May 20, 2025

Senseonics, Incorporated
Mukul Jain
Chief Operating Officer
20451 Seneca Meadows Parkway
Germantown, Maryland 20876-7005

Re: DEN230052
Trade/Device Name: Eversense AP CGM System
Regulation Number: 21 CFR 862.1357
Regulation Name: Integrated continuous glucose monitoring system with sensor containing dexamethasone (or one of its ester forms)
Regulatory Class: Class II
Product Code: SBA
Dated: August 9, 2023
Received: August 9, 2023

Dear Mukul Jain:

This letter corrects our previous classification order, dated June 6, 2024, to clarify that the regulation is inclusive of dexamethasone [or one of its ester forms].

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the Eversense AP CGM System, a prescription device with the following indications for use:

> The Eversense AP CGM System is indicated for continually measuring glucose levels for up to 6 months in people (18 years and older) with diabetes. The system is indicated for use to replace fingerstick blood glucose measurements for diabetes treatment decisions. The system is intended to:
>
> - Provide real-time glucose readings.
> - Provide glucose trend information.
> - Provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia).
>
> Historical data from the system can be interpreted to aid in providing therapy adjustments. These adjustments should be based on patterns and trends seen over time.
>
> The Eversense AP CGM System is also intended to autonomously communicate with digitally connected devices, including automated insulin dosing (AID) systems. The Eversense AP CGM System can be used alone or in conjunction with these digitally connected medical devices for the purpose of managing diabetes.

The system is intended for single patient use and requires a prescription.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Eversense AP CGM System, and substantially equivalent devices of this generic type, into Class II under the generic name integrated continuous glucose monitoring system with sensor containing dexamethasone(or one of its ester forms).

FDA identifies this generic type of device as:

Integrated continuous glucose monitoring system with sensor containing dexamethasone (or one of its ester forms). An integrated continuous glucose monitoring system (iCGM) with sensor containing dexamethasone (or one of its ester forms) is intended to automatically measure glucose in bodily fluids continuously or frequently for a specified period of time. iCGM systems are designed to reliably and securely transmit glucose measurement data to digitally connected devices, including automated insulin dosing systems, and are intended to be used alone or in conjunction with these digitally connected medical devices for the purpose of managing a disease or condition related to glycemic control. The dexamethasone constituent is intended to reduce inflammation at the sensor insertion site.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register announcing the classification.

On August 9, 2023, FDA received your De Novo requesting classification of the Eversense AP CGM System. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Eversense AP CGM System into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the De Novo request FDA has determined that, for the previously stated indications for use, the Eversense AP CGM System can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Identified Risks to Health	Mitigation Measures
Clinical action based on falsely high or falsely low inaccurate glucose values or inaccurate alerts may lead to inappropriate treatment decisions.	Certain design verification and validation activities, including documentation of certain studies and other information. Certain labeling information, including certain limiting statements and performance characteristics.
The inability to make appropriate treatment decisions when glucose values are unavailable due to sensor signal drop-out or loss of communication with digitally connected devices.	Certain design verification and validation activities, including documentation of certain studies and other information. Certain labeling information, including certain limiting statements and performance characteristics.
Patient harm due to insecure transmission of data.	Certain design verification and validation activities, including documentation of certain information.
Use of an iCGM as part of another digitally connected medical device system, such as an AID system, when the iCGM has inadequate analytical or clinical performance to support the intended use of the digitally connected device.	Certain design verification and validation activities, including certain studies and other information. Certain labeling information, including certain limiting statements and performance characteristics.
Adverse reactions to the drug constituent.	Documentation of certain studies and other information including: • Product characterization, including drug substance • Drug quality attribute performance testing, including elution • Stability and shelf-life testing • Pharmaceutical manufacturing information Certain labeling information, including identification of the net content of dexamethasone (or one of its ester forms) for the product and description of safety events attributable to the dexamethasone constituent.
Adverse events related to the insertion and removal of the product.	Certain design verification and validation activities, including documentation of certain

Identified Risks to Health	Mitigation Measures
	studies. Certain labeling information, including certain limiting statements and performance characteristics.

In combination with the general controls of the FD&C Act, the Integrated continuous glucose monitoring system with sensor containing dexamethasone (or one of its ester forms) is subject to the following special controls:

(1) Design verification and validation must include the following:

(i) Robust clinical data demonstrating the accuracy of the product in the intended use population.

(ii) The clinical data must include a comparison between iCGM values and blood glucose values in specimens collected in parallel that are measured on an FDA-accepted laboratory-based glucose measurement method that is precise and accurate, and that is traceable to a higher order (e.g., an internationally recognized reference material and/or method).

(iii) The clinical data must be obtained from a clinical study designed to fully represent the performance of the product throughout the intended use population and throughout the measuring range of the product.

(iv) Clinical study results must demonstrate consistent analytical and clinical performance throughout the sensor wear period.

(v) Clinical study results in the adult population must meet the following performance requirements:
(A) For all iCGM measurements less than 70 milligrams/deciliter (mg/dL), the percentage of iCGM measurements within +/-15 mg/dL of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 85 percent.
(B) For all iCGM measurements from 70 mg/dL to 180 mg/dL, the percentage of iCGM measurements within +/-15 percent of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 70 percent.
(C) For all iCGM measurements greater than 180 mg/dL, the percentage of iCGM measurements within +/-15 percent of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 80 percent.
(D) For all iCGM measurements less than 70 mg/dL, the percentage of iCGM measurements within +/-40 mg/dL of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 98 percent.
(E) For all iCGM measurements from 70 mg/dL to 180 mg/dL, the percentage of iCGM measurements within +/-40 percent of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 99 percent.

(F) For all iCGM measurements greater than 180 mg/dL, the percentage of iCGM measurements within +/-40 percent of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 99 percent.
(G) Throughout the product measuring range, the percentage of iCGM measurements within +/-20 percent of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 87 percent.
(H) When iCGM values are less than 70 mg/dL, no corresponding blood glucose value shall read above 180 mg/dL.
(I) When iCGM values are greater than 180 mg/dL, no corresponding blood glucose value shall read less than 70 mg/dL.
(J) There shall be no more than 1 percent of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dL per minute (/min) when the corresponding true negative glucose rate of change is less than - 2 mg/dL/min as determined by the corresponding blood glucose measurements.
(K) There shall be no more than 1 percent of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dL/min when the corresponding true positive glucose rate of change is greater than 2 mg/dL/min as determined by the corresponding blood glucose measurements.

(vi) Data demonstrating similar accuracy and rate of change performance of the iCGM in the pediatric population as compared to that in the adult population, or alternatively a clinical and/or technical justification for why pediatric data are not needed, must be provided and determined by FDA to be acceptable and appropriate.

(vii) Data must demonstrate that throughout the claimed sensor life, the product does not allow clinically significant gaps in sensor data availability that would prevent any digitally connected devices from achieving their intended use.

(2) Design verification and validation must include a detailed strategy to ensure secure and reliable means of iCGM data transmission to provide real-time glucose readings at clinically meaningful time intervals to devices intended to receive the iCGM glucose data.

(3) Design verification and validation must include adequate controls established during manufacturing and at product release to ensure the released product meets the performance specifications as defined in paragraphs (1) and (2).

(4) The product must demonstrate clinically acceptable performance in the presence of clinically relevant levels of potential interfering substances that are reasonably present in the intended use population, including but not limited to endogenous substances and metabolites, foods, dietary supplements, and medications.

(5) The product must include appropriate measures to ensure that disposable sensors cannot be used beyond its claimed sensor wear period.

(6) Design verification and validation must include results obtained through a usability study that demonstrates that the intended user can use the product safely and obtain the expected glucose measurement accuracy.

(7) The labeling required under 21 CFR 809.10(b) must include:
   (i) Identification of the net content of dexamethasone (or one of its ester forms) for the product (i.e., net content per sensor) in the product labeling.

   (ii) A separate description of the following sensor performance data observed in the clinical study performed in conformance with paragraph (1) for each intended use population, in addition to separate sensor performance data for each different iCGM insertion or use sites (e.g., abdomen, arm, buttock):
      (A) A description of the accuracy in the following blood glucose concentration ranges: less than 54 mg/dL, 54 mg/dL to less than 70 mg/dL, 70 to 180 mg/dL, greater than 180 to 250 mg/dL, and greater than 250 mg/dL.
      (B) A description of the accuracy of positive and negative rate of change data.
      (C) A description of the frequency and duration of gaps in sensor data.
      (D) A description of the true, false, missed, and correct alert rates and a description of the available glucose concentration alert settings, if applicable.
      (E) A description of the observed duration of iCGM life for the product.
      (F) A description of safety events (if any) that may be attributable to the dexamethasone constituent of the product.

(8) The label required under 21 CFR 809.10(a) must include identification of the net content of dexamethasone (or one of its ester forms)for the product (i.e., net content per sensor).

(9) Elution kinetics studies must be conducted to determine the *in vitro* drug release profile from the product lot(s) used for the clinical performance testing studies.

(10) Characterization of the finished product (or alternatively, a justification determined to be appropriate by FDA for why the product tested is representative of the finished product) must demonstrate that critical quality attributes and specifications, including compendial requirements, are met and must include:

   (i) Identification of, and justification for, the drug constituent specification(s), including the specification for dexamethasone (or one of its ester forms).

   (ii) Confirmation that the specifications for dexamethasone (or one of its ester forms)and inactive ingredients or material components conform to any corresponding United States Pharmacopeia (USP) monographs, if available. In addition, the specification for dexamethasone (or one of its ester forms) must also include other tests that ensure the quality of the product, such as appearance, identification, assay, drug content uniformity, related substances, and impurities. Such tests must be conducted using appropriate analytical techniques, such as high performance liquid chromatography (HPLC).

(iii) Identification of, and justification for, the finished product specification(s) to be met on release of each batch and on stability, including description, identification, assay, in vitro elution/drug release, degradation products, impurities, content uniformity, residual solvents, sterility, and endotoxin.

(iv) For the specifications noted in paragraphs (i)-(iii) above, a description of the analytical procedures and a summary of the analytical procedures development and validation must be provided. For in vitro elution/drug release specifications, data must be provided to demonstrate method adequacy (e.g., in terms of discriminating power for changes/differences in critical quality attributes that could impact product performance, stability-indicating potential, and/or *in vitro-in vivo* correlation).

(11) Performance data from testing at release and on stability batches of the finished product (or alternatively, a justification determined to be appropriate by FDA for why the product tested is representative of the finished product) must characterize the drug quality attributes of the finished product (see paragraph (10)), demonstrate product specifications are consistently met, and support the claimed expiration date/shelf-life. This information must include the following:

(i) Finished Product Batch Release Testing: Batch release data on multiple lots of the finished product manufactured using the proposed commercial process (or alternatively, a justification determined to be appropriate by FDA for why the product tested is representative of the finished product) must demonstrate that specifications are met.

(ii) Stability Testing: The finished product manufactured using the proposed commercial process and in the proposed commercial packaging (or alternatively, a justification determined to be appropriate by FDA for why the product tested is representative of the finished product) must be stored under tightly controlled conditions and periodically tested to demonstrate the stability of the finished product. Testing must include three batches placed under long-term storage and accelerated stability conditions and then one batch placed on long-term stability each year. Testing must verify that the acceptance criteria for each specification are met at each stability time point. Parameters that are not expected to change on stability (e.g., elemental impurities, only need to be tested at batch release, and a justification must be provided).

(12) Pharmaceutical manufacturing information must be provided, and appropriate documentation be available on inspection or if requested by FDA, for the drug constituent part and the finished product to demonstrate that the production processes are properly developed, conducted, controlled, and monitored. This information must include the following:

(i) A description of the manufacturing process and controls, including in-process controls, to ensure consistent quality. Such information may be provided by reference to a drug master file (DMF).

(ii) A description of the commercial batch formula, including the quality standard (e.g., USP/National Formulary) to be met for each inactive ingredient or material component, and representative Certificates of Analysis (COAs) to confirm quality.

(iii) Information or reference to one or more DMFs regarding the drug substance to understand the impurity profile, and representative COAs for the drug substance to confirm quality.

(iv) Identification and qualification of in-process hold times for the drug constituent part, where applicable.

(v) A description of how compliance with the current good manufacturing practice (CGMP) requirements is achieved at the facilities manufacturing the drug constituent part and finished product. This includes identification of the activities that occur at each site, and for any facilities for which 21 CFR 211 is not the established CGMP operating system, a description of how the facilities perform the responsibilities related to the subset of 21 CFR 211 requirements established in 21 CFR 4 subpart A.

(13) Performance data must support the claimed expiration date/shelf life by demonstrating continued sterility, stability (see paragraph (11)(ii)), package integrity, and product functionality over the identified expiration date/shelf life. Data to demonstrate continued sterility, stability, packaging integrity, and product functionality must be collected for the finished product (or alternatively, a justification, determined to be appropriate by FDA, must be provided for why the product tested is representative of the finished product). Extension of the expiration date/shelf life must be submitted in a premarket notification and be supported by either:

(i) Real-time data as specified in this special control; or

(ii) A combination of real-time data and a scientifically justified statistical modeling approach to extrapolate expiration date/shelf life.

(14) Performance data must confirm that sterilization has no significant adverse impact (e.g., the generation of new degradants) on the drug quality attributes (e.g., assay, elution) of the finished product.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the integrated continuous glucose monitoring system with sensor containing dexamethasone (or one of its ester forms) they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD&C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see

https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD&C Act; 21 CFR 1000-1050).

A notice announcing this classification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the De Novo request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Carter Swanson at Carter.Swanson@fda.hhs.gov.

Sincerely,

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