September 8, 2023

Cleerly, Inc
% John Smith
Partner
Hogan Lovells US LLP
555 13th St. NW
Washington, District of Columbia 20004

Re: K231335
Trade/Device Name: Cleerly ISCHEMIA
Regulation Number: 21 CFR 870.2200
Regulation Name: Adjunctive cardiovascular status indicator
Regulatory Class: Class II
Product Code: QXZ
Dated: August 11, 2023
Received: August 11, 2023

Dear John Smith:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal

statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

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

Sincerely,

Robert T. Kazmierski -S

for

LCDR Stephen Browning
Assistant Director
Division of Cardiac Electrophysiology,
Diagnostics, and Monitoring Devices
Office of Cardiovascular Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below

510(k) Number *(if known)*

K231335

Device Name

Cleerly ISCHEMIA

Indications for Use *(Describe)*

Cleerly ISCHEMIA analysis software is an automated machine learning-based decision support tool, indicated as a diagnostic aid for patients undergoing CT analysis using Cleerly Labs software. When utilized by an interpreting healthcare provider, this software tool provides information that may be useful in detecting likely ischemia associated with coronary artery disease. Patient management decisions should not be made solely on the results of the Cleerly ISCHEMIA analysis.

Type of Use *(Select one or both, as applicable)*

X Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

Cleerly, Inc.'s Cleerly ISCHEMIA

1. General Information

Sponsor	Cleerly, Inc.
Address	110 16th Street Suite 1400 #104 Denver, CO 80202
Phone	917-671-7746
Contact Person	Candice Bautista-Biddle
Date Prepared	September 8, 2023

2. Device Information

Name of Device	Cleerly ISCHEMIA
Classification Name	21 CFR 870.2200 (Adjunctive Cardiovascular Status Indicator)
Regulatory Class	II
Product Code	QXZ

3. Predicate Device Information

Name of Device	EchoGo Heart Failure (K222463)
Classification Name	21 CFR 870.2200 (Adjunctive Cardiovascular Status Indicator)
Regulatory Class	II
Product Code	QUO

4. Device Description

Cleerly ISCHEMIA is an add-on software module to Cleerly Labs (K202280, K190868) that determines the likely presence or absence of coronal vessel ischemia based on quantitative measures of atherosclerosis, stenosis, and significant vascular morphology from typically-acquired Coronary Computed Tomography Angiography images (CCTA). Cleerly ISCHEMIA, in conjunction with Cleerly Labs, outputs a Cleerly ISCHEMIA Index (CII), a binary indication of negative CII (likely absence of ischemia) or positive CII (likely presence of ischemia) with its threshold equivalent to invasive FFR >0.80 vs. ≤0.80, respectively, as identified in professional societal practice guidelines.

5. Intended Use / Indications for Use

Cleerly ISCHEMIA analysis software is an automated machine learning-based decision support tool, indicated as a diagnostic aid for patients undergoing CT analysis using Cleerly Labs software. When utilized by an interpreting healthcare provider, this software tool provides information that may be useful in detecting likely ischemia associated with coronary artery disease. Patient management decisions should not be made solely on the results of the Cleerly ISCHEMIA analysis.

6. Summary of Technological Characteristics

Cleerly ISCHEMIA is an add-on software module to Cleerly Labs that calculates vessel-specific likely ischemia presence based on quantitative measures of atherosclerosis, stenosis, and vascular morphology from typically acquired CCTA.

The Cleerly ISCHEMIA data workflow begins after the Cleerly Labs outputs are approved for a study. A pre-processing module evaluates the eligibility of a study or vessels within the study for the Cleerly ISCHEMIA algorithm. The presence of certain identified anomalies can make an entire study ineligible, whereas the presence of a stent or exclusion in a vessel can make just that vessel ineligible. For all eligible vessels within a study, relevant Cleerly Labs outputs are aggregated from the default segment level to vessel level as the inputs to the Cleerly ISCHEMIA algorithm to determine the likely presence of ischemia. The results will then be evaluated by a post-processing module, which ensures that vessels subtended to a likely ischemic vessel are also marked as likely ischemic. The Cleerly ISCHEMIA algorithm outputs a Cleerly ISCHEMIA Index (CII), a binary indication of likely ischemia presence vs absence for a given vessel, which is equivalent to invasive FFR ≤0.80 vs. >0.80, respectively. Invasive FFR is a widely accepted gold-standard for determining vessel-specific ischemia. The Cleerly ISCHEMIA algorithm is "locked," meaning it is not a continuous learning algorithm.

Cleerly ISCHEMIA Index (likely ischemia / not likely ischemia) is displayed visually by Cleerly Labs to show the likely presence or absence of ischemia within epicardial coronary artery vessels. Vessels with Cleerly ISCHEMIA Index indicating likely ischemia presence (positive CII) are illuminated red, while vessels with Cleerly ISCHEMIA Index indicating likely ischemia absence (negative CII) are not illuminated. Cleerly ISCHEMIA analysis is intended to non-invasively support the functional evaluation of clinically stable symptomatic patients with coronary artery disease (CAD).

Table 1. Substantial Equivalence Comparison Between Subject and Predicate Device

Characteristic	Cleerly ISCHEMIA Device (Subject device)	EchoGo Heart Failure (K222463)
Regulation	21 CFR 870.2200	21 CFR 870.2200
Generic Device Type	Adjunctive cardiovascular status indicator	Adjunctive cardiovascular status indicator
SaMD	Yes	Yes
Intended Use	Providing adjunctive information a patient's cardiovascular condition (diagnostic aid for ischemia associated with coronary artery disease)	Providing adjunctive information on a patient's cardiovascular condition (diagnostic aid for Heart Failure with Preserved Ejection Fraction (HFpEF))
Indications for Use	Cleerly ISCHEMIA analysis software is an automated machine learning-based decision support tool, indicated as a diagnostic aid for patients undergoing CT analysis using Cleerly Labs software. When utilized by an interpreting healthcare provider, this software tool provides information that may be useful in detecting likely ischemia associated with coronary artery disease. Patient management decisions should not be made solely on the results of the Cleerly ISCHEMIA analysis.	EchoGo Heart Failure 1.0 is an automated machine learning-based decision support system, indicated as a diagnostic aid for patients undergoing routine functional cardiovascular assessment using echocardiography. When utilised by an interpreting clinician, this device provides information that may be useful in detecting heart failure with preserved ejection fraction (HFpEF). EchoGo Heart Failure 1.0 is indicated in adult populations over 25 years of age. Patient management decisions should not be made solely on the results of the EchoGo Heart

Characteristic	Cleerly ISCHEMIA Device (Subject device)	EchoGo Heart Failure (K222463)
		Failure 1.0 analysis. EchoGo Heart Failure 1.0 takes as input an apical 4-chamber view of the heart that has been captured and assessed to have an ejection fraction ≥50%.
Anatomical Site	Cardiovascular	Cardiovascular
Users	Healthcare provider	Interpreting clinician
Machine Learning-Based Algorithm	Yes	Yes
Operating Platform	Client-Server Google Chrome Application.	Hosted on Ultromics' platform or on third party infrastructure.
Risk Management	In accordance with ISO 14971:2019	In accordance with ISO 14971:2019
Usability	Usability assessment determined there were no critical tasks associated with the use of the device.	Complies with IEC 62366-1:2020 and general use of FDA guidance documents on usability engineering. Formative and summative evaluations conducted with accredited cardiac physiologists (N=2) and cardiologists (N=5).
Pre-clinical Performance Testing	No animal studies were conducted.	No animal studies were conducted.
Bench Performance Testing	Technical validation.	Technical validation, numerical stability, and regression testing.
Clinical Performing Testing	Validated on a US/OUS cohort population, comprising 23 independent clinical sites representative of the intended use population.	Validated on a US cohort population, comprising 8 independent clinical sites representative of the intended use population.

7. Performance Data

Non-clinical Testing

Risk assessment, performance, and cybersecurity of Cleerly ISCHEMIA have been evaluated and verified in accordance with software pre-defined specifications and applicable performance standards through software verification testing. Verification testing confirmed that the software requirements fulfilled the pre-defined acceptance criteria.

The nonclinical verification test results established that the device meets its design requirements and intended use. During the development, potential hazards were evaluated and controlled through risk management activities. The performance testing demonstrates that the device meets all its specifications.

Clinical Testing

Clinical validation testing was done to validate the diagnostic performance of Cleerly ISCHEMIA for non-invasive determination of the functional significance of CAD, as referenced to direct invasive

measurement of FFR as the reference standard. The Cleerly ISCHEMIA validation study used data from the CREDENCE Trial (Computed TomogRaphic Evaluation of Atherosclerotic DEtermiNants of Myocardial IsChEmia), a prospective, multicenter trial of 612 stable subjects with suspected, but unconfirmed, CAD who were referred for non-emergent clinically indicated ICA based upon MPI and/or CCTA. CREDENCE enrollees were recruited across 17 centers between 2014 and 2017. Eligibility criteria included referral to non-emergent ICA. All index tests were interpreted blindly by core laboratories. The study population comprised 612 patients with stable symptoms and without a prior diagnosis of CAD referred for non-emergent ICA. Patients were recruited across 23 centers. Trial participants were assigned to 2 subsets with the first half of enrollees at each site assigned to the derivation (n = 307) and the second half to the validation (n = 305) data set.

The primary endpoint analysis is provided in **Table 2** below.

Table 2. Primary Endpoint Results

Endpoint	Result	Lower 95% Confidence Limit
Sensitivity, per-vessel territory	75.9% (167/220)	70.7%
Specificity, per-vessel territory	83.4% (521/625)	80.2%

In addition to the CREDENCE data, device performance was supported by additional studies performed both in the US and outside of the US (OUS). Cumulative results of the CREDENCE data with these other data sources are provided in **Tables 3** and **4** as follows:

Table 3. Pooled Per-Vessel Territory Diagnostic Performance Estimates by US, Outside US (OUS), and Combined US and OUS Patient Cohorts, Along with 95% Confidence Intervals (CI)

	Pooled US (N=149 subjects, 285 vessel territories)		Pooled OUS (N=433 subjects, 1236 vessel territories)		Pooled US + Pooled OUS (N=582 subjects, 1521 vessel territories)	
	Estimate	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Sensitivity	79.5% (58/73)	70.7%, 87.8%	75.5% (259/343)	70.6%, 80.2%	76.2% (317/416)	71.9%, 80.3%
Specificity	82.5% (175/212)	76.5%, 88.1%	85.8% (766/893)	83.3%, 88.1%	85.2% (941/1105)	82.8%, 87.4%
PPV	61.1% (58/95)	51.1%, 70.9%	67.1% (259/386)	61.8%, 72.0%	65.9% (317/481)	61.2%, 70.3%
NPV	92.1% (175/190)	88.1%, 95.6%	90.1% (766/850)	87.9%, 92.3%	90.5% (941/1040)	88.5%, 92.3%
LR+	4.54	-	6.78	-	5.15	-
LR-	0.25	-	0.36	-	0.28	-

Table 4. Per patient territory diagnostic performance estimates by region and in aggregated with 95% CI.

	Pooled US (N=149 subjects)		Pooled OUS (N=433 subjects)		Pooled US + Pooled OUS (N=582 subjects)	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Sensitivity	87.5% (56/64)	77.0%, 93.8%	86.4% (190/220)	81.2%, 90.3%	86.6% (246/284)	82.1%, 90.1%
Specificity	75.3% (64/85)	65.1%, 83.3%	67.6% (144/213)	61.1%, 73.5%	69.8% (208/298)	64.4%, 74.7%
PPV	72.7% (56/77)	61.8%, 81.5%	73.4% (190/259)	67.7%, 78.4%	73.2% (246/336)	68.2%, 77.7%
NPV	88.9% (64/72)	79.3%, 94.5%	82.8% (144/174)	76.4%, 87.7%	84.6% (208/246)	79.5%, 88.6%
LR+	3.54	-	2.67	-	2.87	-
LR-	0.17	-	0.20	-	0.19	-

Cumulatively, these data demonstrate acceptable clinical performance.

8. Cybersecurity

As an add-on module to Cleerly Labs, controls over Cybersecurity risks for Cleerly ISCHEMIA are enacted within Cleerly Labs. Cleerly Labs has implemented security features for device and data protection. Cybersecurity requirements, risk analysis, and mitigation was addressed in accordance with FDA guidance, “Content of Premarket Submission for Management of Cybersecurity in Medical Devices.”

9. Conclusions

Cleerly ISCHEMIA is as safe and effective as the predicate EchoGo Heart Failure device (K222463). Cleerly ISCHEMIA has a similar intended use and indications for use, as well as similar technological characteristics and principles of operation as its predicate device. The minor differences between the indications do not alter the intended use of the device and do not affect its safety and effectiveness when used as labeled. In addition, the minor technological differences between Cleerly ISCHEMIA and its predicate device raise no new issues of safety or effectiveness. Cleerly ISCHEMIA is as safe and effective as the predicate EchoGo Heart Failure (K222463). Thus, Cleerly ISCHEMIA is substantially equivalent.