values during the performance evaluations. However, CIGM data was available to the subjects throughout other periods of the study and was used to guide self-treatment decisions after blood glucose

confirmation. The authors noted that the performance of the Eversense device in the hypoglycemic range, (≤ 75 mg/dL), was less than the overall performance (21.7% vs. 11.6% mean absolute relative difference [MARD], p<0.001). A significant decrease in sensor accuracy was noted in the last month of sensor operation. HbA1c was reported to have improved from a mean of 7.45% at baseline to 7.19% at study completion (p<0.001). Clinical performance, estimated by Clark Error Grid Analysis, indicated 99.2% of samples were in the clinically acceptable error zones A (84.3%) and B (14.9%). Alarm performance during the in-clinic studies resulted in an 81% detection rate for hypoglycemia (< 70 mg/dL) and 88% detection rate for hyperglycemia (> 180 mg/dL). No severe procedure- or device-related adverse events were reported. These results are promising, but additional study is needed to more fully understand the benefits and hazards of the implantable interstitial glucose sensor over conventional transcutaneous CIGM devices.

Two smaller studies have also been made available. The larger of them published by Dehennis and others (2015) involved 24 subjects with type 1 diabetes who had the Eversense Continuous Glucose Monitoring System implanted. The sensors were placed under the skin of the upper arm of each subject for up to 90 days. Each subject attended a series of 8-hour clinic sessions performed every 14 days. During these sessions, sensor glucose values were compared with venous blood glucose reference measurements collected every 15 minutes. Most (22 of 24) sensors reported glucose values for the entire 90 days. No serious adverse events were noted.

The other was a small cohort study involving 12 subjects with type 1 diabetes who underwent implantation with the Eversense sensor in the upper arm and were monitored during in-home use for up to 90 days (Wang, 2015). The purpose of the trial was to evaluate the nocturnal sensor attenuation concept. Additionally, the sensitivity and specificity of the nocturnal hypoglycemic alarm were calculated. The authors reported that mean glucose sensor life-span was 87 days. The mean absolute relative difference over the range of 40-400 mg/dL for the sensors in this home-use study was 12.3% using self-monitoring of blood glucose (SMBG) as the reference. The hypoglycemia alarm threshold was set to sound when detected glucose concentrations fell below 70 mg/dL. The percentage of nights with hypoglycemic alarms triggered for at least 10 min was 13.6%. Recovery of euglycemia within 30 minutes of SMBG testing was obtained in 74% of all episodes (n=20). Hypoglycemia detection sensitivity and specificity were reported to be 77% and 96%, respectively. The authors noted that this study demonstrated excellent performance in nocturnal hypoglycemia detection in subjects with type 1 diabetes. They also commented that the implanted sensor appears to have an apparent lack of nocturnal sensor attenuation, or loss of sensor accuracy and sensitivity sometimes seen with standard CIGM devices, and a high specificity of the hypoglycemic alarm. These attributes expedite the recovery from nighttime hypoglycemia. Both of these case series are limited by their small size and lack of a comparator.

The results of the pivotal PRECISE II trial, a prospective nonrandomized blinded single arm study involving 90 subjects 18 years of age and older with type 1 and type 2 diabetes was published by Christiansen in 2018. Unilateral placement of sensors was done in 75 subjects and bilateral placement in 15 subjects. Subjects were excluded if they had a history of severe hypoglycemia or ketoacidosis requiring an emergency room visit or hospitalization in the previous 6 months. Following implantation, subjects were seen at 1, 30, 60, and 90 days, at which time the sensor was removed. The accuracy of the system was judged in comparison to a conventional blood glucose analyzer (2300 Stat Plus Glucose and Lactate Analyzer; Yellow Springs Instruments [YSI], Yellow Springs, OH). At the 30-, 60-, and 90-day visits, a subset of individuals (n not provided) requiring insulin and without gastroparesis also

underwent hypo- and hyperglycemic challenges. A total of 81 (91%) subjects completed the 90-day data collection period. The mean absolute relative difference (MARD) between the implanted sensor and the conventional glucose analyzer over the glucose range of 40-400 mg/dL was 8.80%. Ninety-three percent of the implanted CGM values were within 20 mg/dL or 20% of the blood glucose analyzer measurements. Ninety-one percent of sensors were functional through day 90. The system identified 93% and 96% of hypo- and hyperglycemic events, although formal sensitivity and specificity data were not provided. A single serious adverse event was reported when surgery was required for sensor removal.

Additional small studies assessing the accuracy and safety of the Eversense device have been published, including the PRECISION study (n=36, Christiansen, 2019) and investigation of the use of the device through 180 days (n=36, Aronson, 2019). The findings from both of these studies provided additional data demonstrating reasonable MARD results. The Aronson study is notable because the subjects were mostly adolescents under the age of 18 years (83.3%).

The real-world use of the Eversense device was investigated by Sanchez and colleagues (2019), who reported on the results of the first 205 subjects to reach the 90-day wear threshold in the Eversense Data management System (DMS) registry. The authors reported that out of 205 subjects, 190 continued to wear the external portion of the system beyond 30 days post insertion, and of those that did, median wear time was 83.6%. Overall MARD was 11.2%. Adverse events reported included transient skin irritation following sensor insertion or removal (5%), mild insertion site infection (2%), self-treated hypoglycemia (1.5%), failed sensor removal on the first attempt (2%), and patch/adhesive-related skin irritation (2.5%).

The use of the Eversense system over multiple 90-day cycles was reported by Deiss (2019). This registry-based study involved 3023 subjects who underwent 5417 sensor implantations. At the time of the report, the number of subjects completing a single implantation cycle was 3023 (55.8%), 1320 subjects (24.4%) completed two cycles, 634 (11.7%) completed three cycles, 280 (5.2%) completed 4 cycles, 94 (1.7%) completed 5 cycles, 44 (0.81%) completed 6 cycles, 19 (0.35%) completed 7 cycles, and 3 (0.056%) completed 8 cycles. The number of subjects discontinuing use of the device was 337 (11%), with the reason for discontinuation cited as unknown for 108 subjects, lack of reimbursement for 97, and temporary discontinuation due to prescription issues or device availability the reason cited for 65 subjects. Device-related adverse events were reported in 117 subjects, with the majority being procedure or device related, including sensor site location infection (n=31), irritation, prolonged healing, or pain; inability to remove the sensor on the first attempt (n=24); and adhesive patch-related skin irritation (n=20). No serious adverse events were reported during the first four implantation cycles. The rate of sensor survival over the intended 90-day period of use was reported to be 91%.

Tweden (2020) reported the results of a registry-based data analysis involving 954 subjects with type 1 diabetes who used the Eversense device in the real-world setting for a minimum of four 90- or 180-day cycles. The data collected included duration of sensor use, sensor accuracy, percentage of sensor glucose measures within specific hypo- and hyperglycemic ranges, and others. Towards the end of the study, as availability of the 180 sensor became more readily available, the number of 180 cycles increased (4% to 88%). The average estimated HbA1c ranged from 7.04% to 7.08%. No comparison from baseline HbA1c was provided. The authors provided data for time < 54 mg/dL (1.1-1.3%), average % of sensor readings < 70 mg/dL (4.6-5.0%), average % time in range (63.2-64.5%),

average percent of sensor readings > 180-250 mg/dL (22.8-23.2%), and < 250 mg/dL (8.1-8.8%). No baseline or historical values were provided as comparison groups so it is not clear what these values mean clinically. The authors concluded that their results demonstrated successful use of the Eversense device in the real world over multiple 180-day cycles with no degradation in sensor performance. No data on adverse events were reported, including infections, explantations, or sensor failures.

A prospective case series study published by Irace and colleagues (2020) described the use of the Eversense device for a single 180 cycle in 100 subjects with type 1 diabetes. HbA1c was reported to have declined from 7.4% to 6.9% over the course of the study period. Time in range (70-180 mg/dL), time below range (< 70 mg/dL), and time above range (> 180 mg/dL) improved from 63% to 69%, which was statistically significant ($p<0.0001$, $p<0.001$, and $p<0.0001$, respectively). No device-related serious adverse events were reported, but two adverse events occurred. The first was implant site infection and the other was an inability to remove the sensor on the first attempt. These results are good and appear to demonstrate clinical utility. However, lack of a control group does not allow comparisons to standard non-implantable devices.

The results of these trials are promising, with the accuracy of the device relative to laboratory blood glucose measures demonstrated as being within accepted standards. However, a head-to-head trial with non-implantable CGM devices would allow a better understanding of the potential role of this implantable device in clinical practice. Additionally, there are multiple noninvasive options for glucose monitoring currently available on the market. A better understanding of the benefits and risks of invasive monitoring, including repeated implantations, is needed before the role of implantable CGM devices in clinical care is fully understood.

Background/Overview

At this time, continuous interstitial glucose monitoring systems (CIGMs) marketed in the United States involve the use of a patch-like sensor device that is adhered to the skin and left in place for 1 to several days before replacement. Some of these devices are wirelessly connected and integrated with CIGMs and insulin pump devices.

The Senseonics Eversense Continuous Glucose Monitoring System involves the use of a small subcutaneously implanted interstitial glucose monitoring sensor about the size of a medication capsule. It is wirelessly connected to a wearable receiver/transmitter which is further connected via Bluetooth to a mobile phone app. The sensor capsule is inserted under the skin of the upper arm through a small incision in the physician's office and is intended to last for 90 days before removal and replacement.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:

For the following procedure codes for all indications, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
0446T	Creation of subcutaneous pocket with insertion of implantable interstitial glucose sensor, including system activation and patient training
0447T	Removal of implantable interstitial glucose sensor from subcutaneous pocket via incision
0448T	Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new implantable sensor, including system activation
ICD-10 Diagnosis	
	All diagnoses

References

Peer Reviewed Publications:

1. Aronson R, Abitbol A, Tweden KS. First assessment of the performance of an implantable continuous glucose monitoring system through 180 days in a primarily adolescent population with type 1 diabetes. Diabetes Obes Metab. 2019; 21(7):1689-1694.
2. Christiansen MP, Klaff LJ, Bailey TS, et al. A prospective multicenter evaluation of the accuracy and safety of an implanted continuous glucose sensor: The PRECISION study. Diabetes Technol Ther. 2019; 21(5):231-237.
3. Christiansen MP, Klaff LJ, Brazg R, et al. A prospective multicenter evaluation of the accuracy of a novel implanted continuous glucose sensor: PRECISE II. Diabetes Technol Ther. 2018; 20(3):197-206.
4. Dehennis A, Mortellaro MA, Ioacara S. Multisite study of an implanted continuous glucose sensor over 90 days in patients with diabetes mellitus. J Diabetes Sci Technol. 2015; 9(5):951-956.
5. Deiss D, Irace C, Carlson G, et al. Real-world safety of an implantable continuous glucose sensor over multiple cycles of use: a post-market registry study. Diabetes Technol Ther. 2020; 22(1):48-52.
6. Irace C, Cutruzzolà A, Nuzzi A, et al. Clinical use of a 180-day implantable glucose sensor improves glycated haemoglobin and time in range in patients with type 1 diabetes. Diabetes Obes Metab. 2020; 22(7):1056-1061.
7. Kropff J, Choudhary P, Neupane S, et al. Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE study: A 180-Day, Prospective, Multicenter, Pivotal Trial. Diabetes Care. 2017; 40(1):63-68.
8. Sanchez P, Ghosh-Dastidar S, Tweden KS, Kaufman FR. Real-world data from the first U.S. commercial users of an implantable continuous glucose sensor. Diabetes Technol Ther. 2019; 21(12):677-681..
9. Tweden KS, Deiss D, Rastogi R, et al. Longitudinal analysis of real-world performance of an implantable continuous glucose sensor over multiple sensor insertion and removal cycles. Diabetes Technol Ther. 2020; 22(5):422-427.
10. Wang X, Ioacara S, DeHennis A. Long-term home study on nocturnal hypoglycemic alarms using a new fully implantable continuous glucose monitoring system in type 1 diabetes. Diabetes Technol Ther. 2015; 17(11):780-786.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Diabetes Association. Standards of Medical Care in Diabetes – 2020. Diabetes Care. 2020; 43(Suppl1):S1-S212.
2. United States Food and Drug Administration. Premarket approval Eversense Continuous Glucose Monitoring System. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160048. Accessed on October 28, 2020.

Websites for Additional Information

1. American Diabetes Association. Type 1 diabetes. Available at: http://www.diabetes.org/diabetes-basics/type-1/. Accessed on October 28, 2020.
2. American Diabetes Association. Type 2 diabetes. Available at: http://www.diabetes.org/diabetes-basics/type-2/?loc=db-slabnav/. Accessed on October 28, 2020.

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Senseonics Eversense Continuous Glucose Monitoring System

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/05/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale and References sections.
Reviewed	11/07/2019	MPTAC review. Updated Rationale and References sections.
Reviewed	11/08/2018	MPTAC review.
Reviewed	07/26/2018	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated Rationale and References sections.
Reviewed	08/03/2017	MPTAC review. Updated Rationale and References sections.
New	05/04/2017	MPTAC review. Initial document development.