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*Delivered via electronic mail:*

RE: Proposing modifications to coverage criteria for implantable continuous glucose monitors

Dear Drs. Campbell and Schaening:

Senseonics, Incorporated (Senseonics) is pleased to submit this letter to the Centers for Medicare and Medicaid Services (CMS) with regard to Part B coverage criteria for implantable continuous glucose monitors (iCGM). As an interested stakeholder and manufacturer of an iCGM system, Senseonics welcomes ongoing efforts by the Medicare Administrative Contractors (MACs) to improve coverage of CGMs for individuals with diabetes. While our technology currently is covered under Part B as included in a medical service, we ask that the recent CGM expanded coverage criteria by the DME MACs be extended to all available CGM systems for Medicare beneficiaries.

Senseonics is the manufacturer of Eversense® E3, the current FDA-approved iCGM system to include a fully implantable, long-term sensor to detect glucose, which received FDA- approval for its therapeutic indications in February 2022. The sensor is implanted under the skin by a physician, nurse practitioner or physician's assistant and lasts for 180-days, unlike traditional continuous glucose monitor (CGM) sensors that must be replaced by the patient every 7-14 days.

Recently, the DME MACs finalized the revised LCD: Glucose Monitors (L33822). The final LCD makes several important changes, including removing the requirement that a beneficiary is insulin-treated with three or more daily administrations of insulin or a continuous subcutaneous insulin infusion (CSII) pump. In addition to allowing coverage for all insulin-treated beneficiaries with diabetes mellitus, the LCD expands coverage for beneficiaries with a history of problematic hypoglycemia. Finally, the updated LCD removes the criterion that the beneficiary's insulin

treatment regimen requires frequent adjustment by the beneficiary on the basis of blood glucose monitor (BGM) or CGM testing results.

We are supportive of these updated criteria, which better reflect the current clinical evidence and standards for the reasonable and necessary use of CGM. Moreover, CMS should consider CGMs as a class and ensure that any expansion of coverage criteria includes all available CGM systems, including implantable CGM for beneficiaries. We have attached the DME LCDs as a reference for your consideration. Below we discuss the evidence in support of these changes.

## I. Revise the requirement that the beneficiary is insulin-treated with multiple daily administrations of insulin or a use a Medicare-covered continuous pump

### A. Summary of Clinical Evidence

There are a number of important studies that have shown the benefit of using CGM in type 2 diabetes patients who use basal insulin only rather than take multiple daily administrations of insulin or use a Medicare-covered insulin pump. These studies supported the DME MACs revised LCD: Glucose Monitors (L33822) and also support our request for the iCGM category as listed above.

Studies done with CGM devices that measure glucose in the interstitial fluid appear to be applicable to all CGM devices measuring in this body compartment when the overall MARD is less than 10% and other accuracy measurements meet FDA criteria for approval as a non-adjunctive CGM device. This is the case with Eversense E3 CGM System, with an overall MARD of 8.5% and FDA approval as a non-adjunctive CGM for use up to 180 days.

There are four main randomized control trials (RCTs)[1-4] that support the use of CGM in patients with type 2 diabetes mellitus (T2DM) who administer basal insulin only. These studies assessed the effects of CGM on HbA1c and/or Time in Range (TIR).

The study conducted by Ehrhardt et al.[1] was a prospective, 12-week, two-arm RCT which compared Real-Time (RT)-CGM (n = 50) to self-monitoring of blood glucose (SMBG) (n = 50) in people with T2DM not taking meal-time insulin, but administering basal insulin daily. The initial HbA1c for the cohort was ≥ 7%. HbA1c decreased by 1.0% (±1.1%) for the RT-CGM users and 0.5% (±0.8%) for the SMBG group at 12 weeks ($p$ = 0.006), which was highly statistically significant in favor of the RT-CGM group. Overall, the RT-CGM group had an adjusted decline in HbA1c of 0.60% greater than the SMBG group ($p$ = 0.002).[1]

Martens et al.[2] conducted an 8-month, open-label, 2:1 randomized, multicenter, clinical trial across 15 centers which evaluated the effectiveness of CGM (n=116) versus SMBG (n=59) in T2DM patients treated with basal insulin only. At the 8-month follow-up, the mean HbA1c levels decreased from 9.1% in the CGM group and 9.0% in the SMBG group to 8.0% vs. 8.4%, respectively (adjusted difference in mean change in HbA1c -0.4% [95%CI, -0.8% to – 0.1%] $p$ =

0.02. In the CGM group, compared with the SMBG group, the mean percentage of time in the range of 70 to 180 mg/dL was 59% vs 43% (adjusted mean difference, 15% [95% CI, 8% to 23%]; $p < 0.001$; equivalent to 3.6 hours more per day).[2]

Aleppo et al.[3] reported on a 6-month extension of the Martens et al. [2] study which aimed to determine the long-term benefits of continued CGM use or the detriments of discontinuing CGM. Upon completion of the 8-month visit for the initial RCT[2], participants in the CGM group were randomly assigned to either discontinue CGM (n=53) or continue CGM (n=53) at a 1:1 ratio with the primary outcome being Time In Range (TIR) between 70-180 mg/dL.[3] In the group that discontinued CGM use, mean TIR 70–180 mg/dL, which improved from 38% before initiating CGM to 62% after 8 months of CGM use, decreased after discontinuing CGM to 50% at 14 months (mean change from 8 to 14 months -12% [95% CI -21% to -3%], $p = 0.01$).[3] In the group that continued CGM use, little change was found in TIR from 8 to 14 months (baseline 44%, 8 months 56%, 14 months 57%, mean change from 8 to 14 months 1% [95% CI -11% to 12%], $p = 0.89$).[3] Comparing the two groups at 14 months, the adjusted treatment group difference in mean TIR was -6% (95% CI -16% to 4%, $p = 0.20$).[3]

Vigersky et al.[4] conducted a randomized controlled trial of 100 adults with T2DM who were not on prandial insulin. This study compared the effects of 12 weeks of intermittent RT-CGM with self-monitoring of blood glucose (SMBG) on glycemic control over a 40-week follow-up period. There was a significant difference in A1C at the end of the 3-month active intervention that was sustained during the follow-up period. The mean, unadjusted A1C decreased by 1.0, 1.2, 0.8, and 0.8% in the RT-CGM group vs. 0.5, 0.5, 0.5, and 0.2% in the SMBG group at 12, 24, 38, and 52 weeks, respectively (P = 0.04). There was a significantly greater decline in A1C over the course of the study for the RT-CGM group than for the SMBG group, after adjusting for covariates (P < 0.0001). The subjects who used RT-CGM per protocol (≥48 days) improved the most (P < 0.0001). The improvement in the RT-CGM group occurred without a greater intensification of medication compared with those in the SMBG group. This study showed that subjects with T2DM not on prandial insulin who used RT-CGM intermittently for 12 weeks significantly improved glycemic control at 12 weeks and sustained the improvement during the 40-week follow-up period, compared with those who used only SMBG. [4]

A retrospective non-interventional single-arm chart review[5] investigated the change in HbA1c in T2DM patients using only basal insulin and commencing use of a Flash-CGM monitoring system. Eligible medical records ($n = 103$) from six diabetes centers in Canada showed HbA1c significantly decreased by 0.8% ± 1.1 mean ± SD (95% confidence interval for change –1.1 to –0.6, $p < 0.0001$) from baseline HbA1c 8.9% ± 0.9 to 8.1% ± 1.0 –6 months after initiation of Flash-CGM use.[5]

Two prospective clinical trials assessed the patterns of hypoglycemia and glycemic variability in adult patients with insulin treated and non-insulin treated T2DM.[6,7] In a study conducted by Munshi et al.[6], a blinded CGM measured interstitial glucose levels at intervals of 5 minutes for a 3-day period while T1DM (n=12) or T2DM (n=28) participants conducted their usual daily activities and conducted SMBG 4 times a day.[6] Of a total of 102 hypoglycemic episodes, 95

(93%) were unrecognized by SMBG or symptoms despite only 2 patients reporting "hypoglycemia unawareness". In a study conducted by Gehault et al.[7], a total of 108 patients with T2DM wore a blinded CGM for 5 days which tracked the severity, timing, and the number of hypoglycemic events while the participants kept daily 4-point SMBG logs and tracked any self-perceived hypoglycemic episodes.[7] Episodes of hypoglycemia were detected in 49.1% (53 of 108 patients), which extrapolated to 1.74 ± SD 2.54 episodes per patient per 5 days of CGM. Out of the 53 patients who had hypoglycemic episodes, 10 (18.9%) were on none of the medications that typically cause low glucose levels. The majority (75%) of patients were not aware of their hypoglycemic episodes detected by CGM ($p < 0.001$).[7] These two studies showed that clinically significant episodes of hypoglycemia go undetected without CGM.

Three systematic reviews with meta-analyses attempted to examine the efficacy of CGM use in patients with T2DM compared to SMBG.[8-10] CGM use was associated with a significant reduction in HbA1c levels for the combination of T2DM patients (insulin and non-insulin treated) in all three of these reviews with meta-analyses. [8-10] Only one SRMA reported data related to hypoglycemia with the combined CGM group from 3 trials exhibiting shorter time spent with hypoglycemia than the SMBG group (SMD, −0.35; 95% CI, −0.59 to −0.10; $p = 0.006$; I2 = 0% $p = 0.86$). [8]

In addition, an abstract has been submitted and accepted for presentation at the American Diabetes Association Annual Scientific sessions in June, 2023. The abstract that will be published in Diabetes 2023, described the Eversense post market study data, which is a prospective, multicenter, one year comparison of SMBG to Eversense in CGM naïve adults with diabetes in US sites. The cohort consisted of 90.5% T2DM subjects, on basal-bolus, basal insulin only or no insulin therapy. After baseline assessment including HbA1c, patients used SMBG for 6 months (phase 1) followed by Eversense for 6 months (phase 2). Sensors were inserted at the start of phase 2. Visits occurred q 90 days to collect SMBG or CGM data and assess adverse events. HbA1c was measured at 6 and 12 months. Time in Range (TIR) was also assessed in both phases. In 15 sites, 84 users completed the study as of the abstract submission in January, 2023 (mean 47.6% male, 57.2 years age). The data that will be presented at the American Diabetes Association meeting this June (the data are sanctioned until the presentation) support that RT-CGM using the Eversense CGM System allowed for improvement in glycemic control compared to SMBG in a cohort of patients with mainly T2DM.

B. Discussion of Treatment Standards

The major Associations in the US have made favorable recommendations for the use of RT-CGM in particular for patients with T2DM on basal insulin only (not taking meal-time insulin).

The American Diabetes Association (ADA) Standards of Medical Care in Diabetes 2022[11] specify that RT-CGM (Grade: A) or intermittently scanned continuous glucose monitoring (isCGM) (Grade: C) can be used for diabetes management in adults with diabetes on basal insulin who

are capable of using devices safely, meaning that the ADA supports the use of any Real-Time CGM product, such as the Eversense E3 CGM system. The choice of device should be made based on patient circumstances, desires, and needs.[11]

The American Association of Clinical Endocrinology (AACE) Clinical Practice Guideline on the use of Advanced Technology in the Management of Persons with Diabetes Mellitus in 2021[12] recommends CGM for all individuals with problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness) (Grade A; Intermediate-High Strength of Evidence; BEL 1). The AACE guideline further states that CGM may be recommended for individuals with T2DM who are treated with less intensive insulin therapy. (Grade B; Intermediate Strength of Evidence; BEL 1).[12] The AACE and American College of Endocrinology Consensus Conference on Continuous Glucose Monitoring in 2016[13] unanimously agreed that RT-CGM should be available to all insulin-using patients regardless of diabetes type, however this conclusion was based entirely on studies conducted in type 1 diabetes mellitus (T1DM) at the time of the recommendation.

The Endocrine Society Clinical Practice Guideline for the treatment of diabetes in older adults in 2019[14] recommends frequent fingerstick glucose monitoring and/or continuous glucose monitoring (to assess glycemia) for patients aged 65 years and older with insulin treated diabetes. Continuous glucose monitors (CGMs) are primarily used to help in the management of Type 1 diabetes, although the devices can be useful for people with type 2 diabetes, as well. CGMs measure glucose levels in the fluid between the body's cells every few minutes throughout the day and night. The technology can tell the user whether glucose levels are rising or falling, and monitor trends from the past several hours. The devices also feature alarms to warn users when glucose levels are too high or too low. The guideline task force gave its strongest recommendation in support of using CGM technology in individuals with Type 1 diabetes who are able and willing to use the monitors. The task force also suggested that CGMs can be used on a for individuals with Type 2 diabetes whose blood glucose is above targeted levels.

## II. Remove the requirement that the beneficiary's insulin treatment regimen requires frequent adjustment by the beneficiary on the basis of BGM or CGM testing results

For patients taking basal insulin and no prandial doses of insulin, there is no requirement for frequent adjustments of the basal insulin dosage on the basis of BGM or CGM results. Basal insulin doses are infrequently changed once the appropriate dosage is established.

## III. Conclusion

Currently, CMS coverage criteria for implantable CGM systems include several requirements that are inconsistent with clinical evidence and accepted treatment standards. We respectfully request that the recently expanded coverage criteria for CGMs be extended all systems,

including implantable CGMs. If you have any questions, please reach out to me at Francine.Kaufman@senseonics.com. Thank you for your attention to this matter.

Sincerely,

Francine R. Kaufman, MD
Chief Medical Officer
Senseonics, Incorporated
Distinguished Professor Emerita of Pediatrics, University of Southern California Keck School Medicine
Past President of the American Diabetes Association

Attachment A – DME LCDs

cc: Chiquita Brooks-LaSure, Administrator
Jonathon Blum, Principal Deputy Administrator & Chief Operating Officer
Lee Fleisher, M.D., Chief Medical Officer & Director, Center for Clinical Standards & Quality
Tamara Syrek-Jensen, Director, Coverage & Analysis Group, Center for Clinical Standards & Quality

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