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**DE NOVO CLASSIFICATION REQUEST FOR
CADSCOR SYSTEM**

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## REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Coronary artery disease risk indicator using acoustic heart signals.** A coronary artery disease risk indicator using acoustic heart signals is a device that records heart sounds including murmurs and vibrations to calculate a patient-specific risk of presence of coronary artery disease, as an aid in cardiac analysis and diagnosis.

> **NEW REGULATION NUMBER:** 21 CFR 870.1420

> **CLASSIFICATION:** Class II

> **PRODUCT CODE:** QMW

## BACKGROUND

> **DEVICE NAME:** CADScor System

> **SUBMISSION NUMBER:** DEN190047

> **DATE DE NOVO RECEIVED:** November 4, 2019

> **SPONSOR INFORMATION:**

> > Acarix A/S
> > Mette Munch
> > Ryvangs Alle 81-83
> > DK-2900 Hellerup
> > Denmark

## INDICATIONS FOR USE

The CADScor System is indicated as follows:

> The intended use of the CADScor System is to record heart sounds, murmurs and vibration for calculation of a patient specific score, indicating the risk of presence of coronary stenosis, as an aid in cardiac analysis and diagnosis.

> ### LIMITATIONS

> The sale, distribution, and use of the CADScor System are restricted to prescription use in accordance with 21 CFR 801.109.

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

**DEVICE DESCRIPTION**

The CADScor System is a digital stethoscope for recording and quantifying acoustic noise from micro-turbulence originating from stenosis of the coronary arteries. Computational processing of a recording obtained from the chest surface of a patient is used to determine a coronary artery disease (CAD) risk score and associated risk classification.

Three components make up the CADScor System: the Docking station, the Acoustic Recording Sensor and the Patch. The docking station is responsible for charging and qualifying the sensor. These functionalities only happen when the Acoustic Recording Sensor is in direct contact with the docking station. An LED light indicates the status of the sensor. The Acoustic Recording Sensor contains a display, a microphone and an on/off button. The heart sound is recorded through a microphone and once the CAD risk score is calculated, it appears on the display screen. The patch is directly in contact with the patient's chest at the fourth left inter costal space (IC4-L) region. The patch provides a tight seal between the chest surface and the microphone to reduce the external noise that is picked up by the sensor. The patch is for single use only and is discarded after a CAD-score is calculated. A radiofrequency identification (RFID) tag in the patch is used to prevent the patch from being used more than once.



Figure 1. The three components of the CADScor System: Docking station, Acoustic recording station, and Patch

An algorithm is used to calculate a coronary artery disease (CAD) risk score. The algorithm analyzes 8 features of the acoustic recording and three clinical features that are manually inputted into the device by the clinician. The clinical inputs are age, gender and presence of hypertension. The eight acoustic features are put through a linear discriminate analysis and then put through a logistic regression with the clinical features. The risk score and associated categorization color are displayed on the acoustic sensor screen. There are two risk categories: low risk and elevated risk (Figure 2). Clinicians can use the score and categorization to aid in a clinician's determination of whether further testing is needed for a CAD diagnosis.

| CAD-score ≤20 | CAD-score >20 |
|---|---|
| Low risk | Elevated risk |

Figure 2. CAD score categorization

## SUMMARY OF NONCLINICAL/BENCH STUDIES

### BIOCOMPATIBILITY/MATERIALS

Biocompatibility testing was performed according to 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 sponsor tested cytotoxicity, skin sensitization and skin irritation of the patch. The patch is intended to be on the patient for no longer than 45 minutes; therefore, the sponsor tested according to the guidelines for short-term, intact skin contact.

| Test | Purpose | Method | Acceptance Criteria | Results |
|------|---------|--------|---------------------|---------|
| Cytotoxicity | To identify any cytotoxic effects to the patient | ISO 10993-1 | No evidence of toxicity or cell lysis | PASS |
| Sensitization | To identify tissue reactions from the patch | ISO 10993-1 | No evidence of tissue reaction | PASS |
| Irritation | To identify tissue irritation | ISO 10993-1 | No evidence of tissue irritation | PASS |

### ELECTROMAGNETIC COMPATIBILITY & ELECTRICAL SAFETY

The CADScor System conforms to the FDA-recognized standards for basic safety and essential performance of Medical Electrical Equipment. These standards include:

- IEC 60601-1-2:2014- Medical Electrical Equipment, Part 1-2: General requirements for safety- Collateral Standard: Electromagnetic compatibility- Requirements and tests
- IEC 60601-1:2006 + A1:2013- Medical Electrical Equipment, Part 1: General requirements for basic safety and essential performance

### SOFTWARE

Software documentation was provided in accordance with the FDA Guidance Document, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," (issued May 11, 2005) for a Moderate Level of Concern (LOC). A Moderate LOC is deemed appropriate as malfunction of the device software or a latent design flaw in the device software may lead to an erroneous diagnosis or a delay in the delivery of appropriate medical care, which would likely result in minor injury but would likely not result in serious injury or death due to the availability of patient history, and vital signs to aid in the clinician's diagnosis.

Verification and validation testing were performed to confirm that the device software met the software requirements.

Algorithm unit testing was performed to demonstrate that the device software met the software requirements. This testing was performed using privately collected patient data. Additional details are provided in the "Summary of Clinical Information" section.

**PERFORMANCE TESTING - BENCH**

Acoustic Performance Testing
Acoustic Performance testing was performed to determine that both the heart and ambient noise microphones function as expected and can correctly record the frequencies that are clinically meaningful for this device.

| Test | Purpose | Method | Acceptance Criteria | Results |
|---|---|---|---|---|
| Free Field Acoustic Testing | Ensure the manufactured parts of the CADScor systems are performing according to test specifications | (b)(4) samples were measured at (b)(4) (b)(4) up to (b)(4) Hz using a loud speaker as a source transmitter | Heart and ambient microphone sensitive within 5dB throughout the range of frequencies tested | PASS |
| Microphone Sensitivity Testing | Test microphone sensitivity before and after production | Set-up: Functional generator for output control, loud speaker and B&K (b)(4) sound level meter with receiving microphone | Sensitivity of the heart and ambient microphones are stable at 5, 10, 20, 140 Hz before and after the plotting process | PASS |
| Acoustic Verification Testing | Ensure the manufactured CADScor Sensor functionality and performance | The calibration frequency of (b)(4) (b)(4) (b)(4) and (b)(4) Hz were tested to determine if the sensor and ambient noise detectors respond. Additionally, broad band white noise source signal was tested. | The sensor and ambient noise detectors respond uniformly to all seven frequencies. | PASS |

Mechanical Testing

| Test | Purpose | Method | Acceptance Criteria | Results |
|---|---|---|---|---|
| Mechanical Testing- Design Verification | Verify the specified geometric proportions and mechanical lifetime | Force Tests, Dimensions of each | Manufactured to correct dimension specifications | PASS |

| | | | |
|---|---|---|---|
| for the following components of the CADScor system: mechanical couplers, electrical contacts, sensor push button and dimensions and weight | component of the device | Force to remove sensor from docking station is 5N. Qualification successful before and after 1000 insertions of the sensor onto the docking station | |

## USABILITY TESTING

Usability Testing was provided in accordance with the FDA Guidance Document, "Applying Human Factors and Usability Engineering to Medical Devices- Guidance for Industry and Food and Drug Administration Staff" (issued February 02, 2016).

[(b)(4)] subjects belonging to a user group of medical doctors/physicians with valid medical authorization, [(b)(4)] subjects belonging to a user group of registered nurses with valid authorization and [(b)(4)] subjects belonging to a user group of service technicians (non-clinical user group) participated in the usability testing. The testing was performed in a simulated- use environment using a sequence of tasks including but not limited to correct patch positioning of the device on the patient's chest, entering clinical features and other inputs correctly, and reading the display text and symbols/icons.

## SUMMARY OF CLINICAL INFORMATION

A prospective, multicenter, randomized clinical study was conducted to support the safety and effectiveness of the CADScor System for the proposed indication for use. Subjects were over the age of [(b)(4)] years and were suspected of ischemic heart disease. To determine the subject's diagnosis, which was compared to the result of the CADScor System, the patient underwent coronary computed tomography angiography (CCTA). Subjects who are diagnosed via CCTA to have CAD are defined to have at least one significant stenosis, which has a minimum [(b)(4)]% diameter reduction (DS) of a coronary vessel. Subjects who are classified as Non-CAD are defined as having CT calcium score of zero and no CT stenosis. The primary objective of this study is to determine specificity and sensitivity of the CAD-score in patients with low-intermediate risk for ischemic heart disease.

The device was tested on [(b)(4)] patients, who were independent from the algorithm training set. The patient population had a 10.7% prevalence of coronary artery disease. The results show that the sensitivity, specificity and area under the curve for the testing group are 87.5%, 37.5% and 71.5%, respectively, for the threshold score of 20. The positive predictive value (PPV) and negative predictive value (NPV) were reported to be 14.4% and 96.2%, respectively. With the NPV of 96.2%, the Agency has determined that this device could be beneficial for clinicians to use as a "rule-out" device for patients over the age of [(b)] years who are presenting with symptoms of ischemic heart disease.

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**

The labeling of the device satisfies the special controls listed below:
- A description of what the device measures and outputs to the user;
- Instructions for proper placement of the device;
- Instructions on care and cleaning of the device;
- Warnings identifying sensor acquisition factors that may impact measurement results and instructions for mitigating these factors
- The expected performance of the device for all intended use populations and environments.

**RISKS TO HEALTH**

The table below identifies the risks to health that may be associated with use of the coronary artery disease risk indicator using acoustic heart signals and the measures necessary to mitigate these risks.

| Identified Risks to Health | Mitigation Measures |
|---|---|
| Adverse tissue reaction | Biocompatibility evaluation, Labeling, and Usability testing |
| Skin burn/irritation | Electrical safety testing, and Electromagnetic compatibility testing |
| False positive leading to unnecessary medical procedures | Software verification, validation, and hazard analysis; Usability testing; Acoustic performance testing Clinical performance testing; and Labeling |
| False negative leading to failure to detect coronary artery disease | Software verification, validation, and hazard analysis; Usability testing; Acoustic performance testing; Clinical performance testing; and Labeling |
| Delay in calculation due to device failure resulting in a delay of treatment | Software verification, validation, and hazard analysis; Clinical performance testing; Usability testing; Acoustic performance testing; and Labeling |

## SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the coronary artery disease risk indicator using acoustic heart signals is subject to the following special controls:

(1) Clinical performance testing must fulfill the following:
   a. Testing must include a discussion of the patient population and any statistical techniques used for analyzing the data; and
   b. Testing must be representative of the intended use population for the device. Any selection criteria or sample limitations must be fully described and justified.
(2) Acoustic performance testing must evaluate microphone sensitivity, sound acquisition bandwidth, and amplitude accuracy. The acoustic sensor specifications and mechanism used to capture heart sounds must be described.
(3) A scientific justification for the validity of the algorithm(s) must be provided. This justification must fulfill the following:
   a. All inputs and outputs of the algorithm must be fully described;
   b. The procedure for segmenting, characterizing and classifying the acoustic signal must be fully described; and
   c. This justification must include verification of the algorithm calculations and validation using an independent data set.
(4) The patient-contacting components of the device must be demonstrated to be biocompatible.
(5) Software verification, validation, and hazard analysis must be performed.
(6) Human factors/usability testing must demonstrate that the user can correctly use the device, including device placement, based solely on reading the directions for use.
(7) Performance data must demonstrate the electromagnetic compatibility (EMC) and electrical safety of the device.
(8) Labeling must include the following:
   a. A description of what the device measures and outputs to the user;
   b. Instructions for proper placement of the device;
   c. Instructions on care and cleaning of the device;
   d. Warnings identifying sensor acquisition factors that may impact measurement results and instructions for mitigating these factors; and
   e. The expected performance of the device for all intended use populations and environments.

## BENEFIT-RISK DETERMINATION

The risks associated with use of the device are based on data collected in a clinical study described above. One risk to a patient is myocardial infarction. This poses a risk to patients when they receive a false negative result where they are classified as "low risk" but may have needed to go through further testing to determine that their symptoms are from CAD. The probability of this occurring is low because the negative predictive value (NPV) is 96.2%. Additionally, the clinician is not intended to use this device as a sole diagnostic decision maker and are instructed in the labeling to recommend to patients categorized in the low risk group to seek medical attention if their symptoms persist or worsen.

A risk to a patient categorized in the "elevated risk" group can be excessive testing but are found to be "low risk" after further testing. With a relatively low specificity, it is expected that a false positive result could lead to unnecessary testing. However, without this device, it is likely that the entire patient population would undergo other tests, i.e. stress tests.

Additionally, tissue irritation could occur from the patch; however, the probability of this occurring is very low because no adverse events occurred during the biocompatibility testing. and labeling instructs the clinician to not leave the patch on the patient's chest for longer than 45 minutes.

The probable benefits of the device are also based on data collected in a clinical study as described above. By using the CADScor system to evaluate the patient's risk of Coronary Artery Disease, a "low risk" score can help the clinician identify patients who are at low risk of CAD and avoid unnecessary additional testing, which come with their own respective risks. Additionally, this device can be used in the clinician's office to provide results in a timely manner. The probability of correctly identifying a patient who is low risk for CAD is high based on the NPV of 96.2%.

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 intended use of the CADScor System is to record heart sounds, murmurs and vibration for calculation of a patient specific score, indicating the risk of presence of coronary stenosis, as an aid in cardiac analysis and diagnosis.

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

## CONCLUSION

The De Novo request for the CADScor System is granted and the device is classified as follows:

> Product Code: QMW
> Device Type: Coronary artery disease risk indicator using acoustic heart signals
> Regulation Number: 21 CFR 870.1420
> Class: II