DE NOVO CLASSIFICATION REQUEST FOR PILL SENSE SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Ingestible gastrointestinal blood detection capsule. An ingestible gastrointestinal blood detection capsule is a prescription device that uses spectrophotometry (light absorption technology) to detect the presence or absence of blood in the gastrointestinal tract.

NEW REGULATION NUMBER: 21 CFR 876.1390

CLASSIFICATION: Class II

PRODUCT CODE: QUD

BACKGROUND

DEVICE NAME: Pill Sense System

SUBMISSION NUMBER: DEN220065

DATE DE NOVO RECEIVED: September 29, 2022

SPONSOR INFORMATION:

EnteraSense Ltd.
% MedDRA Assistance, Inc.
55 Peaceful Way
Tiverton, Rhode Island 02878

INDICATIONS FOR USE

The Pill Sense System is indicated as follows:

The Pill Sense System is a prescription only device consisting of a reusable receiver and single-use ingestible capsule, intended to be used for the detection of blood in the upper gastrointestinal tract in hemodynamically stable adults suspected of having upper gastrointestinal bleeding (UGIB).

Pill Sense is not a standalone diagnostic device, but an adjunct for clinical decision making. A negative or normal result obtained by Pill Sense System does not exclude presence of pathology, if symptoms persist, further evaluation should be performed.

LIMITATIONS

The sale, distribution, and use of the Pill Sense System is restricted to prescription use in accordance with 21 CFR 801.109.

The device is not intended to be used as a stand-alone diagnostic device.

A negative or normal result obtained by the Pill Sense System does not exclude presence of pathology, if symptoms persist, further evaluation should be performed.

The device is contraindicated for patients with known gastrointestinal obstructions or strictures.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Pill Sense system is designed to detect blood in the upper gastrointestinal tract. The overall system consists of a Pill Sense Capsule and Pill Sense Receiver. The capsule and receiver components are packaged and sold separately or as a system.

The capsule is a single-patient use, battery-powered capsule that features sensors that detect blood and wirelessly transmit data to an external receiver. The capsule makes its way through the gastrointestinal tract and is then passed naturally from the body. The reusable receiver collects and displays real-time information gathered by the capsule. The receiver interprets the data and displays a sensor output value. It plots these values on a chart using data acquisition and when completed displays a "blood detected" or "no blood detected" message. The software supports entering of the patient information, pairing of the receiver and capsule and data interpretation and display.

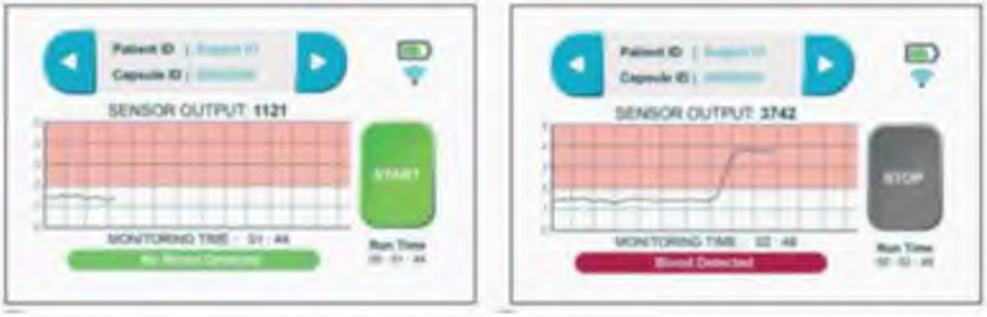
Figure 1. Pill Sense Capsule and Pill Sense Receiver

Within the ingestible capsule, four lights with distinct wavelengths and a photodetector are located within a sensing well in the center of the capsule. Each light is sequentially pulsed to emit light into the capsule sensing well and based on the liquid in the sensing gap, the emitted light is partially or fully absorbed. The remaining light is received by the photodetector, which converts an electrical signal proportional to the amount of light.

Once a "blood detected" message is displayed, it remains on the screen and does not change during the rest of the monitoring. If the monitoring is stopped by the user before 5 minutes has elapsed, an "Inconclusive results" message will be displayed. Only one final readout is given at the end of the 5-minute monitoring period, and there is no quantification of blood detected. The overall time from capsule activation, ingestion and display of a reading takes less than 10 minutes. By design, the user is required to

monitor for a minimum of 5 minutes and the monitoring automatically stops after 10 minutes. As soon as a "Blood Detected" message is received, the user can stop monitoring at any time. If deemed necessary, the user can continue monitoring for up to 40 minutes.

Figure 2. Schematic of Pill Sense Receiver display



SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The Pill Sense capsule is classified as mucosal membrane contacting with a cumulative duration of exposure of < 30 days. Capsule biocompatibility was evaluated in accordance with ISO 10993-1, Biological evaluation of medical devices and FDA Guidance: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process." The following biocompatibility endpoints were evaluated:

- cytotoxicity
- sensitization
- irritation
- materials mediated pyrogenicity
- chemical extractable study

The results of these evaluations support the biocompatibility of the Pill Sense Capsule.

The Pill Sense Receiver is non-patient contacting and biocompatibility assessment was not necessary. The receiver only comes in contact with the intact skin of the health care provider.

SHELF LIFE/STERILITY

The Pill Sense System is not provided sterile. Pill Sense Capsules are routinely monitored during manufacturing for bioburden levels to ensure the total bioburden on the device does not negatively impact human health. Packaging and shelf-life testing confirmed that the Pill Sense System packaging maintained integrity and device performance over the 1 year labeled shelf life.

ELECTROMAGNETIC CAPABILITY & ELECTROMAGNETIC SAFETY

The Pill Sense System conforms to the requirements for electrical safety and electromagnetic compatibility in ANSI AAMI ES60601-1:2005/(R)2012, A1:2012, C1:2009/(R)2012 and A2:2010/(R)2012; IEC 60601-1-11:2015; IEC 60601-1-2:2014.

SOFTWARE

The software was reviewed according to the "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," dated May 11, 2005. Appropriate software documentation consistent with a "Moderate" level of software concern were provided.

Cybersecurity was reviewed according to FDA guidance document "Content of Premarket Submission for Management of Cybersecurity in Medical Devices" dated October 2, 2014.

USABILITY TESTING

Usability testing was provided per FDA guidance document "Applying Human Factors and Usability Engineering to Medical Devices" dated February 3, 2016, to demonstrate that the Pill Sense System meets the user need/performance needs and has acceptable usability. The intended user population included trained clinicians and nurses.

PERFORMANCE TESTING - BENCH

The performance of the Pill Sense System was evaluated with the nonclinical bench testing summarized in Tables 1 and 2.

Table 1. Performance Testing for Pill Sense Capsule

Test	Purpose	Method	Acceptance Criteria
Visual Inspection and Dimensional Verification	Visually check all attributes and dimensions	Inspect capsules with normal vision and 2.5x magnification and measure device dimensions	External surface shall be free from extraneous matter or surface defects that could impact performance or safety.
Bite Resistance	Ensure the capsule can withstand accidental biting of the capsule	Load capsule into (b)(4)	Verify no cracks, sharp edges that could cause harm.
pH Solution Test	Ensure the capsule can withstand the pH levels in the gastrointestinal tract		Verify no damage to capsule
Capsule Leak Resistance Test	Evaluate if the capsule can withstand the pH levels and pressure experienced while		Absence of dye solution within the capsule enclosure

	moving through the gastrointestinal tract	(b)(4)	
Blood Detection Test	Evaluate if the capsule can detect different forms of blood (fresh blood, aged blood, clotted blood, partially digested blood, and blood mixed with other red liquids or foods)		Capsules placed in a solution of blood should produce a reading of "blood detected" and those in only gastric fluid should read "No blood detected". Capsules placed in non-blood red liquids or foods produce a reading of "no blood detected' and capsules placed in solutions of blood with red liquids of food produce a reading of "blood detected".
Battery Life	Evaluate if the capsule can operate for the length of the evaluation period		The battery shall operate the capsule for a minimum of 6 hours
Wireless	Evaluate if the capsule and receiver can adequately communicate with each other		Capsule and receiver can communicate wirelessly. The capsule shall transmit enough data to successfully complete a monitoring session at a range of 0.5 meters when contained in a simulated model.

Table 2. Pill Sense Receiver Testing

Test	Purpose	Method	Acceptance Criteria
Visual and dimensional verification	Visually check all attributes and dimensions	(b)(4)	The external surface shall be free from surface defects that could negatively impact performance

		(b)(4)	or safety of the device
Battery Life	Evaluate if the receiver can operate for the length of the evaluation period		The battery shall operate the device for a minimum of 1 hour

SUMMARY OF CLINICAL INFORMATION

Study Overview

The sponsor conducted the DETECT-1 study, which was a prospective, single-center, single-arm comparative clinical investigation designed to evaluate safety and effectiveness of the Pill Sense System when used for the detection of blood within subjects suspected to have an upper gastrointestinal bleed. The Pill Sense System performance for blood detection was compared with esophagogastroduodenoscopy (EGD) that was performed within 4 hours of the Pill Sense system reading. The investigators performing the EGD were blinded to the results provided by the Pill Sense System.

Subjects were monitored for capsule passage during hospitalization. An X-ray was taken before discharge if the Pill Sense capsule passage was not confirmed. Subjects were provided with a capsule retrieval kit and were instructed to monitor their stools for capsule passage. Follow-up visits were performed within 7 days of capsule administration. If capsule passage was confirmed, the subject exited the study. Otherwise, the subject was required to return for another follow-up between Day 8 and Day 21. If during the follow-up visit, capsule passage was not confirmed, an X-ray was performed before exiting the patient from the study. During hospitalization and at each in-person visit and telephone follow-up, occurrence of adverse events was assessed.

Study Endpoints

The co-primary endpoints are as follows:

- Sensitivity of the Pill Sense System for detecting upper GI bleeding defined as the proportion of observations in which the Pill Sense System and EGD findings agree in subjects determined to have blood in the UGI by EGD. The study hypothesis investigated whether the true value for sensitivity of the Pill Sense System was greater than a performance goal established to be 75%.

- Specificity of the Pill Sense System for detecting upper GI bleeding defined as the proportion of observations in which the Pill Sense System and EGD findings agree in subjects determined not to have blood in the UGI by EGD. The study hypothesis investigated whether the true value for specificity of the Pill Sense System was greater than a performance goal established to be 60%.

The secondary endpoints are as follows:

- Positive predictive value (PPV) of the Pill Sense System
- Negative predictive value (NPV) of the Pill Sense System
- Transit of the Pill Sense Capsule through the GI tract (yes/no)

Pill Sense System Accuracy was also calculated and presented.

Safety was assessed based on the presence of adverse events.

Results

The study enrolled 131 subjects 18 and older who had symptoms of upper gastrointestinal bleeding. Two subjects withdrew consent, one subject was withdrawn due to the need for emergent EGD before capsule ingestion. An additional two subjects were unable to swallow the capsule leaving 126 subjects for the safety population. Table 3 provides the full demographic information for patients in the study.

Table 3. Baseline Demographic Data for Safety Population (126 Subjects)

	Without Blood (N=98)	With Blood (N=28)	Total (N=126)
Mean Age (±SD)	62.0 (13.48)	63.9 (17.12)	62.4 (14.31)
Median Age (Min, Max)	64.5 (27, 89)	71.5 (31, 84)	66.0 (27, 89)
Male	58	17	75
Female	40	11	51
Hispanic or Latino	4	0	4
Not Hispanic or Latino	94	28	122
America-Indian or Alaska Native	3	0	3
Asian	4	0	4
Black or African American	1	0	1
White or Caucasian	89	28	117
Other	1	0	1
Mean Weight (kg) (±SD)	91.9 (27.8)	86.2 (17.54)	90.6 (25.92)
Median Weight (kg) (Min, Max)	85.2 (49, 191)	80.3 (46, 128)	83.5 (46, 191)
Mean Height (cm) (±SD)	171.6 (10.22)	171.2 (9.87)	171.5 (10.10)
Median Height (cm) (Min, Max)	172.7 (150, 198)	170.6 (152, 190)	172.0 (150, 198)

Within the safety population, based on the EGD, there were 98 subjects without blood and 28 with blood, resulting in an overall prevalence of upper gastrointestinal bleeding of 22.6%. Baseline demographics did not differ among the two subpopulations. The Pill Sense capsule was administered by trained research staff, including non-physician health care professionals. The Pill Sense system provided a response on average in about 6.71±1.17 minutes. The overall time from Pill Sense capsule ingestion to EGD was 55.1±43.46 minutes. Two subjects were excluded from the mITT analysis due to devices not providing valid readings as intended and therefore there was no data to be compared with the EGD results. Among the 124 patients included in the mITT cohort, 28 had bleeds and 96 were without bleeds based on EGD evaluation:

Table 4. Comparison of Pill Sense System Results to EGD Findings, mITT cohort

		EGD Findings		
		Blood	No Blood	Total
Pill Sense Capsule Findings	Blood	26	9	35
	No Blood	2	87	89
Total		28	96	124

Table 5. Primary and Secondary Endpoints

Parameter	Result (95% Confidence Interval)
Sensitivity	92.9% (76.5%, 99.1%)
Specificity	90.6% (82.9%, 95.6%)
NPV	97.8% (92.1%, 99.7%)
PPV	74.3% (56.7%, 87.5%)
Accuracy	91.1% (84.7%, 95.5%)

The sensitivity of the Pill Sense System was 92.9% (95%CI, 76.5%, 99.1%) and for specificity it was 90.6% (95%CI, 82.9%, 95.6%). The alternative hypotheses that the true values for Pill Sense sensitivity and specificity would exceed the performance goals of 75% and 60% were satisfied with respective p values of 0.0248 and <0.0001; therefore, both endpoints were satisfied.

In the total cohort of 126 subjects, 110 subjects had objective evidence of the Pill Sense capsule elimination either via photographic documentation or X-ray confirmation. For these subjects the mean time to capsule excretion was 3.6 days ±2.35 days. Sixteen of the subjects did not provide final Pill Sense excretion data. In one case, during the confirmatory EGD, the capsule was noted to be in the gastric pouch of a patient that had undergone gastric bypass. Although not meeting the definition of capsule retention, the capsule was endoscopically removed in the best interest of the patient. Although excretion was not documented for the other 15 patients, because they prematurely withdrew from the study or were lost to follow-up prior to their confirmation X-ray, review of their medical records did not identify any adverse events indicative of capsule retention.

Safety Results

Adverse events (AEs) were defined as an adverse event that began or worsened during or after Pill Sense capsule administration. Adverse events were assessed during hospitalization and at each in-person and telephone follow-up. There were no unanticipated adverse device effects or device-related adverse events. Among the safety population of 126 subjects, 23 experience at least one adverse event and 15 experienced at least one serious adverse event. There was a total of 28 adverse events, of which 19 were considered serious and 13 severe. The most common events were reports of abdominal complaints in 6 subjects and gastrointestinal bleeding in 5 subjects. Other events included alcohol withdrawal, epistaxis, haemobilia, and urinary tract infection, among others.

Overall, 13 subjects experienced at least one gastrointestinal related adverse event with a total of 14 gastrointestinal events. Gastrointestinal adverse events include abdominal pain, distention or discomfort, bleeding, diarrhea and duodenitis. Nine of these events were mild to moderate in severity, and 5 were considered severe. The rate of gastrointestinal adverse events is consistent with that of an elderly population presenting with pre-existing gastrointestinal pathology. The adverse events are also consistent with a patient population undergoing EGD. There were no events of capsule aspiration, obstruction, or retention.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

Physician labeling includes the device indications for use, a description of the device, warnings and precautions, clinical data on the device, and instructions for the safe and effective use of the device. The labeling satisfies the requirements of 21 CFR 801.109 Prescription devices. Per the Special Controls for this type of device, labeling includes a summary of device effectiveness and device related adverse events.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of ingestible gastrointestinal blood detection capsule and the measures necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Adverse tissue reaction	Biocompatibility evaluation
Failure to accurately detect blood leading to misdiagnosis or delayed diagnosis	Clinical performance testing Non-clinical performance testing Software validation, verification, and hazard analysis Labeling
Infection	Non-clinical performance testing Shelf life and package integrity testing Labeling
Device failure/malfunction leading to injury	Electrical, thermal, and mechanical safety testing Software validation, verification, and hazard analysis Usability testing Non-clinical performance testing Shelf-life testing Labeling
Device failure to function as intended due to interference with other devices (e.g., interference with data acquisition)	Electromagnetic compatibility testing Labeling
Failure to excrete the capsule leading to injury	Clinical performance testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the ingestible gastrointestinal blood detection capsule is subject to the following special controls:

(1) Clinical performance testing must demonstrate the device performs as intended under anticipated conditions of use. Testing must evaluate:
   (i) Detection of presence or absence of blood when compared to endoscopic procedures used to detect upper gastrointestinal bleeding;
   (ii) Capsule excretion and recovery; and
   (iii) All adverse events.

(2) Non-clinical performance testing must demonstrate the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   (i) Dimensional testing must verify device dimensions;
   (ii) Performance testing must verify functional aspects of the device design;
   (iii) Battery life testing must be performed to demonstrate the capsule's operating time is not constrained by the battery capacity;

(iv) Leak testing must verify device integrity under worst case clinical conditions;
(v) Bite testing must demonstrate that the device can withstand bite forces;
(vi) pH resistance testing must evaluate integrity of the capsule when exposed to a physiological relevant range of pH values;
(vii) Control and monitoring of capsule bioburden must demonstrate the device does not pose an infection risk; and
(viii) Blood detection testing must demonstrate that the device can detect different forms of blood seen under anticipated conditions of use.

(3) Software validation, verification, and hazard analysis must be performed.
(4) Electrical safety, thermal safety, mechanical safety, and electromagnetic compatibility (EMC) testing must be performed.
(5) Usability assessment must demonstrate that the intended users(s) can safely and correctly use the device.
(6) The patient-contacting components of the device must be demonstrated to be biocompatible.
(7) Performance testing must support the shelf life of the device by demonstrating continued package integrity and device functionality over the identified shelf life.
(8) Physician labeling must include:
(i) A detailed summary of the clinical testing pertinent to use of the device, including information on effectiveness and device- and procedure- related complications;
(ii) Warning that the device is not a standalone diagnostic device and does not replace clinical decision making; and
(iii) A shelf life.
(9) Patient labeling must include:
(i) An explanation of the device and the mechanism of operation;
(ii) The patient preparation procedure;
(iii) A brief summary of the clinical study; and
(iv) A summary of the device- and procedure- related complications pertinent to use of the device.

BENEFIT-RISK DETERMINATION

The probable benefits of the device are based on the data collected in the clinical study described above. The clinical study demonstrated use of the capsule device to detect blood in hemodynamically stable patients suspected of having gastrointestinal bleeding. In certain populations, such as those with significant comorbidities that require anesthesia care, it can be useful to detect if there is blood in the gastrointestinal tract prior to proceeding to endoscopy. The capsule device provides a binary 'blood detected' or 'not detected' result that does not require any additional analysis, such as required for analysis of endoscopic images. Use of the device also does not require sedation and can be administered in a clinical setting that does not require the use of a specialized endoscopy suite. The device is also capable of producing a result in under 10 minutes, compared to endoscopy which can take much longer.

The risks of the device are also based on data collected in clinical studies. Among the safety population of 126 subjects, ingestion of the capsule was well-tolerated, with only 2 patients reporting the inability to swallow the capsule. There were no unanticipated adverse events, or any device related adverse events reported. The incidence of gastrointestinal adverse events, including abdominal pain, distention or discomfort, bleeding, diarrhea, haemobilia, and duodenitis, was reported in 10.3 % of patients. This is considered a low occurrence, given the elderly study population that had pre-existing gastrointestinal pathology. In patients suspected of having gastrointestinal bleeding and those undergoing EGD, abdominal pain and recurrence of bleeding are expected events. There were no reports of capsule retention, aspiration, or intestinal obstruction. Capsule passage was confirmed in all but 16 patients, who

prematurely withdrew from the study or were lost to follow-up prior to their confirmation X-ray. Review of the patient's medical records did not identify any symptoms/events indicative of capsule retention. The other risks of the device include the risk of false negative results, which could lead to misdiagnosis or delay in treatment for patients. To mitigate this risk, the patient labeling clearly states that the device should be used in conjunction with current triage methods and not as a standalone diagnostic. There is also the risk of false positives, but this does not pose as much of a concern because those with a false positive result would proceed to receive an upper endoscopy, which is already the standard of care.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> The Pill Sense System is a prescription only device consisting of a reusable receiver and single-use ingestible capsule, intended to be used for the detection of blood in the upper gastrointestinal tract in hemodynamically stable adults suspected of having upper gastrointestinal bleeding (UGIB).
>
> Pill Sense is not a standalone diagnostic device, but an adjunct for clinical decision making. A negative or normal result obtained by Pill Sense System does not exclude presence of pathology, if symptoms persist, further evaluation should be performed.

The probable benefits outweigh the probable risks for the Pill Sense System. The device provides benefits, and the risks can be mitigated by the use of the general controls and the identified special controls.

CONCLUSION

The De Novo for the Pill Sense System is granted, and the device is classified as follows:

> Product Code: QUD
> Device Type: Ingestible gastrointestinal blood detection capsule
> Regulation Number: 21 CFR 876.1390
> Class: II