SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Continuous glucose monitor (CGM), implanted, adjunctive use
Device Trade Name:	Eversense Continuous Glucose Monitoring System
Device Procode:	QCD
Applicant's Name and Address:	Senseonics, Incorporated 20451 Seneca Meadows Pkwy Germantown, MD 20876
Date of Panel Recommendation:	March 29, 2018
Premarket Approval Application (PMA) Number:	P160048
Date of FDA Notice of Approval:	June 21, 2018

II. INDICATIONS FOR USE

The Eversense CGM System is indicated for continually measuring glucose levels in adults (age 18 and older) with diabetes for up to 90 days.

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).

The system is a prescription device. Historical data from the system can be interpreted to aid in providing therapy adjustments. These adjustments should be based on patterns seen over time.

The system is indicated for use as an adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices.

III. CONTRAINDICATIONS

The following contraindications are included in the labeling

- The Sensor and Smart Transmitter are incompatible with magnetic resonance imaging (MRI) procedures. DO NOT undergo an MRI procedure while the sensor is inserted

or when wearing the smart transmitter. Should an MRI be required, please contact your physician to arrange for sensor removal before the procedure.

- The system is contraindicated in people for whom dexamethasone or dexamethasone acetate may be contraindicated.

- Mannitol or sorbitol, when administered intravenously, or as a component of an irrigation solution or peritoneal dialysis solution, may increase blood mannitol or sorbitol concentrations and cause falsely elevated readings of your sensor glucose results. Sorbitol is used in some artificial sweeteners, and concentration levels from typical dietary intake do not impact sensor glucose results.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Eversense Continuous Glucose Monitoring System labeling.

V. DEVICE DESCRIPTION

The Eversense Continuous Glucose Monitoring System (Eversense System, or System) provides continuous glucose measurements over a 40-400 mg/dL range. The system provides real-time glucose values, glucose trends, and alerts for high and low glucose through a mobile application installed on a compatible mobile device platform (e.g., Android or iOS device). The Eversense System consists of a fluorescence-based glucose sensor (Eversense Sensor) that is inserted under the skin by a physician with Insertion Tools; an externally worn Eversense Smart Transmitter (Transmitter); and the Eversense Mobile Medical Application (MMA), which runs on a compatible mobile device. The inserted Sensor is a radiofrequency (RF) powered device that collects readings and sends them to the Transmitter. The Transmitter calculates, stores, and transmits the glucose data via Bluetooth Low Energy (BLE) to the MMA on the mobile device.

The System consists of four principal components:

1. **Sensor:** The sensor uses a fluorescence sensing mechanism to detect glucose in the interstitial fluid (ISF). The sensor is inserted subcutaneously by a physician, and receives RF-power from the Transmitter to measure interstitial fluid glucose every 5 minutes. The sensor sends fluorescence measurements to the Transmitter for calculation and storage of glucose values. The sensor has a silicone collar component that contains 1.75 mg of an anti-inflammatory steroid drug (dexamethasone acetate) that elutes locally to reduce tissue inflammation around the sensor. The sensor operating life is the lesser of 90 days or until the device's end-of-life is reached. The sensor is provided sterile to the physician, for single use in a sensor holder. The Sensor is inserted by a qualified physician using the provided insertion tools.

2. **Transmitter:** The transmitter, worn externally over the inserted Sensor, is a device that powers the Sensor, calculates the glucose values from the Sensor-measured

fluorescence readings, and using secure BLE wirelessly sends the glucose information to the MMA for display on the handheld device (HHD). An adhesive patch holds the transmitter in place. The transmitter contains a rechargeable battery which is charged with a charging cradle powered by a USB connection. The transmitter also provides vibration signals for alerts and notifications, such as low glucose levels, irrespective of whether the MMA is in the vicinity or not.

3. **MMA:** The MMA is a software application that runs on a compatible mobile device for display of glucose information provided by the transmitter. The MMA receives and displays the calculated glucose information from the transmitter, including glucose trend information and glucose alerts. The MMA also allows the user to calibrate the CGM System by input of blood glucose measurements. It also communicates with the Senseonics server for a one-time download of calibration parameters specific for each Sensor. The MMA also provides the user an option to upload the data to Senseonics Data Management System (DMS) for historic viewing and storing of glucose data.

4. **Insertion Tools:** Insertion Tools (a Blunt Dissector and Insertion Tool) are provided to the physician for Sensor implantation. The Blunt Dissector is used to create the subcutaneous space in which the Sensor is placed. The Sensor Holder in which the Sensor is stored during transport and sterilization is used to transfer the Sensor to Insertion Tool. The Insertion Tool is used to place the Sensor into the subcutaneous space.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are a number of alternative practices used for managing diabetes, and often more than one practice is recommended by health care providers. This includes oral and/or injectable medications, as well as self-monitoring of blood glucose using home blood glucose monitoring devices. Self-monitoring blood glucose meters and test strips provide a blood glucose measurement at a single point in time, whereas CGM provides continuous glucose measurements. Additionally, behavior changes related to physical activity and healthy eating can aid in successful diabetes management.

Each alternative has its own advantages and disadvantages. Patients should thoroughly discuss the alternatives with their physician to choose the method that best suits individual expectations and lifestyles.

VII. MARKETING HISTORY

The Eversense CGM System has not been marketed in the United States.

A different version of the Eversense CGM System has been approved for commercial distribution in the European Union and European Economic Area countries requiring CE Mark since May 2016.

The system has not been withdrawn from commercial distribution for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with use of the device.

Potential adverse effects related to insertion, removal and wear of the sensor include:

- Allergic reaction to adhesives
- Bleeding
- Bruising
- Infection
- Pain or discomfort
- Scarring or skin discoloration
- Sensor fracture during removal
- Skin inflammation, thinning, discoloration or redness

There are risks relating to difficulty with sensor removal, and potential risks associated with subsequent procedures required for sensor removal. Five instances of difficulty with sensor removal, one of which was reported as a serious adverse event, where subjects were referred to a general surgeon for successful sensor removal, were documented in the clinical studies reviewed. Based on postmarket data available with a different version of this device marketed in Europe, and the results observed in these clinical studies, the occurrence of these events is low.

There is a risk of sensor breakage leaving a sensor fragment under the skin. Two instances of sensor breakage were documented in the clinical studies reviewed. Based on postmarket data available with a different version of this device marketed in Europe, and the results observed in these clinical studies, the occurrence and severity of these events is low.

There may be potential risks relating to repeated insertion and removal procedures, including buildup of scar tissue over time at the sensor insertion site, in a small range of locations on the outside surface of the upper arms. Based on postmarket data available with a different version of this device marketed in Europe, and the results observed in these clinical studies, these risks are not expected to occur.

The Eversense CGM System has a drug component, consisting of 1.75 mg of dexamethasone acetate (DXA), contained in a dexamethasone eluting silicone collar to the outside of the Eversense Sensor. Based on information and clinical evaluations performed, the sponsor has demonstrated that risks relating to both local and potential systemic exposure the dexamethasone component of the device, as well as repeated exposure to the dexamethasone component of the device, are not expected to occur. These risks appear to be remote based on the results observed in these clinical studies,

although these clinical studies did not include subjects taking dexamethasone (or other glucocorticoid medications).

A minor risk of this device is that users may need to perform unnecessary fingersticks to evaluate their blood glucose when the CGM gives false positive hypoglycemic and hyperglycemic readings or alerts. Inaccurate calculation of the rate of change of glucose could also lead to unnecessary additional blood glucose tests or inappropriate measures to stop a trend of increasing or decreasing glucose level which could result in hyperglycemia or hypoglycemia. There is a minor risk of skin irritation, inflammation, or infection due to either the sensor needle or the adhesive.

There are risks due to missed alerts and false negative hypoglycemia and hyperglycemic readings related to patients not being alerted to the need to perform a fingerstick to detect hypoglycemia or hyperglycemia, particularly since users of this device may rely on these alerts in certain situations to guide their self-treatment strategy (e.g., to alert them to potential nighttime hypoglycemia). There is a risk to false alerts and false positive hypoglycemia and hyperglycemia readings related to the need to perform unnecessary fingersticks to confirm an erroneous low or high reading. Inaccurate calculation of the rate of change of glucose by the CGM could prevent a patient from performing additional blood glucose tests or taking measures to stop a trend of increasing or decreasing glucose levels which could lead to serious hypoglycemia or hyperglycemia if no action is taken to stop these glucose trends. Inaccurate calculation of the rate of change of glucose could also lead to unnecessary additional blood glucose tests or inappropriate measures to stop a trend of increasing or decreasing glucose level which could result in hyperglycemia or hypoglycemia.

There is a risk if patients make decisions on diabetes management based on inaccurate sensor readings alone without confirmation by blood glucose testing. The device labeling states this device is intended to be used to complement, not replace, blood glucose testing.

The body-worn transmitter component of the system provides an alternate means of delivering alerts to users through vibratory feedback. The level of information necessary to understand the safety aspects of the user interface, and how it supports the user and reduces the potential for use error was provided by the sponsor, and found to be adequate. There may be an additional risk that the display, or alerts or alarms related to the CGM device may not be able to override other applications or functions (phone, camera, SMS) within the mobile device. This risk could potentially result in missed alerts or alarms, or temporary loss of access to the display. Missed alerts, alarms, or inability to access the display could result in missed opportunities to detect or prevent hypoglycemia or hyperglycemia, and are discussed above. Human factors studies conducted assessed the safety of the user interface of the mobile app (sole display) for this device, and the ability for users to be receive and understand alerts and notifications via the transmitter vibration feature. The human factors study sufficiently assessed the potential for user error associated with comprehension of the impact of mobile device and app settings on notifications and Bluetooth communications, as well as use of the audio override feature.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Pre-clinical testing has been conducted to demonstrate the Eversense CGM System performs as intended and meets its product requirements (see Table 1). The verification and validation tests included compliance with international standards and/or guidance documents where available. The CGM System and its components have various levels of specifications and technological characteristics. Therefore, a combination of full system testing, subsystem and component level testing was performed to demonstrate that the device meets its requirements and is safe for use.

Device and Electrical Safety: The Transmitter has undergone testing to demonstrate that the device meets the requirements for medical device safety, including electrical safety, according to the following international standards: IEC 60601-1, 3rd Edition, Medical electrical equipment – General requirements for basic safety and essential performance.

Electromagnetic Compatibility: The Transmitter has undergone testing to demonstrate the device meets the following international standard: IEC 60601-1-2, 4th Edition, Medical electrical equipment – Part 1-2, General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic disturbances – Requirements and tests.

Home Health Care Products: The Transmitter has undergone testing to demonstrate that the device meets the requirements for medical device safety for home health care products, according to the following international standards: IEC 60601-1-11, 2nd Edition. Medical electrical equipment – General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment.

Battery Standards: The Transmitter batteries have undergone testing to demonstrate that the batteries meet the requirements for safety for batteries containing alkaline or other non-acid electrolytes, according to the following international standards: IEC 62133, 2nd Edition. Secondary cells and batteries containing alkaline or non-acid electrolytes – Safety requirements for portable sealed secondary cells, and for batteries made from them for use in portable applications.

Electrical Testing for Batteries and Bluetooth Function: Transmitters were subjected to the electrical verification testing summarized in Table 1. Protocols, test reports and acceptance criteria were reviewed and found to be acceptable. The device met the pre-determined acceptance criteria for battery recharge, and communication longevity.

Table 1: Summary of Preclinical Testing of the Eversense Smart Transmitter

Test Name/ Description	Test Purpose	Acceptance Criteria
Device Safety and Electrical Testing	To verify compliance with IEC 60601-1, 3rd Edition	Complies with standard
EMC Testing	To verify compliance with IEC 60601-1-2, 4th Edition	Complies with standard
Home Health Care Products	To verify compliance with IEC 60601-1-11, 2nd Edition	Complies with standard
Battery Standards	To verify compliance with IEC 62133, 2nd Edition	Complies with standard
Power 1 – Initial Charge	To verify length of time to fully charge dormant Transmitter	Battery should be fully charged in less than 120 minutes
Power 2 - Transmitter Battery Recharge Time	To verify whether the charger can recharge the battery within the specified time	Battery in the fully empty condition should be fully recharged in less than 20 minutes
Power 3 – Low Battery Indication	To verify the Transmitter lasts for at least 4 hours after low battery indication	Battery shall last at least 4 hours after 10% battery remaining indication before entering dormant mode
Cycled Battery Charge Time	To verify the battery life after 100 charge/discharge cycles	Battery when fully charged should last a minimum of 36 hours after 100 charge/discharge cycles
	To verify the battery life after 400 charge/discharge cycles	Battery when fully charged should last a minimum of 8 hours after 400 charge/discharge cycles
Bluetooth Range	To verify whether the Transmitter provides reliable communication via Bluetooth within the specified range, and re-establishes communication after moving to and from maximum specified range	Transmitter should communicate with hand-held device within a maximum of 10 meters (32.8 feet)
Antenna 1	To verify peak frequency	13.56 Mhz ± 7 Khz
Antenna 2 - NFC Read performance at 12mm	To verify the Transmitter can communicate with the Sensor from the specified distance	Transmitter shall be able to communicate with the Sensor from the 12 mm maximum distance
Charging Cradle Reliability	To verify charging cradle function following 1200 cycles of inserting and detaching the Transmitter to/from the charging cradle	After 1200 cycles, the charging cradle charges the Transmitter, and the Transmitter remains connected to the charging

Test Name/ Description	Test Purpose	Acceptance Criteria
		cradle
Button Reliability	To verify Transmitter button function after actuation (Phoenix Transmitter System High Level Functional Test Procedure)	Verify that after 3000 button presses that the Transmitter's button does not have significant physical damage or wear, and is able to pass all steps of the High Level Functional Test Procedure that involve system responses to button presses
Adhesive Patch Operational Test	To verify adhesive patch function following submersion in water for 30 minutes (Phoenix Transmitter System High Level Functional Test Procedure)	Verify that the adhesive patch passes the functionality test

Transmitter Environmental Exposure and Mechanical Testing: Transmitters were subjected to the following functional and environmental tests. Protocols, test reports and acceptance criteria were reviewed and found to be acceptable. The device met the pre-determined acceptance criteria, as described in Table 2 below.

Table 2: Mechanical Testing of the Eversense Smart Transmitter

Test Name/ Description	Test Purpose	Acceptance Criteria
Shipping	To verify devices as packaged can meet functional requirements after simulated shipping conditions, including conditioning based upon ISTA 3A and Shipping Simulation testing according to ASTM D4169-16 Cycle 13, Assurance Level I	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Thermal Shock	To verify devices function following thermal shock	Devices must pass Phoenix Transmitter System High Level Function Test Procedure
Storage Conditions	To verify devices function following storage at low and high temperatures (0 and 35ºC)	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Operating Conditions Test – Temperature	To verify devices function following exposure to extreme temperatures and humidity (5 to 40ºC and relative	Devices must pass Phoenix Transmitter System High Level Function Test Procedure

Test Name/ Description	Test Purpose	Acceptance Criteria
and Humidity	humidity 15 to 90%)	
Mechanical Shock	To verify devices function following mechanical shock conditions as specified in IEC 60601-1-11	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Vibration	To verify devices function following vibration conditions	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Drop	To verify devices function as intended following repeated drops from a height of 1 meter unto a hardwood board	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Push	To verify devices function following application of a steady force of 250 N ± 10 N (56.2 lb ± 2.2 lb) for a period of 5 seconds, using a test tool which provides contact over a circular plane surface 30mm	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Operational Life Test	To verify devices ability to function over a 1 year life	Devices must pass functional requirements
Water Ingress Test	To evaluate transmitter compliance with IP67 rating and charging cradle compliance with IP22 rating of IEC 60529	Transmitter must demonstrate no water ingress. Transmitter and charging cradle must pass a comprehensive functional test procedure following exposure to the water ingress stress conditions

Insertion Tools Environmental Exposure and Mechanical Testing: Insertion Tools (Insertion Tool and Blunt Dissector) were subjected to the following functional and environmental tests described in Table 3. Protocols, test reports and acceptance criteria were reviewed and found to be acceptable. The device met the pre-determined acceptance criteria.

Table 3: Mechanical and Environmental Testing of the Eversense Insertion Tools

Test Name/ Description	Test Purpose	Acceptance Criteria
Actuation Mechanism Test	To evaluate the mechanism of actuation of the insertion tool by locking and unlocking	Verification of lock and unlocked positions
Push and Pull Test	To evaluate the mechanical strength of the cannula of the insertion tool and metal portion of the blunt dissector following compression and tension	Withstand minimum push or pull force of 44.5 N
Actuation Force Test	To evaluate the force needed for the actuation mechanism of the insertion tool	Actuate with less than 2.2 lbf
Marking Durability	To evaluate the markings on the tool remains visible	Marks remain visible and do not degrade
Shipping and Handling Extremes	To evaluate whether the devices within their packaging can withstand exposure to extreme temperatures and humidity	Verification of package integrity and device function

Sensor Environmental Exposure and Electrical Testing: Sensor verification testing was performed to evaluate the Sensor electronics and glucose indicator to verify the design meets the essential performance described in Table 4. Sensors were subjected to testing to evaluate label marking durability through shipping tests, dimensional, and maintaining electrical essential performance. Protocols, test reports and acceptance criteria were reviewed and found to be acceptable. The device met the pre-determined acceptance criteria.

Table 4: Environmental and Electrical Testing of the Eversense Sensor

Test Name/ Description	Test Purpose	Acceptance Criteria
Sensor Electro-optical Interface Circuit Testing	To evaluate functionality of the near field communication and electro-optical circuitry	Sensor electronic can communicate via the ISO 15693 protocol, and are able to excite the fluorescent glucose indicator and detect its emitted fluorescent light according to Specification limits
Sensor Glucose Indicator Test	To evaluate the glucose responsivity of the fluorescent glucose indicator	Sensor must meet specification limit for fluorescent signal strength and sensitivity to glucose levels
Marking Durability	To evaluate that the Sensor package marking is protected against the effects of temperature and humidity.	The marking on the sensor packaging shall not visibly deteriorate upon humidity exposure.
Shipping and	To evaluate whether the devices	Following the shipping exposure,

Test Name/ Description	Test Purpose	Acceptance Criteria
Handling Extremes	within their packaging can withstand exposure to extreme temperatures and humidity	the samples shall meet the essential performance requirement

Biocompatibility Testing: Biocompatibility studies were selected and performed in consultation with international recognized safety standards (ISO 10993-1, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing) and in accordance with the FDA guidance document entitled "Use of International standard ISO 10993-1, Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process" dated June 16, 2016. All studies cited in this section were conducted in compliance with 21 CFR Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies (GLPs). All studies had passing results. Results of the biocompatibility studies are summarized in Table 5,
Table 6, and Table 7.

Table 5: Summary of the Biocompatibility Tests and Results for the Eversense Sensor

Biocompatibility Test	ISO Standard	Test Method	Results
Cytotoxicity	ISO 10993-5	MEM Elution	Pass – Not cytotoxic
Sensitization	ISO 10993-10	Maximization Sensitization	Pass - Not Sensitizing
Irritation	ISO 10993-10	Intracutaneous Reactivity	Pass – Nonirritant
Systemic Toxicity	ISO 10993-11	Acute Systemic Toxicity	Pass - Not toxic
Systemic Toxicity	ISO 10993-11	Material Mediated Pyrogen	Pass – Not pyrogenic
Subchronic Toxicity and Implantation	ISO 10993-6	4 and 13 Week Systemic Toxicity in Rats-Subcutaneous Implant	Pass - Not systemically toxic
Chronic Toxicity and Implantation	ISO 10993-6	26 Week Systemic Toxicity in Rats-Subcutaneous Implant	Pass - Not systemically toxic
Genotoxicity/Carcinogenicity	ISO 10993-3	Bacterial Reverse Mutation	Pass - Non-mutagenic
Genotoxicity/Carcinogenicity	ISO 10993-3	Mouse Lymphoma	Pass - Non-mutagenic
Genotoxicity/Carcinogenicity	ISO 10993-3	Peripheral Blood Micronucleus Test	Pass - No damage to chromosomes
Chemical Characterization	ISO 10993-17 ISO 10993-18	Exhaustive Extraction	Pass - no leachables/extractables from the Sensor are

Biocompatibility Test	ISO Standard	Test Method	Results
		Infrared Analysis Semi-volatile Organics by GC-MS Non-volatile Organics by UPLC-MS Volatile Organic Compounds by GC-MS Headspace ICP-MS for inorganic metals and elements	likely to cause adverse effects in patients
Particulate Tests	ISO 14708-1	Light Obscuration Method	Pass - Particulate count did not exceed requirement

Table 6: Summary of the Biocompatibility Tests and Results for the Eversense Transmitter and Adhesive Patch

Biocompatibility Test	ISO Standard	Test Method	Results
Cytotoxicity	ISO 10993-5	Transmitter: MEM Elution Adhesive Patch: Agarose Overlay Method	Pass – Not cytotoxic
Sensitization	ISO 10993-10	Transmitter: Maximization Sensitization Adhesive Patch: Maximization Sensitization	Pass - Not Sensitizing
Irritation	ISO 10993-10	Transmitter: Primary Skin Irritation Adhesive Patch: Primary Skin Irritation	Pass – Nonirritant

Table 7: Summary of the Biocompatibility Tests and Results for the Eversense Insertion Tools

Biocompatibility Test	ISO Standard	Test Method	Results
Cytotoxicity	ISO 10993-5	MEM Elution	Pass – Not cytotoxic
Sensitization	ISO 10993-10	Maximization Sensitization	Pass - Not Sensitizing
Irritation	ISO 10993-10	Intracutaneous Reactivity	Pass – Nonirritant
Systemic Toxicity	ISO 10993-11	Acute Systemic Toxicity	Pass - Not toxic
Systemic Toxicity	ISO 10993-11	Material Mediated Pyrogen	Pass - Non-pyrogenic

Interference Testing: Interference in the Eversense CGM system was assessed using *in vitro* testing. During *in vitro* testing, sensors were placed into glucose solutions to which potentially interfering substances were then added. The sponsor based the selection of concentrations of potential interferents on recommendations from interference testing standards/guidelines (e.g. Clinical & Laboratory Standards Institute (CLSI) EP7A2), FDA guidance documents for other glucose measurement devices (e.g. "Self-Monitoring blood glucose test systems for over-the-counter use" issued October, 2016), or based on information available in literature. In some cases, information on ISF concentration of potential interferants was not available. In these situations, plasma concentrations were used to assess interference; this approach represents a worst-case scenario, as ISF concentrations are unlikely to be higher than plasma concentrations. Most tested substances occur in ISF due to diffusion of the substance into ISF from the bloodstream.

Substances were tested at 2 glucose concentrations – a low concentration of 72 mg/dL and a high concentration of 324 mg/dL. The glucose level measured by the sensors was recorded before and after the addition of the potential interferant, and the degree of bias was calculated.

Senseonics defined significant interference as a bias greater than 10 mg/dL for glucose levels below 100 mg/dL, or greater than 10% for glucose levels above 100 mg/dL.

Based on the results of this testing, the following statements are included in the product labeling:

- Mannitol or sorbitol, when administered intravenously, or as a component of an irrigation solution or peritoneal dialysis solution, may increase blood mannitol or sorbitol concentrations and cause falsely elevated readings of your sensor glucose results. Sorbitol is used in some artificial sweeteners, and concentration levels

from typical dietary intake do not impact sensor glucose results.
- Antibiotics of the tetracycline class may falsely lower sensor glucose readings. You should not rely on sensor glucose readings while taking tetracyclines.

Software: The applicant performed software verification and validation testing in accordance with the FDA guidance document entitled "Guidance for the Contents of Premarket Submissions for Software Contained in Medical Devices," dated May 11, 2005. Verification and validation testing included units test, system level verification tests (which included functional testing to demonstrate the device meet its requirements), code review, traceability linking and validation testing to ensure the software conforms to user needs and intended uses.

Human Factors/Usability: Human factors Validation testing was conducted per the FDA guidance entitled "Applying Human Factors and Usability Engineering to Medical Devices" dated February 3, 2016. The Human Factors Validation testing considered the intended users, uses and use environments in the design of the simulated use testing.

Human factors studies were conducted to evaluate patient users as well as physician users who perform the sensor insertions.

Patient user human factors studies evaluated adult users with a variety of smartphone experience and an approximately equal distribution of iPhone and Android users. The initial human factors study evaluated usability tasks such as performing initial setup and pairing, setting alerts, calibrating sensor, and responding to alerts. A supplemental human factors study evaluated critical use-related tasks for the Eversense mobile app such as notification setup and responding to alert notifications including low and high glucose alerts, transmitter disconnect alert and battery low alert. In one scenario, study participants were asked to use their mobile device for a distracting task with the Eversense app in the background. While the app was in the background, study staff triggered low battery alerts for the system. Two study participants using the Android version of the app said that they noticed the transmitter vibration and correctly understood that this indicated an alert, but they did not want to stop what they were doing to check the Eversense app immediately. This failure was not observed for users of the iOS app, as the iOS app had implemented banner type notifications for instances when the Eversense app was in the background. In response to this observation, the applicant implemented banner type notifications for the Android version of the app.

A physician human factors study evaluated physician's ability to successfully perform sensor insertion procedures after receiving training. Sensor insertions were performed using simulated tissue products designed to mimic real arm tissue where insertions would normally be done. Each participant completed a sensor insertion scenario encompassing the full procedure from patient and equipment preparation to wound closure. All 16 physicians successfully used the blunt dissector tool to create the

subcutaneous pocket for the sensor. One physician participant (out of 16) failed to successfully insert the sensor into the subcutaneous pocket. During debriefing, it was determined that the physician did not successfully load the sensor into the insertion tool. During real use scenarios, for their first insertions physicians are monitored by Senseonics training staff. Training staff were not included in this roll during the human factors assessment. As this type of use error has not been observed in any clinical studies to date, the risk appears to be well mitigated in practice.

The human factors validation evaluation and testing demonstrates that the device can be used by the intended users without serious use errors or problems, for the intended uses and under the expected use conditions.

Sterility: The Sensor with its holder is a provided sterile for single-use and is sterilized using ethylene oxide (EO). The sterilization process was validated in accordance with ISO 11135-1, Sterilization of Health Care Products – Ethylene oxide – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices and in consideration of ISO 11135-2, Sterilization of Health Care Products – Ethylene oxide – Part 2: Guidance on the application of ISO 11135-1. The device is sterilized to a sterility assurance level (SAL) of 10^{-6}. EO and ethylene chlorohydrin (ECH) residuals are monitored and meet the limits specified in ISO 10993-7, Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals. The Sensor is provided pyrogen free.

The Insertion Tools are provided sterile for single-use, and are sterilized using EO. The sterilization process was validated in accordance with ISO 11135-1, Sterilization of Health Care Products – Ethylene oxide – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices, and in consideration of ISO 11135-2, Sterilization of Health Care Products – Ethylene oxide – Part 2: Guidance on the application of ISO 11135-1. The device is sterilized to a SAL of 10^{-6}. EO and EC residuals are monitored and meet the limits specified in ISO 10993-7, Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals.

Shelf Life and Packaging: The Sensor with the sensor holder is provided sterile for single use with recommended storage between 2°C and 8°C (36°F and 46°F) and a labeled expiration date set at 1 month. Shelf life studies of the Sensor are ongoing under an approved protocol and the shelf life will be updated upon successful completion of each subsequent test time point. The Insertion Tools are provided in a single package, sterile for single use with recommended storage at room temperature and a labeled shelf life of 6 months.

B. Animal Studies

A separate animal study was conducted to compare the biocompatibility of the Sensor with steroid eluting collar to a steroid eluting pacing lead, (an approved medical device) that elutes the same drug (dexamethasone acetate) from a silicone carrier. The

Sensor and the pacing lead were implanted subcutaneously in Sprague Dawley rats (one device per animal) in a 90-day implantation study and local tissue histology analyzed after 30 and 90 days of implantation. No adverse tissue reactions were observed after 30 or 90 days with either the Sensor or the pacing lead.

C. Sensor Insertion Tools

The applicant changed the design of one of the sensor insertion tools after the completion of the clinical studies.

The insertion tools, as pictured below, were used during the Eversense CGM clinical studies.

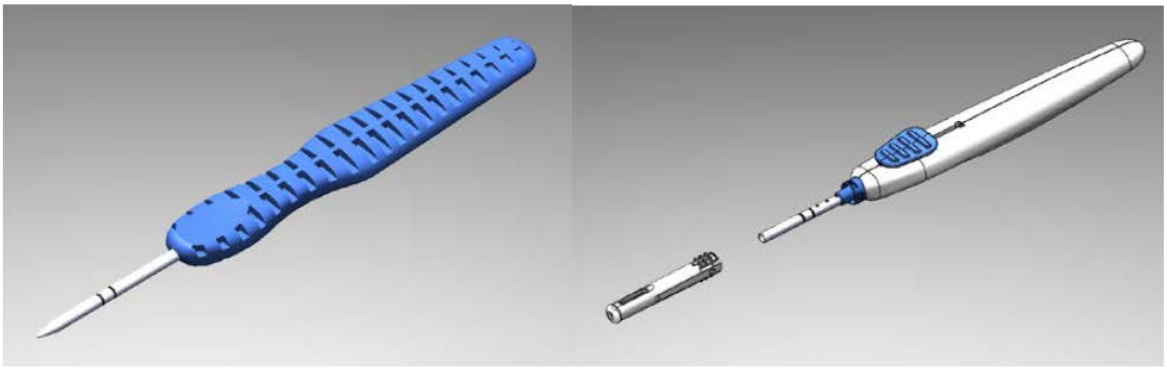

Figure 1 - Sensor Insertion tools that were used for the PRECISE II and PRECISION clinical studies

Senseonics has developed a new version of the Blunt Dissector tool (Figure 2 below). Senseonics states that this re-design is being made to mitigate the risk of physicians inserting sensors too deeply. This was observed once during the PRECISE II study, and the result was that exploratory surgery with the patient under general anesthesia was required to remove the sensor; this was categorized as a serious adverse event. This event happened three times during the PRECISION study, and a surgeon was able to remove the sensor in each case using local anesthesia.

The new blunt dissector design has not been used in clinical studies. The design of the blunt dissector has been updated to add two guides (indicated by an orange arrow in figure 15 below). Also, the metal dissector portion is now shorter, and the user inserts it fully into the subdermal space. Previously, there were two lines etched onto the metal portion of the dissector to indicate how deep it should be inserted (see Figure 1 above).

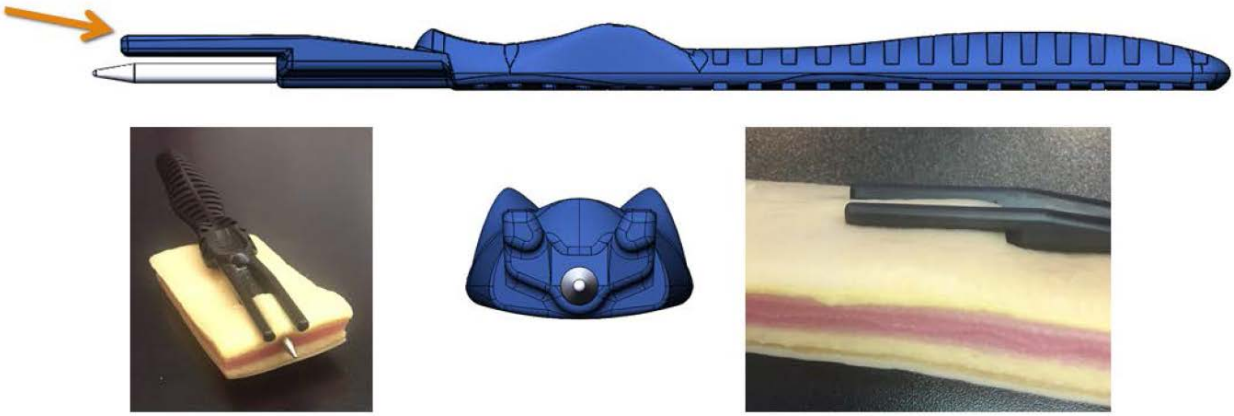

Figure 2 - Updated design of the Blunt Dissector tool, and examples of how it would be used (pictured with synthetic tissue samples).

To validate the new blunt dissector tool, Senseonics performed a human factors study. The human factors study participants included 16 healthcare providers who treat patients with diabetes. Participants completed sessions that included a system overview, watching a training video, a discussion of the package insert, and product training using simulated skin and the insertion tools. The synthetic tissue used for this process was a commercially available product. This was followed by a decay period of at least one hour before participants completed a usability testing scenario. This usability test involved participants performing a complete sensor insertion procedure on simulated skin installed in a model human arm (to mimic realistic arm position). Participants had an assistant available to assist with ancillary tasks (i.e. handling materials so sterility could be maintained). Successful use of the blunt dissector was judged based on the final insertion depth of the sensor in the simulated skin. Correct sensor depth was judged based on whether the sensor could be palpated after implantation. A selection of these synthetic tissue specimens (four of the fifteen) were dissected later and the actual sensor depth was measured and found to be within the intended insertion depth of 3-5mm (actual depths ranged from 3.3 to 3.9 mm).

Senseonics concluded that all participants were able to use the tool successfully to create a satisfactory sensor pocket in synthetic tissue. The one error scenario reported was when a participant failed to load a sensor into the insertion tool before inserting the tool into the sensor pocket in the artificial tissue.

Clinical use of the blunt dissector tool will be further assessed in the post-approval study phase.

D. <u>Sensor Design</u>

The applicant changed the design of the sensor after the completion of the clinical studies.

The Eversense sensor includes a plastic end cap that is attached using epoxy after the electronics assembly is installed. The function of the cap is to seal the end of the

sensor and to provide a smooth, uniform surface.

During sensor removal procedures in the clinical studies, there were several instances where the end cap of the sensor was broken off or missing after sensor removal. In some cases, the broken end caps were located, and in other cases the end caps were not located. A root-cause analysis into this failure concluded that the cause was most likely physicians grasping the end cap with the forceps during removal, instead of grabbing the sensor body. To reduce the potential for this failure, Senseonics redesigned the sensor end cap (see Figure 3 below) to be flush with the end of the sensor.

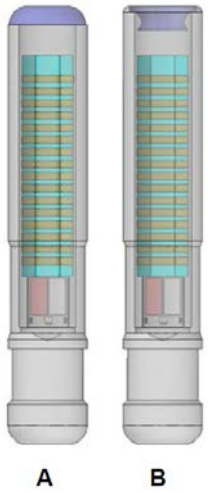

Figure 3 - (A) Sensor design used in PRECISE II and PRECISION studies, and (B) the proposed new sensor design with modified end cap. This design has not been used in any clinical studies to date.

This updated sensor design has not been studied in any clinical study. Senseonics has provided the results of manufacturing validation studies to demonstrate that the new sensors are being manufactured to the correct specifications. Part of this testing includes simulating the forces involved during sensor removal to demonstrate that the new end cap design can withstand greater forces than the previous design. This design change is not expected to affect clinical performance of the Eversense system. The effectiveness of this change in reducing the frequency of sensor fragmentation will be monitored during a post-approval study.

E. Additional Studies

The Eversense Sensor was exposed to X-ray and ultrasonic energy test conditions stated in EN 45502-1. Essential performance was verified on the samples after the completion of exposure.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a pivotal clinical study (PRECISE II) to evaluate the performance of the Eversense CGM System to support 90 days of use. An additional clinical study (PRECISION) was performed to collect additional system accuracy data. Both clinical studies were conducted under IDE # G150165. Data from these two clinical studies served as the primary clinical studies for this premarket approval application.

Glucose Determination Algorithm

One key element of the system that is responsible for Sensor performance and accuracy is the glucose determination algorithm (which includes the finger-stick calibration algorithm). The glucose determination algorithm is pre-programmed in the transmitter firmware, and it converts the raw data collected by the Sensor into glucose readings.

After the two clinical studies were completed, the applicant implemented a modified glucose determination algorithm. The applicant stated that the purpose of this algorithm change was to improve system accuracy, particularly in the early sensor wear period and in the hypoglycemic range.

The version of this algorithm that was used during the US clinical studies is referred to as the "study software" and is abbreviated "study SW." The new version of the algorithm is referred to as "software version 602" and is abbreviated "SW 602."

The algorithm changes within the SW 602 algorithm version targeted accuracy improvement in: 1) the early Sensor life, and 2) the hypoglycemic range throughout the Sensor life. The clinical accuracy data from a 71-subject European pivotal study, PRECISE (Kropff, Choudhary, Neupane, & Barnard, 2017), was used for as a training set for this new algorithm. Data from the PRECISE II study and PRECISION study were not used to develop the new algorithm (SW 602).

The applicant has not studied this new algorithm (SW 602) in real-time in a clinical trial. Rather, they have post hoc processed the raw sensor data from the PRECISE II and PRECISION studies using the new algorithm. The applicant stated that the raw sensor data is independent of this algorithm, so performing this processing post-hoc yields the same final glucose values as if the algorithm had been used during the study.

All data below and in the approved labeling for this device are from the SW 602 analysis.

A. Study Design

The PRECISE II study was a non-randomized, blinded, prospective, single-arm, multi-center study, evaluating 90 adult subjects with diabetes mellitus in the United States at 8 sites. The investigation included both clinic visits and home use of the Eversense CGM System. 75 subjects had one sensor inserted in the upper arm by trained investigators. A subset of 15 subjects, at one clinical site, had two Sensors inserted. The accuracy of the CGM System was evaluated during clinic visits on days

1, 30, 60 and 90 by comparing Sensor glucose values and plasma glucose values drawn every 5 to 15 minutes for a period of approximately 4 ½ to 12 ½ hours and measured on a bedside glucose analyzer. During Sensor accuracy clinic visits, qualifying subjects participated in hyperglycemia and hypoglycemia challenges, as well as upper arm exercise sessions and separate compression sessions for a duration of 30 minutes each.

The first subject was enrolled on January 15, 2016. The last subject was completed on July 26, 2016. Eighty-seven (87) subjects completed the study; 2 subjects withdrew consent and 1 subject was lost to follow-up. Eighty-two (82) subjects completed the day 90 visit with accuracy data collection.

The CGM glucose values and all glucose-related alerts were blinded to both the subjects and the investigators for the duration of the study. All diabetes care decisions were based on SMBG blood glucose values and clinical standard of care, rather than CGM System results. The subjects did use the device for non-glucose related notifications such as calibration reminders and battery levels.

The subject visit schedule, which included 7 visits over a period of approximately 5 months, is summarized in Figure 4 below:

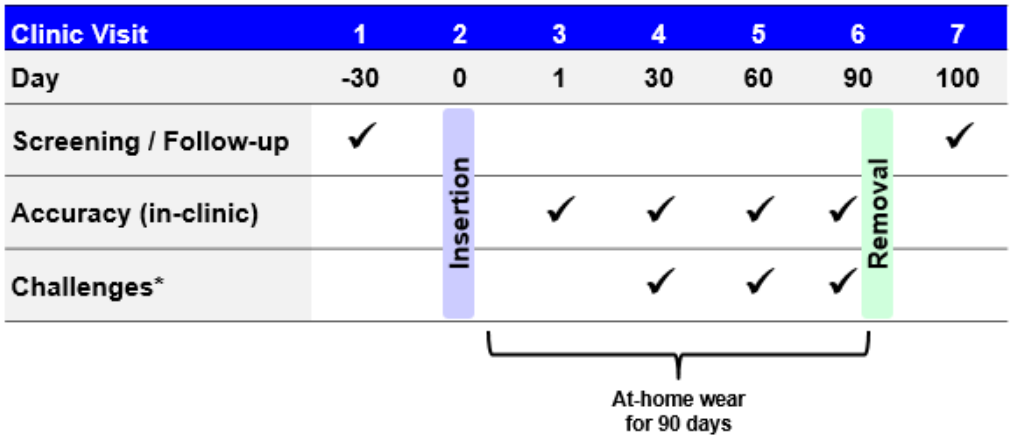

Figure 4: Primary Clinical Study Visit Schedule for PRECISE II

In the PRECISION study, the first subject was enrolled on July 25, 2017. The final subject was completed on February 1, 2018. The study evaluated 35 subjects, all of whom completed the study through the day 90 accuracy evaluation. Eight subjects were inserted with one Sensor (left arm) and 27 subjects were inserted with two Sensors (one in each arm). The PRECISION study shared the same design as the PRECISE II with the following exceptions (see Figure 5). Additional accuracy assessments were added on Day 7 and Day 14 to characterize Sensor accuracy during this period of wear, and patients underwent sleep assessments to evaluate accuracy and system performance during sleep. In addition, patients were not blinded to the glucose values and alerts during the

PRECISION study.

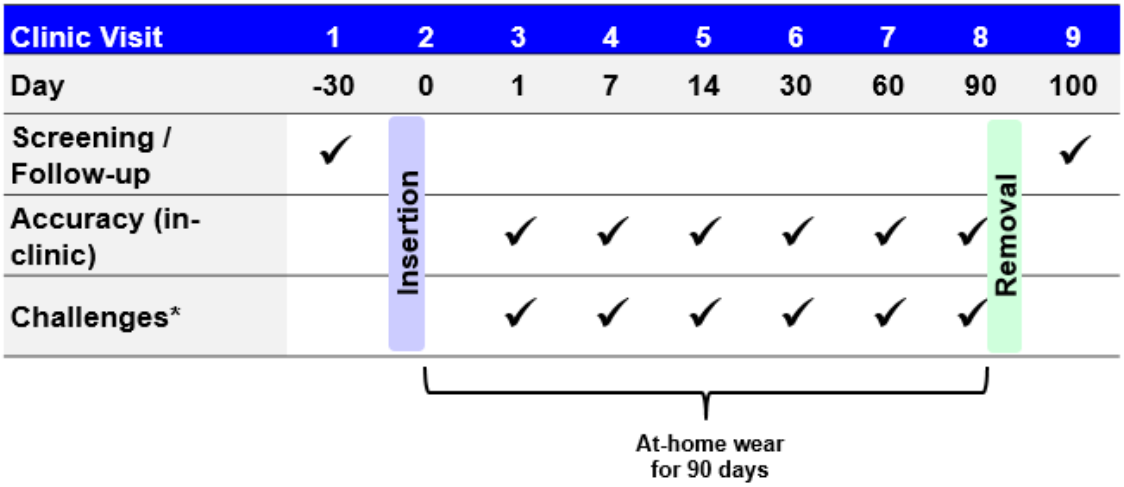

Figure 5: Primary Clinical Study Visit Schedule for PRECISION

1. Inclusion/Exclusion Criteria for the Studies

Inclusion Criteria:

Male and Female Subjects meeting the following inclusion criteria were included in these studies:

1. Adult subjects, age ≥18 years
2. Clinically confirmed diagnosis of diabetes mellitus for ≥1 year
3. Subject has signed an informed consent form and is willing to comply with protocol requirements

Exclusion Criteria:

Subjects meeting any of the following exclusion criteria at the time of screening were excluded from these studies:

1. History of severe hypoglycemia in the previous 6 months. Severe hypoglycemia is defined as hypoglycemia resulting in loss of consciousness or seizure
2. History of diabetic ketoacidosis requiring emergency room visit or hospitalization in the previous 6 months
3. Female subjects of childbearing capacity (defined as not surgically sterile or not menopausal for ≥ 1 year) who are lactating or pregnant, intending to become pregnant, or not practicing birth control during the course of the study.
4. A condition preventing or complicating the placement, operation, or removal of the Sensor or wearing of transmitter, including upper extremity

deformities or skin condition.

5. Symptomatic coronary artery disease; unstable angina; myocardial infarction, transient ischemic attack or stroke in the past 6 months; uncontrolled hypertension (systolic>160 mm Hg or diastolic >100 mm Hg at time of screening); current congestive heart failure; history of cardiac arrhythmia (benign PACs and PVCs allowed). Subjects with asymptomatic coronary artery disease (e,g, CABG, stent placement or angioplasty) may participate if negative stress test within 1 year prior to screening and written clearance from Cardiologist documented.
6. Hematocrit <30% or >55%
7. History of hepatitis B, hepatitis C, or HIV
8. Current treatment for a seizure disorder unless written clearance by neurologist to participate in study
9. History of adrenal insufficiency
10. Currently receiving (or likely to need during the study period): immunosuppressant therapy; chemotherapy; anticoagulant/antithrombotic therapy (excluding aspirin); glucocorticoids (excluding ophthalmic or nasal). This exclusion does include the use of inhaled glucocorticoids and the use of topical glucocorticoids (over sensor site only); antibiotic for chronic infection (e.g. osteomyelitis, endocarditis)
11. A condition requiring or likely to require magnetic resonance imaging (MRI)
12. Known topical or local anesthetic allergy
13. Known allergy to glucocorticoids
14. Any condition that in the investigator's opinion would make the subject unable to complete the study or would make it not in the subject's best interest to participate in the study. Conditions include but are not limited to psychiatric conditions, known current or recent alcohol abuse or drug abuse by subject history, a condition that may increase the risk of induced hypoglycemia or risk related to repeated blood testing. Investigator will supply rationale for exclusion
15. Participation in another clinical investigation (drug or device) within 2 weeks prior to screening or intent to participate during the study period
16. The presence of any other active implanted device (as defined further in protocol)
17. The presence of any other CGM sensor or transmitter located in upper arm (other location is acceptable)

2. Follow-up Schedule

At the end of the Day 90 Clinic Visit, the Sensor was removed per the Eversense Physician Insertion & Removal Instructions; all the Sensor insertion sites were examined and evaluated by the study staff. A follow-up visit was scheduled 10 days later for evaluation of the Sensor site and close out. All used and unused Systems and sub-components, except for used insertion tools, were returned by study staff to Senseonics for examination. Study investigators documented any Adverse Device Effects and evaluated safety issues related to system use during the study.

3. Clinical Endpoint

The study characterized the performance of the System in comparison with the laboratory reference venous plasma sample measurements and assessed the system-reference matched pairs obtained in the in-clinic sessions.

Safety data for the Eversense System were also collected and characterized by incidence, severity and relatedness. Device incidents and malfunctions were also collected.

B. Accountability of Study Subjects and Time of Exposure

In the PRECISE II study, 90 subjects were inserted with the Sensor and 87 (97%) completed the study. The mean duration of Sensor use was 92.2 days and the median duration was 93.0 days, resulting in 9,773 in vivo days of Sensor use in 90 subjects to assess safety. A total of 106 sensors were inserted, including 75 subjects with 1 Sensor and 15 with 2 Sensors, and 1 Sensor replacement during the study. Two subjects withdrew consent and had Sensors removed on Days 62 and 92. One subject was lost to follow up, but subsequently returned to the site and had the sensor removed 196 days after insertion.

In the PRECISION study, 36 subjects were enrolled and 35 were inserted with Sensors with 8 receiving one (1) Sensor and 27 receiving two (2) Sensors. All 35 subjects completed all visits at Day 1, 7, 14, 30, 60 and 90.

C. Study Population Demographics and Baseline Parameters

A summary of demographic characteristics is presented in Table 8 and Table 9.

Table 8: Demographic Information

Demographic	**PRECISE II (n=90)**	**PRECISION (n=35)**
Gender [n (%)]		
Male	54 (60)	18 (51)
Female	36 (40)	17 (49)
Age (years) [mean (SD)]	45(16)	52 (16)
Min, Max	18, 77	18, 75
Race n (%)		
Caucasian	77 (86)	32 (91)
Black or African American	7 (8)	1 (3)
Asian	3 (3)	2 (6)
American Indian or Alaska Native	2 (2)	0 (0)
Native Hawaiian or Other Pacific Islander	1 (1)	0 (0)
Dominant Hand [n (%)]		
Right	78 (87)	33 (94)
Left	12 (13)	2 (6)

Demographic	PRECISE II (n=90)	PRECISION (n=35)
Body Mass Index Class [n (%)] [mean (SD)] Min, Max	29 (6) 19, 50	28 (5) 19, 44
Normal (<25 kg/m^2)	22 (24)	9 (26)
Overweight (≥25 and <30)	27 (30)	11 (31)
Obese (≥30)	41 (46)	15 (43)

Table 9: Diabetic History

Diabetic History	PRECISE II (n=90)	PRECISION (n=35)
Years since diabetes diagnosis (years) [mean(SD)] Min, Max	26.0 (14.3) 4, 57	20.1 (13.7) 1, 53
Diabetes type (n/%) Type I Type II	 25 (71.4) 10 (28.6)	 61 (67.8%) 29 (32.2%)
Type of insulin therapy (n/%) None Multiple daily injections Continuous insulin infusion pump Other	 5 (14.3) 11 (31.4) 19 (54.3)	 20 (22.2%) 24 (26.7%) 43 (47.8%) 3 (3.3%)
History of ketoacidosis (n/%)	0 (0.0)	0 (0%)
History of hypoglycemia (n/%)	0 (0.0)	1 (1.1%)

Of the 125 subjects in both studies, 86 had Type I diabetes (61 in PRECISE II study and 25 in the PRECISION study). A total of 62 subjects had continuous insulin infusion pump (43 in the PRECISE II study and 19 in the PRECISION study).

A. Safety and Effectiveness Results

1. Safety Results

The safety endpoints and evaluations performed in the PRECISE II study and the PRECISION study were the same. At each study visit a safety evaluation was performed. Sensor sites were evaluated and assessed for any signs of irritation or infection, including increased temperature, pain, redness, warmth, swelling or purulence. In addition, subjects were queried at each visit for Sensor site assessment between visits, as well as other adverse events. Subjects were asked at the beginning of each visit if anything had changed medically since their last visit. All adverse events identified, regardless of relatedness to the device or insertion/removal procedure, were documented.

The primary safety analysis was based upon all subjects in the investigation who were not screen failures or withdrawals prior to a first insertion attempt. Ninety

(90) subjects were successfully inserted with a Sensor in the PRECISE II Study and 35 in the PRECISION Study, forming the basis of the safety populations. In the PRECISE II study, 15 subjects had two (2) Sensors inserted (one in each arm) and 75 subjects had one (1) Sensor inserted. One subject had a replacement Sensor inserted after the primary Sensor had a suspected electrical or mechanical failure. In the PRECISION study, 8 subjects had one (1) Sensor inserted and 27 had two (2) Sensors inserted (one in each arm).

The primary safety endpoint was the incidence of device-related or Sensor insertion/removal procedure-related serious adverse events (SAE) through 90 days post insertion or Sensor removal and follow-up. An adverse event relationship was considered non-related, possibly related, related or unknown based upon review and categorization by the independent medical monitor. An analysis was provided through Sensor removal as shown in Table 10. The proportion of subjects experiencing a serious adverse event is presented together with the associated 95% confidence interval.

Table 10: Safety Endpoints in the PRECISE II and PRECISION Studies

SAEs by Relationship to Study	PRECISE II (N=90)	PRECISION (N=35)
	Number of Subjects with SAEs (%)	Number of Subjects with SAEs (%)
All SAEs	1 (1.1%)	3 (8.6%)
Device-Related SAEs	0 (0.0%)	0 (0.0%)
Sensor Insertion/Removal Procedure-Related SAEs	1 (1.1%)	0 (0.0%)
Study Procedure-Related SAEs	0 (0.0%)	0 (0.0%)
Unrelated to Study SAEs	0 (0.0%)	3 (8.5%)

The secondary safety endpoints included:

- Incidence of device-related or insertion/removal procedure-related serious adverse events over the operating life of the Sensor.
- Incidence of insertion/removal procedure or device-related adverse events in the clinic and during home use.
- Incidence of all adverse events in the clinic and during home use.
- Incidence of hospitalizations due to hypoglycemia, hyperglycemia or ketoacidosis occurring during home use.
- Incidence of reported hypoglycemic and hyperglycemic events occurring during home use.

Table 11, below, shows the safety data from each study. Fourteen (14) adverse events that were determined to be device- and/or insertion/removal procedure-related or possibly related, including the one (1) SAE (in which the initial attempt to remove a sensor was unsuccessful and a surgeon later removed the sensor using general anesthesia), occurred in the PRECISE II study among 7 (7.7%) subjects. All events adjudicated as related or possibly related to the device and/or insertion/removal procedures had complete resolution by study completion with exception of one subject. One subject had a delayed report of intermittent pain adjudicated as possibly related. Eight (8) adverse events occurred in 5 subjects (14.3%) in the PRECISION study, and all device-related adverse events were mild or moderate in severity and resolved within 2 weeks of Sensor removal. Importantly, most subjects received two Sensors in the PRECISION study, which resulted in higher device-related adverse events rate when compared to PRECISE II study. There were no unanticipated adverse events and no UADEs. There were no infections observed in either study, resulting in an infection rate of 0.0%.

Table 11: Adverse Events Related or Possibly Related to the Study Device or Insertion/removal Procedure

	PRECISE II (n=90)		**PRECISION (n=35)**	
	Number of Events	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**
Event Physiologic System	**14**	**7 (7.7%)**	**8**	**5 (14.3%)**
Dermatological	**8**	**4 (4.4%)**	**6**	**4 (11.4%)**
Bruising	2		0	
Erythema	2		0	
Pain/Discomfort	4		2	
Dermatitis	0		2	
Hyperpigmentation of skin	0		2	
Musculoskeletal/Rheumatologic	**1**	**1 (1.1%)**	**0**	**0 (0.0%)**
Pain/Discomfort	1		0	
Neurological	**2**	**2 (2.2%)**	**0**	**0 (0.0%)**
Paresthesia	1		0	
Syncope-vasovagal	1		0	
Other	**3**	**3 (3.3%)**	**2**	**1 (2.9%)**
Device fragment not recovered	2		0	
Additional procedure to remove Sensor	1		2	

Assessment of Dexamethasone Exposure

During the PRECISION Study, a subset of 8 subjects with one Sensor inserted into the left arm had blood samples drawn at 30 minutes, 2 hours and 4 hours post-insertion and then daily for at least the first 8 days of Sensor wear for additional DXA evaluation and to determine blood draw time points during the

first week of Sensor wear for the remaining subjects. The assay used to measure DXA in plasma had a limit of quantitation (LoQ) of 50 pg/mL. The analysis showed that DXA greater than 50 pg/ml was not detected in any subject during the first 8 days nor at subsequent visits through 90 days in this group.

The remaining subjects had 2 Sensors inserted, one in each arm, and underwent blood draws for DXA evaluation 2 hours after insertion and at every clinic visit including 2 draws on clinic visits that spanned two calendar days. There were 18 of 27 (66%) subjects with two Sensors that had detectable levels above 50 pg/ml in the first 8 days. In all cases in these 18 subjects, the plasma DXA was below the LoQ of 50 pg/mL by day 8 post-insertion. The maximum level detected was 114 pg/ml at day 2 in one subject which fell below the detection limit by day 7. DXA greater than 50 pg/ml was not detected at subsequent visits through 90 days in this group.

The results from the DXA measurements taken throughout this study are provided below in Table 12 below.

Table 12: Plasma DXA measurements in subjects during the PRECISION clinical study. Subjects with 1 sensor implanted had serial measurements collected on the day of sensor insertion, all of which showed DXA values below the assay LoQ of 0.050 ng/mL.

Time After Insertion	Subjects with 1 Sensor (n=8)	Subjects with 2 Sensors (n=27)
	Detections >0.050 ng/mL	Detections >0.050 ng/mL
Day 0 (Immediate Post Insertion)	0	0
Day 1	0	18
Day 2*	0	10
Day 3	0	0
Day 4	0	0
Day 5	0	0
Day 6	0	0
Day 7	0	1
Day 8	0	1
Day 9	0	0
Day 14	0	0
Day 15	0	0
Day 30	0	0

* Highest detected amount was 114 pg/mL on Day 2

Sensors removed from patients in clinical studies were returned to the applicant for evaluation of residual DXA content. Explanted Sensors retained approximately 80-90% of their original DXA content at 90 days. This corresponds to approximately 0.18 - 0.35 mg of DXA being released into the body from a single Sensor over the

course of 90 days.

2. Effectiveness Results

The analysis of effectiveness was based on the observed accuracy of sensors in 90 evaluable patients in the PRECISE II study who contributed 15,753 CGM-comparator matched glucose data pairs, and 35 evaluable patients in the PRECISION study who contributed 15,170 CGM-comparator matched glucose data pairs.

All effectiveness analyses presented in this document were performed using the approved glucose determination algorithm, referred to as the "SW-602" algorithm.

The following tables show the rate at which the Eversense CGM System agreed with a laboratory comparator method (CM). The tables are organized by CM system glucose ranges, and they tabulate the percent of CGM system measurements that were within a given range of paired comparator measurements. The ranges included below are 15, 20, 30, 40, and greater than 40. For comparator values below 80 mg/dL, the units of the range value are mg/dL. For CGM values above 80 mg/dL, the units of the range value are percent.

The data which are tabulated in Table 13 below is a combination of data collected on four different days of the PRECISE II study: days 1, 30, 60, and 90 of sensor wear.

Table 13: CGM System and Comparator Agreement in Different Comparator Glucose Ranges, PRECISE II Study, SW-602 data

CM Glucose Range (mg/dL)	Number of Paired Eversense CGM and CM	Percent of CGM System Readings Within				
		Percent 15/15% of CM	Percent 20/20% of CM	Percent 30/30% of CM	Percent 40/40% of CM	Percent Greater than 40/40% of CM
Overall (40-400)	15753	86.8	94.3	98.6	99.6	0.4
< 40	7	71.4	71.4	100.0	100.0	0.0
40 - 60	488	89.5	95.1	98.8	99.8	0.2
61 - 80	1159	84.5	92.0	97.7	99.1	0.9
81 - 180	7540	85.6	93.0	98.0	99.4	0.6
181 - 300	5378	88.4	95.9	99.4	99.9	0.1
301 - 350	820	88.4	97.4	99.8	100.0	0.0
351 - 400	326	86.5	96.6	98.5	100.0	0.0
> 400	35	91.4	100.0	100.0	100.0	0.0

The data which are tabulated in the following table are a combination of data collected on six different days of the PRECISION study: days 1, 7, 14, 30, 60, and 90 of sensor wear.

Table 14: CGM System and Comparator Agreement in Different Comparator Glucose Ranges, PRECISION Study, SW-602 data

CM Glucose Range (mg/dL)	Number of Paired Eversense CGM and CM	Percent of CGM System Readings Within				
		Percent 15/15% of CM	Percent 20/20% of CM	Percent 30/30% of CM	Percent 40/40% of CM	Percent Greater than 40/40% of CM
Overall (40-400)	15170	85.4	92.8	98.1	99.3	0.7
< 40	15	60.0	73.3	86.7	100.0	0.0
40 - 60	1267	86.8	92.6	98.1	99.1	0.9
61 - 80	2212	85.8	93.0	98.5	99.3	0.7
81 - 180	5685	80.6	89.4	96.7	98.8	1.2
181 - 300	3210	87.4	94.9	98.6	99.8	0.2
301 - 350	1527	91.4	97.8	100.0	100.0	0.0
351 - 400	1174	93.4	97.5	99.7	100.0	0.0
> 400	80	81.3	93.8	97.5	100.0	0.0

The following two tables provide the number and percentage of CM measurements collected while the continuous glucose monitor read 'low' (<40 mg/dL) or 'high' (>400 mg/dL) during the PRECISE II and PRECISION clinical studies.

Table 15: The number and percentage of Comparator values collected when CGM readings displayed 'Low' (less than 40 mg/dL) or 'High' (greater than 400 mg/dL); PRECISE II Study, SW-602 algorithm

Comparator mg/dL							
CGM Readings	CGM-Ref pairs	<55	<60	<70	<80	>80	Total
'LOW'	n	0	1	2	2	0	2
	%	0%	50%	100%	100%	0%	100%
Comparator mg/dL							
CGM Readings	CGM-Ref pairs	>340	>320	>280	>240	<240	Total
'HIGH'	n	67	68	68	68	0	68
	%	98.5%	100%	100%	100%	0%	100%

Table 16: The number and percentage of Comparator values collected when CGM readings displayed 'Low' (less than 40 mg/dL) or 'High' (greater than 400 mg/dL); PRECISION Study, SW-602 algorithm

Comparator mg/dL							
CGM Readings	CGM-Ref pairs	<55	<60	<70	<80	>80	Total
'LOW'	n	6	7	9	9	0	9
	%	66.7%	77.8%	100%	100%	0%	100%
Comparator mg/dL							
CGM Readings	CGM-Ref pairs	>340	>320	>280	>240	<240	Total
'HIGH'	n	359	383	399	404	1	405
	%	88.6%	94.6%	98.5%	99.8%	0.2%	100%

The following tables show the rate of concurrence between the Eversense CGM System and a laboratory comparator method. The tables are organized by CGM system glucose ranges, and they tabulate the percent of paired CM measurements that were in the identical range (shaded diagonal), as well as those CM measurements that were in glucose ranges above and below the paired CGM readings. Cells with dashes '--' indicate zero percent (0%).

Table 17: CGM System concurrence to Comparator organized by CGM glucose ranges; data pooled from accuracy assessments on days 1, 30, 60, and 90 combined of the PRECISE II clinical study, analyzed using SW-602 algorithm

CGM (mg/dL)	**Percent of Matched Pairs in Each CM Glucose Range for Each CGM Range (mg/dL)**											
	Number of Paired CGM-CM	**<40**	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**>400**
40-60	480	1%	63%	34%	3%	--	--	--	--	--	--	--
61-80	1111	--	16%	63%	20%	1%	--	--	--	--	--	--
81-120	3066	--	--	9%	76%	14%	--	--	--	--	--	--
121-160	3245	--	--	--	11%	73%	15%	--	--	--	--	--
161-200	2812	--	--	--	--	15%	64%	21%	--	--	--	--
201-250	2614	--	--	--	--	--	13%	68%	18%	--	--	--
251-300	1484	--	--	--	--	--	1%	17%	58%	23%	1%	--
301-350	692	--	--	--	--	--	--	1%	19%	59%	20%	--
351-400	249	--	--	--	--	--	--	--	--	20%	66%	13%

Table 18: CGM System concurrence to Comparator, organized by CGM glucose ranges; data pooled from accuracy assessments on days 1, 7, 14, 30, 60, and 90 combined of the PRECISION clinical study, analyzed using SW-602 algorithm

CGM (mg/dL)	Percent of Matched Pairs in Each CM Glucose Range for Each CGM Range (mg/dL)											
	Number of Paired CGM-CM	<40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	>400
40-60	1236	1%	63%	34%	2%	--	--	--	--	--	--	--
61-80	2003	--	22%	67%	10%	--	--	--	--	--	--	--
81-120	2524	--	2%	17%	71%	10%	--	--	--	--	--	--
121-160	2342	--	--	--	18%	71%	11%	--	--	--	--	--
161-200	1727	--	--	--	1%	24%	59%	16%	--	--	--	--
201-250	1502	--	--	--	--	1%	19%	65%	14%	1%	--	--
251-300	1257	--	--	--	--	--	1%	18%	51%	27%	3%	--
301-350	1628	--	--	--	--	--	--	1%	10%	57%	32%	1%
351-400	951	--	--	--	--	--	--	--	2%	26%	65%	7%

The following tables show the consistency of sensor clinical performance during the sensor wear period by comparing the CM values to their paired sensor points collected on days 1, 30, 60, and 90 of the PRECISE II study, and on days 1, 7, 14, 30, 60, and 90 of the PRECISION study.

Table 19: Sensor stability (accuracy over time); PRECISE II Study, SW-602

Day	Number of Readings	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)	Percent of CGM System Readings Within				
				Percent within 15/15% CM	Percent within 20/20% CM	Percent within 30/30% CM	Percent within 40/40% CM	Percent greater than 40/40% CM
1	1708	10.7	8.2	76.8%	87.1%	96.3%	98.5%	1.5%
30	5081	7.4	5.5	90.7%	96.0%	99.3%	99.8%	0.2%
60	4725	8.2	6.3	87.3%	94.7%	98.8%	99.8%	0.2%
90	4239	9.1	7.3	85.4%	94.7%	98.6%	99.6%	0.4%

Table 20: Sensor stability (accuracy over time); PRECISION study, SW-602

Day	Number of Readings	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)	Percent of CGM System Readings Within				
				Percent within 15/15% CM	Percent within 20/20% CM	Percent within 30/30% CM	Percent within 40/40% CM	Percent greater than 40/40% CM
1	2665	11.6	8.5	79.1%	88.9%	95.8%	98.5%	1.5%
7	2926	9.8	6.8	86.1%	93.3%	98.1%	99.0%	1.0%
14	2997	9.0	6.6	88.1%	94.6%	98.8%	99.6%	0.4%
30	2284	8.9	6.8	88.0%	94.3%	98.9%	100.0%	0.0%
60	2133	8.7	6.9	86.9%	93.7%	98.5%	99.6%	0.4%
90	2165	9.7	7.8	83.9%	92.2%	98.5%	99.3%	0.7%

The tables below provide the percent agreement of the Eversense CGM system and comparator method (CM) within a specific time range after calibration for the PRECISE II and PRECISION studies.

Table 21: Agreement rates for every 2-hour period post calibration; PRECISE II, SW-602

Time from Calibration	Number of Paired CGM and CM	Percent of CGM System Readings Within				
		Percent within 15/15% CM	Percent within 20/20% CM	Percent within 30/30% CM	Percent within 40/40% CM	Percent greater than 40/40% CM
(0, 2) Hours	4347	85.0%	92.2%	97.8%	99.3%	0.7%
[2, 4) Hours	2800	87.5%	94.8%	98.9%	99.7%	0.3%
[4, 6) Hours	2396	85.5%	93.8%	98.5%	99.7%	0.3%
[6, 8) Hours	2115	87.6%	95.6%	99.1%	99.6%	0.4%
[8, 10) Hours	2019	87.8%	95.9%	99.3%	100.0%	0.0%
[10, 12) Hours	1815	88.9%	95.8%	98.8%	99.6%	0.4%

Table 22: Agreement rates for every 2-hour period post calibration; PRECISION, SW-602

Time from Calibration	Number of Paired CGM and CM	Percent of CGM System Readings Within				
		Percent within 15/15% CM	Percent within 20/20% CM	Percent within 30/30% CM	Percent within 40/40% CM	Percent greater than 40/40% CM
(0, 2) Hours	4034	86.0%	93.6%	98.0%	99.3%	0.7%
[2, 4) Hours	3979	85.6%	92.8%	98.4%	99.5%	0.5%
[4, 6) Hours	2308	84.3%	92.2%	97.7%	99.0%	1.0%
[6, 8) Hours	1614	84.3%	92.7%	97.8%	99.4%	0.6%
[8, 10) Hours	1372	88.0%	94.4%	98.5%	99.6%	0.4%
[10, 12) Hours	1295	86.1%	92.9%	98.1%	99.2%	0.8%

The following tables provide data to present sensor accuracy at detecting specific glucose rates of change. These concurrence tables provide the percent of matched CM pairs to CGM values over specific glucose rates of change as observed during the PRECISE II and PRECISION studies.

Table 23: Concurrence of CGM and Comparator Method (CM) rate of change stratified by different CGM rate ranges; PRECISE II, SW-602

CGM Trend (mg/dL/Min)	Comparator Rate of Change (mg/dL/Min) Percent of Matched Pairs in Each Comparator Trend Range for Each CGM Trend Range					Total
	< -2	[-2, -1)	[-1, 1]	(1, 2]	> 2	
< -2	33%	44%	23%	0%	0%	212
[-2,-1)	4%	39%	56%	1%	0%	1202
[-1,1]	0%	5%	88%	6%	1%	11546
(1,2]	0%	1%	49%	38%	12%	1101
> 2	0%	1%	17%	34%	48%	503
Total	159	1161	11471	1262	511	14564

Table 24: Concurrence of CGM and Comparator Method (CM) rate of change stratified by difference CGM rate ranges; PRECISION, SW-602

CGM Trend (mg/dL/Min)	Comparator Rate of Change (mg/dL/Min) Percent of Matched Pairs in Each Comparator Trend Range for Each CGM Trend Range					Total
	< -2	[-2, -1)	[-1, 1]	(1, 2]	> 2	
< -2	22%	36%	41%	0%	1%	473
[-2,-1)	4%	24%	71%	1%	0%	1115
[-1,1]	1%	5%	89%	5%	1%	10655
(1,2]	0%	1%	55%	35%	9%	997
> 2	0%	1%	32%	39%	27%	529
Total	212	990	11137	1085	345	13769

Table 25 and Table 26 below provide the Eversense sensor percent difference with respect to comparator method (CM) values. The comparator method used during this study was the Yellow Springs Instruments 2300 glucose analyzer.

Table 25: Difference measures between Eversense CGM System and Comparator Readings (CM), PRECISE II study using SW-602

CM Glucose Range (mg/dL)	Number of Paired CGM- CM	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)
Overall	15753	8.5	6.5
< 40*	7	13.0	8.0
40-60*	488	7.8	6.0
61-80*	1159	8.7	6.0
81-180	7540	8.2	6.1
181-300	5378	7.6	6.2
301-350	820	7.9	6.9
351-400	326	7.5	6.1
> 400	35	8.3	7.4

*For CM ≤ 80 mg/dL, the differences in mg/dL are included instead of percent difference (%).

Table 26: Difference measures between Eversense CGM System and Comparator Readings, PRECISION study using SW-602

CM Glucose Ranges (mg/dL)	Number of Paired CGM- CM	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)
Overall	15170	9.6	7.1
<40*	15	16.2	14
40-60*	1267	8.1	6
61-80*	2212	8.6	7
81-180	5685	9.7	7.5
181-300	3210	7.7	5.9
301-350	1527	6.8	5.7
351-400	1174	6.5	5.5
>400	80	11.2	10.5

*For CM ≤ 80 mg/dL, the differences in mg/dL are included instead of percent difference (%).

Precision Analysis

Precision of the System was evaluated by comparing the results from two separate sensors worn on the same subject at the same time. During the PRECISE II study, a total of 15 subjects contributed 10,371 between-sensor matched pairs. During the PRECISION study, a total of 27 subjects contributed 37,307 between-sensor matched pairs. The tables below tabulate the results from both studies, including the Percent Absolute Relative Difference (PARD), standard deviation (SD), and Percent Coefficient of Variation (% CV).

Table 27: System precision statistics; PRECISE II study, SW-602

Level of Mean Glucose (mg/dL)	Mean Difference (Sensor 1 - Sensor 2) (mg/dL)	SD of Difference (mg/dL)	N Pairs
< 70	-7.2	11.1	146
71-180	-1.6	16.3	7033
> 180	0.4	21.8	3192
All	-1.1	18.2	10371
PARD	9.0%		
% CV	6.4%		

Table 28: System precision statistics; PRECISION study, SW-602

Level of Mean Glucose (mg/dL)	Mean Difference (Sensor 1 - Sensor 2) (mg/dL)	SD of Difference (mg/dL)	N Pairs
< 70	0.6	10.5	2367
70-180	0.8	18.3	19793
> 180	-3.1	26.6	15147
All	-0.8	21.8	37307
PARD	9.9%		
% CV	7.0%		

Alert Performance

The Eversense System includes threshold alerts and optional predictive alerts. A threshold alert is issued if measured glucose is below or above the user-defined low or high alert set point. A predictive alert is issued if measured glucose is predicted to go below or above the user-defined low or high alert set point within the next 15 minutes.

Alert performance was evaluated to obtain ‘true alert’ and ‘false alert’ rates, and ‘confirmed event’ and ‘missed event’ detection rates. The descriptions and tables below describe the alert rate performance of the device within these two clinical

studies:

- The confirmed event detection rate the rate that the device alerted when it should have alerted. It is the ratio of the number of times an alert was sounded when blood glucose was below the threshold to the total number of times blood glucose went below the threshold (for hypoglycemic alerts).
- The Missed Event Detection Rate is the rate at which the device did not alert when it should have. It is the rate at which blood glucose, as measured by comparator method, was below the low glucose alert threshold and the device did not sound an alert (for hypoglycemic events). This is the complement of the confirmed event detection rate.
- The true alert rate is the ratio of the number of times an alert was sounded while blood glucose was below the alert threshold to the total number of times an alert was sounded
- The false alert rate is the complement of the true alert rate (i.e. if the true alert rate is 90%, the false alert rate would be 10%).

Table 29: In-Clinic Hypoglycemic Event Detection, Threshold Alert Performance; PRECISE II Study

Low Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
60	78%	22%	81%	19%
70	87%	13%	91%	9%
80	94%	6%	90%	10%
90	95%	5%	89%	11%

Table 30: In-Clinic Hypoglycemic Event Detection, Threshold and Predictive Alert Performance; PRECISE II Study

Low Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
60	89%	11%	72%	28%
70	96%	4%	84%	16%
80	96%	4%	85%	15%
90	98%	2%	85%	15%

Table 31: In-Clinic Hypoglycemic Event Detection, Threshold Alert Performance; PRECISION Study

Low Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
60	89%	11%	77%	23%
70	95%	5%	92%	8%
80	97%	3%	93%	7%
90	98%	2%	93%	7%

Table 32: In-Clinic Hypoglycemic Event Detection, Threshold and Predictive Alert Performance; PRECISION Study

Low Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
60	76%	24%	81%	19%
70	90%	10%	95%	5%
80	94%	6%	96%	4%
90	96%	4%	95%	5%

Table 33: In-Clinic Hyperglycemic Event Detection, Threshold Alert Performance; PRECISE II Study

High Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
120	99%	1%	97%	3%
140	98%	2%	97%	3%
180	96%	4%	95%	5%
200	94%	6%	94%	6%
220	93%	7%	93%	7%
240	91%	9%	92%	8%
300	80%	20%	89%	11%

Table 34: In-Clinic Hyperglycemic Event Detection, Threshold and Predictive Alert Performance; PRECISE II Study

High Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
120	99%	1%	97%	3%
140	99%	1%	96%	4%
180	98%	2%	93%	7%
200	96%	4%	93%	7%
220	95%	5%	90%	10%
240	94%	6%	89%	11%
300	87%	13%	85%	15%

Table 35: In-Clinic Hyperglycemic Event Detection, Threshold Alert Performance; PRECISION Study

High Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
120	99%	1%	96%	4%
140	99%	1%	96%	4%
180	98%	2%	95%	5%
200	98%	2%	95%	5%
220	98%	2%	95%	5%
240	98%	2%	95%	5%
300	93%	7%	94%	6%

Table 36: In-Clinic Hyperglycemic Event Detection, Threshold and Predictive Alert Performance; PRECISION Study

High Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
120	99%	1%	96%	4%
140	99%	1%	95%	5%
180	98%	2%	93%	7%
200	98%	2%	93%	7%
220	97%	3%	92%	8%
240	97%	3%	92%	8%
300	94%	6%	90%	10%

Sensor Life

Sensors can be worn for up to 90 days. To estimate how reliably a sensor will work over 90 days, 106 sensors were evaluated during the PRECISE II study and 62 sensors were evaluated during the PRECISION Study.

During the PRECISE II study, nine sensors failed prior to the intended 90-day sensor life out of a total of 106 sensors inserted during the study. Of these nine sensor failures, three failures occurred in the first two months post-insertion and the remaining six occurred between days 60 and 90. Overall, 99% of Sensors were functional through 30 days, 97% functioned through 60 days, and 92% functioned through 90 days.

During the PRECISION study, 100% of Sensors were functional through 90 days.

Number of Readings Provided

The system is capable of providing a reading every 5 minutes (up to 288 readings per day). For a variety of reasons (e.g., sensor failure), the System may not display a glucose reading and readings are "skipped." The number of actual Sensor values provided to subjects over the entire 90-day period and the corresponding percentage is summarized in the table below.

Table 37: Number of readings provided by each sensor of 90-days; PRECISE II Study

% of Total Possible Readings Provided	Total Readings Provided Min, Max	% of Systems Providing that Number of Readings
0 - 25%	--	0%
26 - 50%	--	0%
51 - 75%	58 out of 98*, 18189 out of 24485	3%
76 - 100%	2667 out of 2701, 26718 out of 26798	97%

* Subject did not return after Day 1 and later withdrew from the study

Table 38: Number of readings provided by each sensor of 90-days; PRECISION Study

% of Total Possible Readings Provided	Total Readings Provided Min, Max	% of Systems Providing that Number of Readings
0 - 25%	--	0%
26 - 50%	--	0%
51 - 75%	--	0%
76 - 100%	10455 out of 12788 26441 out of 26565	100%

3. Subgroup Analyses
   CGM System performance was evaluated within study population subgroups, such as diabetes type, body mass index, gender, and type of diabetes treatment. Although not powered for analysis of subpopulations, no significant differences in performance were noted based on these subgroups.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

B. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The primary clinical studies included 8 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A previous version of the Eversense CGM system became commercially available in Europe in June, 2016 and has been modified since initial approval. The currently-approved version of the device in Europe uses the same sensor that was studied in the PRECISE II and PRECISION studies in the US, it uses the Gen-2 transmitter, and it uses the original software algorithm (Study Software).

As part of the CE mark authorization, the applicant agreed to conduct a Post Market Clinical Follow-up registry to collect safety data on long term use of the Eversense CGM System, specifically repeat Sensor insertions. Fourteen (14) countries with 350 centers are currently enrolling patients into the registry. For simplicity, this study is referred to as the European Patient Registry.

In these countries, every patient who receives an Eversense CGM System is enrolled. The European Patient Registry as of February 2, 2018 remains open and is enrolling all inserted patients.

The Eversense sensor initially approved in Europe had a different design. The sensor design was later updated before the start of the PRECISE II study in the US.

The system approved for use in Europe uses a different version of the blunt dissector than what has been approved for use in the US. The insertion tools currently used in Europe are the same ones used during the US clinical studies.

As of February 2, 2018, 1,686 patients have enrolled in the registry. These patients have received 2,386 insertions under real-world use conditions. One-hundred and fifty-one (151) patients have discontinued use of the system. The sponsor states that eighty-five (85) of these patients discontinued use after the first insertion cycle due to reimbursement issues. The table below provides a summary of the current enrollment status.

Table 39: European patient registry enrollment summary

Number of Patients	**1st Insertion Cycle**	**2nd Insertion Cycle**	**3rd Insertion Cycle**	**4th Insertion Cycle**	**5th Insertion Cycle**	**6th Insertion Cycle**	**7th Insertion Cycle**
Total inserted	1686	443	143	58	39	14	3
Currently wearing	1114	285	78	19	25	11	3
Continued to next insertion	443	143	58	39	14	3	0
Discontinued	129	15	7	0	0	0	0

Sixty-six (66) adverse events have been reported as of February 2, 2018. There have been no serious adverse events related to the device or the insertion/removal procedure and no unanticipated adverse events. Table 40 provides a summary of the adverse events considered potentially related to the device and/or insertion/removal procedure.

Table 40: Summary of AEs from European Registry data related or probably/possibly related to device and/or procedure

Device and/or procedure related (or probably/possibly related) AEs	**Number of Events**	**Percentage of Occurrence (N=1686)**	**AE Rate per 100 Patient-Years**
SAEs	0	0	0
Sensor location site infection	14	0.8	2.9
Skin atrophy over sensor	1	0.1	0.2
Skin atrophy over sensor with discoloration	3	0.2	0.6
Skin discoloration	3	0.2	0.6

Adhesive patch location site irritation	7	0.4	1.5
Prolonged wound healing after procedure	3	0.2	0.6
Sensor location site pain/discomfort	1	0.1	0.2
Unable to remove sensor at first attempt	9	0.5	1.9
Bruising	3	0.2	0.6
Sensor site redness/reaction to dressing	3	0.2	0.6
Other – sensor broke during removal	3	0.2	0.6
Other – patient fainted during procedure	1	0.1	0.2
Other - Hematoma	1	0.1	0.2

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on March 29, 2018, the Clinical Chemistry and Toxicology Devices Panel of the Medical Devices Advisory Committee voted 8 to 0 (with no abstentions) that there is reasonable assurance the device is safe, 8 to 0 (with no abstentions) that there is reasonable assurance that the device is effective, and 8 to 0 (with no abstentions) that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication.

A summary of the panel meeting is available here: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ClinicalChemistryandClinicalToxicologyDevicesPanel/ucm602654.htm

The panel did not specify any conditions of approval.

B. FDA's Post-Panel Action

During the March 29, 2018 Advisory Panel Meeting, there was agreement among panel members that performance characteristics of the device were consistent with safe and effective use of the device for its proposed indications for use. Panelists concluded that although the final design of the sensor insertion tools had not been studied clinically, the results of the completed human factors study were sufficient to demonstrate that physicians could use the device safely. Similarly, panelists were satisfied that the information provided to support changes in the sensor end-cap design, glucose determination algorithm, and transmitter design were sufficient to provide reasonable assurance of safety and effectiveness for the system. The panel recommended that a post-approval study be used to confirm the safety profile of the final system design.

FDA concurs with the recommendations of the panel and is approving this device as an adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices. Discussion during the panel meeting was helpful in

FDA's consideration of how the available clinical data and reports of significant human experience with the device could inform FDA's decision on the reasonable assurance of safety and effectiveness for this device.

To resolve concerns expressed by panel members FDA has reviewed device labeling to ensure that it is adequate to support safe and effective use. In particular, the user guide and physician labeling have been updated to include a warning against the use of the tetracycline class of antibiotics. The final draft of labeling provided by the applicant was found to be acceptable.

Further, FDA has worked with the applicant to develop a post-approval study for the device. This study will evaluate the safety and effectiveness of the marketed version of the device in the hands of naïve users over an extended period of time. It is expected to provide robust safety information about the sensor implantation and removal procedure, and address panelist requests for a post-approval study that could directly address safety.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The results of the clinical studies, discussion and recommendations of the Clinical Chemistry and Toxicology Devices Panel of the Medical Devices Advisory Committee on March 29, 2018, and input provided by the public, including patients and caregivers regarding their significant experience with the device, provided a reasonable assurance of the effectiveness of the device.

The primary effectiveness measurements for the clinical studies were based on the performance evaluation of the Eversense CGM System compared to the blood glucose values measured by the laboratory glucose analyzer during the in-clinic sessions that spanned the wear period of the device (days 1, 7, 14, 30, 60, and 90).

The performance data presented above are also comparable to currently approved adjunctive CGM device performance. The data support acceptable accuracy across the claimed measuring range (40 to 400 mg/dL), precision, 90-day wear period claims for the Sensor, and effective alerts for detection and prediction episodes of hypoglycemia and hyperglycemia.

The clinical and analytical studies demonstrate that the Eversense CGM System is effective in the study population designed to be representative of the intended use population.

B. Safety Conclusions

The risks of the device are based on the preclinical laboratory data, as well as data collected in the clinical studies described in section X above.

The following related adverse events were observed from using the Eversense CGM system: pain/discomfort, bruising, erythema, retained Sensor fragment, failure to remove Sensor on first attempt, skin hyperpigmentation, dermatitis at patch location, paresthesia, and syncope-vasovagal.

There are potential risks related to either an inaccurate sensor value outside of the patient's normal range or a false alert that results in performing an unnecessary additional blood glucose test to confirm the erroneous reading. The risk of medical harm is mitigated through labeling and training, which emphasizes that patients should confirm all CGM readings prior to making treatment decisions.

There are potential risks due to missed alerts and false negative hypoglycemic and hyperglycemic readings related to patients not being alerted to the need to perform a fingerstick. Additionally, there is a risk associated with false alerts and false positive readings related to the need to perform unnecessary fingersticks to confirm an erroneous low or high reading. However, since patients who only use blood glucose meters to manage their diabetes without the aid of a CGM would also be unaware of the need to perform additional testing to detect an abnormal blood glucose level (unless they were exhibiting symptoms of an abnormal blood glucose), the risk of inaccurate results related to the use of this device is no greater than the risk of managing diabetes with a meter alone unless patients omit a blood glucose test that they would have otherwise performed if they were not using the sensor or the sensor was not reading within their target glucose range.

Inaccurate calculation of the rate of change of glucose by the CGM could prevent a patient from performing additional blood glucose tests or taking measures to stop a trend of increasing or decreasing glucose levels, which could lead to serious hypoglycemia or hyperglycemia if not action is taken to stop these glucose trends. However, as patients often do not test frequently enough with a meter to calculate the rate of change, this risk is not greater than with traditional glucose monitoring with a meter. Inaccurate estimation of the rate of change of glucose could also lead to unnecessary additional blood glucose tests or inappropriate measures to stop an incorrect trend of increasing or decreasing glucose level. However, the risk of medical harm is limited to instances where the user relies on the rate of change calculated by the sensor without confirmation by a blood glucose meter. This risk is partially mitigated by the requirement for users to base treatment decisions on blood glucose levels.

C. Benefit-Risk Conclusions

Summary of Benefits:

The probable benefits of the device are based on data collected in clinical and analytical studies conducted to support PMA approval as described above.

The device is intended to supplement self-monitoring of blood glucose to track and

trend glucose levels related to estimates of blood glucose excursions. Patients are notified of potential hyperglycemia and hypoglycemia events via customizable settings that alert them to the need to use their blood glucose meter to confirm their blood glucose value and take appropriate action as needed to treat or prevent a hyper- or hypoglycemic event.

The use of a continuous glucose monitor gives patients and physicians glucose tracking and trending information not available from traditional self-monitoring blood glucose devices as blood glucose meters only provide discrete, episodic blood glucose values. CGM measurements are performed every 5 minutes for up to 90 days via the inserted sensor and unlike SMBG, CGM measurements do not require use of a lancing device to capture each measurement. Additionally, unlike other CGM systems, the long term sensor eliminates the need for patients to insert a new sensor every 7 days, and the transmitter can be removed without ending the sensor life.

Patients and physicians can also review the tracking and trending data by day and time of day, such as nighttime when fewer fingersticks are performed. The historical CGM data trends and patterns may reveal the need to adjust therapy for improved diabetes management, such as changes to basal rates, bolus dose calculations, carbohydrate intake, and oral medication adjustments.

Furthermore, the continuous glucose monitor provides real time knowledge of glucose levels that can be displayed on a handheld device. The system can be set to provide notifications and alerts based upon Sensor trends and threshold settings adding information unavailable by traditional discrete monitoring. Trending information can be used to provide rate of change alerts that notify the user that glucose level is increasing or decreasing at a rate that raises concern for hyperglycemia or hypoglycemia. Predictive high and low thresholds can be set to notify the user that the Sensor glucose is approaching a threshold of concern. These alerts may be especially helpful for users with hypoglycemia unawareness (that is, individuals who may develop severe hypoglycemia without the normal warning symptoms), those with nocturnal hypoglycemia, or during times when users may be less aware of the warning symptoms. These alerts may also be very helpful at identifying hyperglycemia, which is associated with long term complications. Traditional blood glucose monitoring is not able to capture the data that can show patterns of potentially dangerous episodes of asymptomatic hypoglycemia and episodes of hyperglycemia. Therefore, if used as intended, the device provides significant benefits to users not available using traditional glucose monitoring.

Use of a mobile device as the primary display is beneficial to patients, as it offers convenience in terms of decreasing the number of devices required to be with the patient to utilize this CGM device.

This system is able to provide these benefits to users for an expected life of up to 90 days, far longer than any of the continuous glucose monitors currently commercially available. The longer-term sensor could result in increased utilization of CGM

technology by patients.

Summary of Risks:

Adverse events observed during the clinical studies were similar to those for other approved CGM systems, and the most adverse events were dermatological in nature. There are potential risks related to insertion, removal and wear of the sensor, which include allergic reactions, bleeding, bruising, infection, pain or discomfort, scarring or skin discoloration, sensor fracture during removal, skin inflammation, thinning, discoloration or redness.

There are risks relating to difficulty with sensor removal, and potential risks associated with subsequent procedures required for sensor removal. Based on postmarket data available with a different version of this device marketed in Europe, and the results observed in these clinical studies, the occurrence of these events is low.

There is a risk of sensor breakage leaving a sensor fragment under the skin. This event was reported infrequently with previously approved CGM sensors. Two instances of sensor breakage were documented in the clinical studies reviewed. Based on postmarket data available with a different version of this device marketed in Europe, and the results observed in these clinical studies, the occurrence and severity of these events is low.

There may be potential risks relating to repeated insertion and removal procedures, including buildup of scar tissue over time at the sensor insertion site, in a small range of locations on the outside surface of the upper arms. Based on postmarket data available with a different version of this device marketed in Europe, and the results observed in these clinical studies, these risks are not expected to occur.

The Eversense CGM System has a drug component, consisting of 1.75 mg of dexamethasone acetate (DXA), contained in a dexamethasone eluting silicone collar to the outside of the Eversense Sensor. Based on information and clinical evaluations performed, the sponsor has demonstrated that risks relating to both local and potential systemic exposure the dexamethasone component of the device, as well as repeated exposure to the dexamethasone component of the device, are not expected to occur. These risks appear to be remote based on the results observed in these clinical studies, although these clinical studies did not include subjects taking dexamethasone (or other glucocorticoid medications).

There are risks related to potentially inaccurate sensor glucose readings from this device. There are risks due to missed alerts and false negative hypoglycemia and hyperglycemic readings related to patients not being alerted to the need to perform a fingerstick to detect hypoglycemia or hyperglycemia, particularly since users of this device may rely on these alerts in certain situations to guide their self-treatment strategy (e.g., to alert them to potential nighttime hypoglycemia). There is a risk to

false alerts and false positive hypoglycemia and hyperglycemia readings related to the need to perform unnecessary fingersticks to confirm an erroneous low or high reading. Inaccurate calculation of the rate of change of glucose by the CGM could prevent a patient from performing additional blood glucose tests or taking measures to stop a trend of increasing or decreasing glucose levels which could lead to serious hypoglycemia or hyperglycemia if no action is taken to stop these glucose trends. Inaccurate calculation of the rate of change of glucose could also lead to unnecessary additional blood glucose tests or inappropriate measures to stop a trend of increasing or decreasing glucose level which could result in hyperglycemia or hypoglycemia.

A potential risk of the system is that users might be inclined to use the CGM data in an unapproved way to determine their insulin dose or make therapy decisions. Under these conditions of off-label use, inaccurate glucose concentration data or alerts could result in inappropriate administration (including delayed administration) of insulin or ingestion of carbohydrates leading to the development or exacerbation of hypo- or hyperglycemia. The labeling states users should always take a fingerstick blood glucose reading before making treatment decisions and if their symptoms do not match the sensor glucose value.

A minor risk of this device is that users may need to perform unnecessary fingersticks to evaluate blood glucose when the CGM gives a false positive or false negative reading or alerts.

The body-worn transmitter component of the system provides an alternate means of delivering alerts to users through vibratory feedback. The level of information necessary to understand the safety aspects of the user interface, and how it supports the user and reduces the potential for use error was provided by the sponsor, and found to be adequate. There may be an additional risk that the display, or alerts or alarms related to the CGM device may not be able to override other applications or functions (phone, camera, SMS) within the mobile device. This risk could potentially result in missed alerts or alarms, or temporary loss of access to the display. Missed alerts, alarms, or inability to access the display could result in missed opportunities to detect or prevent hypoglycemia or hyperglycemia, and are discussed above. Human factors studies sufficiently assessed the safety of the user interface of the mobile app (sole display) for this device, and the evaluation determined that the safety and usability of the mobile app was adequate.

Patient Perspective:

Patient perspectives considered during the review included patients' preference for longer CGM sensor wear times, elimination of frequent self-insertion, and a totally subcutaneous sensor. Patient input was provided during the public advisory panel meeting held on March 29, 2018. The comparatively short sensor life of 6-14 days for other CGM systems, the need to self-insert the sensor, the need for the transmitter to remain adhered to the skin for the sensor duration, and the inconveniences of wearing a percutaneous sensor that can be dislodged during normal activities have been main sources of patient dissatisfaction. The benefits of the Eversense CGM System may

result in increased utilization of CGM technology.

D. Overall Conclusions

In conclusion, the Eversense CGM has demonstrated effectiveness and safety in bench, pre-clinical, and clinical studies. The data in this application support the reasonable assurance of the safety and effectiveness of this device when used in accordance with the indication for use.

The benefits of using the System, as discussed above, outweigh the risks.

XIV. CDRH DECISION

CDRH issued an approval order on June 21. The final conditions of approval cited in the approval order are described below.

The applicant is required to conduct a Post Approval Study (PAS) to demonstrate the long-term safety and effectiveness of the Eversense Continuous Glucose Monitoring (CGM) System. This is a prospective, multi-center, single-arm study of adults with diabetes utilizing the Eversense CGM system. Patients will participate for up to 24 months of CGM use. The occurrence of adverse events related to device use or the sensor insertion and removal procedures will be captured.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.