May 26, 2023

Edwards Lifesciences, LLC
Sara Pesian
Manager, Regulatory Affairs
One Edwards Way
Irvine, CA 92614

Re: K223651
Trade/Device Name: Cerebral Adaptive Index (CAI) Algorithm
Regulation Number: 21 CFR 870.2700
Regulation Name: Oximeter
Regulatory Class: Class II
Product Code: MUD, QEM
Dated: April 28, 2023
Received: April 28, 2023

Dear Sara Pesian:

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,

Patrick Antkowiak -S

Patrick Antkowiak
Acting Assistant Director
DHT5A: Division of Neurosurgical,
Neurointerventional
and Neurodiagnostic Devices
OHT5: Office of Neurological
and Physical Medicine Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

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)*
K223651

Device Name
Cerebral Adaptive Index (CAI) Algorithm

Indications for Use *(Describe)*
Cerebral Adaptive Index (CAI) Algorithm is an informational index to help assess the level of coherence or lack thereof between Mean Arterial Pressure (MAP) and the Absolute Levels of Blood Oxygenation Saturation (StO2) in patient's cerebral tissue. MAP is acquired by the HemoSphere Pressure Cable and StO2 is acquired by the ForeSight Oximeter Cable.

CAI is intended for use in patients over 18 years of age receiving advanced hemodynamic monitoring.

CAI is not indicated to be used for treatment of any disease or condition and no therapeutic decisions should be made based solely on the Cerebral Adaptive Index (CAI) Algorithm.

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

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

**CONTINUE ON A SEPARATE PAGE IF NEEDED.**

**510(k) Summary – Cerebral Adaptive Index (CAI) Algorithm**

| | |
|---|---|
| **Sponsor:** | Edwards Lifesciences LLC<br>One Edwards Way<br>Irvine, CA 92614 |
| **Establishment Registration Number:** | 2015691 |
| **Contact Person:** | Sara Pesian<br>Manager, Regulatory Affairs<br>One Edwards Way<br>Irvine, CA 92614<br>sara_pesian@edwards.com<br>Telephone: (949) 250-2232 |
| **Date:** | May 26, 2023 |
| **Trade Name:** | Cerebral Adaptive Index (CAI) Algorithm |
| **Common Name:** | Oximetry |
| **Classification Name:** | Oximeter 21 CFR 870.2700 |
| **Product Code:** | MUD, Class II<br>QEM, Class II |
| **Primary Predicate Device:** | HemoSphere ForeSight Oximeter Cable on HemoSphere Advanced Monitoring Platform, manufactured by Edwards Lifesciences, K213682 cleared June 22, 2022, is being utilized for substantial equivalence since it contains the same $StO_2$ algorithm as the subject device, and similar indications for use/intended use and principle of operation and technology as the subject CAI Algorithm. |
| **Reference Predicate Device (s)** | FORE-SIGHT ELITE Absolute Tissue Oximeter, manufactured by Edwards Lifesciences, K190205 cleared August 29, 2019 and HemoSphere Pressure Cable, manufactured by Edwards Lifesciences, K180881 cleared November 16, 2018 are being utilized as reference devices |

**Device Description:**

Cerebral Adaptive Index (CAI) Algorithm is a derived parameter that quantifies the dynamic relationship between two existing hemodynamic parameters, Mean Arterial Pressure (MAP) and the Absolute Levels of Blood Oxygenation Saturation ($StO_2$) in the cerebral tissue. CAI is intended to show the level of coherence between MAP and cerebral $StO_2$. The output will be represented as an index value and a trended graph.

MAP is acquired from the HemoSphere Pressure Cable (initially cleared in K180881 on November 16, 2018). $StO_2$ used for computing CAI is acquired from the ForeSight Oximeter Cable (cleared in K201446 on October 1, 2020).

The CAI parameter can enhance clinician's understanding of the underlying hemodynamic changes behind cerebral desaturation events. It helps the clinician recognize/ identify possible causes of, for example, decrease in $StO_2$ and clinical events related to $StO_2$ decrease (e.g., hypotension as opposed to inadequate oxygen content).

CAI will be continuously displayed at 20-second rate. The parameter will not have any alarm ranges and will only be represented as a number with a range between 0 to 100. A high CAI value (CAI $\geq$45) means that MAP and $StO_2$ have a greater coherence and informs the clinician that alterations in MAP may result in concomitant changes in cerebral oxygen saturation Whereas a low CAI value (CAI < 45) means there is lesser coherence between the two parameters, and therefore alterations in MAP may not result in concomitant changes in cerebral oxygen saturation.

**Indications for Use:**

Cerebral Adaptive Index (CAI) Algorithm is an informational index to help assess the level of coherence or lack thereof between Mean Arterial Pressure (MAP) and the Absolute Levels of Blood Oxygenation Saturation ($StO_2$) in patient's cerebral tissue. MAP is acquired by the HemoSphere pressure cable and $StO_2$ is acquired by the ForeSight oximeter cable. CAI is intended for use in patients over 18 years of age receiving advanced hemodynamic monitoring. CAI is not indicated to be used for treatment of any disease or condition and no therapeutic decisions should be made based solely on the Cerebral Adaptive Index (CAI) Algorithm.

**Intended Use:**

Cerebral Adaptive Index (CAI) Algorithm is intended to be used by qualified personnel or trained clinicians in a critical care environment in a hospital setting. The algorithm is intended to show the level of coherence between MAP and cerebral $StO_2$.

**Comparison to Predicate Device:**

The HemoSphere ForeSight Oximeter Cable (K213682 most recently cleared June 22, 2022) is chosen as the predicate since it contains the same $StO_2$ algorithm, and similar indications for use/intended use and principle of operation and technology as the subject CAI algorithm when used in conjunction with MAP data. The subject

CAI and the existing $StO_2$ algorithms both use the measurement of absolute regional hemoglobin oxygen saturation of blood under the sensor in their calculations. When sensors are applied to patient's cerebral region, CAI uses the $StO_2$ signals in conjunction with MAP signals and calculates the coherence between the measured cerebral $StO_2$ and MAP. Hence the HemoSphere ForeSight Oximeter Cable is being used to establish substantial equivalence for the subject CAI.

The following verification activities were performed in support of a substantial equivalence determination for CAI Algorithm and HemoSphere Foresight Oximeter Cable and to ensure the safety and effectiveness of the Cerebral Adaptive Index (CAI) Algorithm.

**Performance Data (Bench and/or Clinical):**

**Software Verification**

Software verification was performed per FDA's Guidance for Industry and FDA Staff, *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (issued May 11, 2005). The Cerebral Adaptive Index was tested at the algorithm level to ensure the safety of the device. The validation of the CAI Algorithm was performed as follows:

1. Validation using simulated time-series data
2. Validation using data retrospectively collected from animals

The algorithm passed all testing.

**Clinical Performance Data**

The following clinical performance data was submitted to support a determination of substantial equivalence:

Demographics:

The demographics of CAI Algorithm validation dataset are captured in **Table 1-1** below.

Patient Baseline Characteristics:

The validation dataset had no inclusion/exclusion criteria related to patient baseline characteristics. In general, adult surgical patients (cardiac surgery, general surgery and surgical ICU) whose $StO_2$ and MAP were being monitored respectively via Foresight Sensors and Flotrac Sensors were randomly selected for the retrospective analysis.

Enrollment:

The validation dataset was retrospectively obtained from 4 different clinical sites within US (Northwestern University, Chicago; UC Davis, Sacramento; University of Minnesota, Minneapolis; Stanford University, Stanford). A total of 145 subjects aged 18 or older were randomly selected for inclusion in the CAI Algorithm

validation study. **Table 1-1** provides the number of patients enrolled from each site as well as the patient demographics and the surgery types from all four sites.

**Table 1-1 Summary of patient demographic information for the 4 sites used in the clinical data performance analysis. Data for Age, Height and Weight are Mean ± 1std and full range [max, min]**

| Site | N° of patients | Age (years) | Gender | Height (cm) | Weight (Kg) | Clinical Environment |
|---|---|---|---|---|---|---|
| Northwestern University, Chicago (NWU) | 29 | 60.1±12.3 [31, 76] | 7 Females 22 Males | 174.1±9.7 [155.0, 191.0] | 84.8±15.0 [46, 111.6] | Cardiac surgery |
| UC Davis, Sacramento (UCD) | 43 | 62.9±15.9 [26, 87] | 20 Females 23 Males | 170.3±10.3 [152.4, 195.6] | 84.8±19.0 [41.5, 119.2] | General surgery |
| University of Minnesota, Minneapolis (UoM) | 67 | 63.1±10.1 [39, 84] | 14 Females 53 Males | 175.4±7.9 [154.0, 188.0] | 93.8±20.5 [48.0, 139.1] | Cardiac surgery |
| Stanford University, Stanford (SU) | 6 | 54.0±17.4 [22, 66] | 3 Females 3 Males | 178.8±9.7 [167.0, 190.0] | 94.6±38.2 [56.0, 157.0] | Surgical ICU |
| All | 145 | 61.9±12.8 [22, 87] | 44 Females 101 Males | 173.6±9.3 [152.4, 195.6] | 89.0±20.2 [41.5, 157.0] | OR/ICU |

General Summary:

The following is a summary of the validation procedure performed:

MAP and $StO_2$ time-series data obtained from adult (18 years and older) patients were used for the validation testing. To validate and assess the performance of CAI, a Receiver Operating Characteristic (ROC) analysis was performed based on weak/moderate and strong MAP-$StO_2$ association. Labeling of weak/moderate versus strong MAP-$StO_2$ association states is conducted based on the computed values of the Pearson's Correlation Coefficient (Corr) between MAP and $StO_2$ in the utilized time-series clinical data. Specifically, $0 \leq Corr < 0.7$ were labeled as weak/moderate MAP-$StO_2$ association and $Corr \geq 0.7$ were labeled as strong MAP-$StO_2$ association.

Performance Metrics:
Using this data, the following performance metrics were calculated:

• Sensitivity: The true positive rate; ratio of true positives to total number of positive events. (True positives (TP) are defined as positive events that have a CAI value greater or equal than a given threshold. True negatives (TN) are defined as negative events that have a CAI value smaller than a given threshold.)

• Specificity: The false positive rate; ratio of true negatives to total number of negative events (False positives (FP) are defined as negative events that have a CAI value greater or equal than a given threshold. False negatives (FN) are defined as positive events that have a CAI value smaller than a given threshold.)

• ROC AUC: the area under the ROC curve (AUC) summarizes the performance as a single number (0.5 to 1) with a higher AUC associated with a better performing algorithm.

Performance Goals:
The performance goals for CAI algorithm are defined as follows:
Sensitivity and Specificity ≥ 80 % at the CAI threshold of 45.

Results of Clinical Performance Testing:
The performances of CAI for the chosen threshold of 45 on the 145 subjects enrolled, are reported in **Table 1-2** below.

**Table 1-2 ROC analysis results for clinical data (N=145)**

| ROC Analysis for Clinical Data | | | |
|---|---|---|---|
| **ROC AUC** | **Sensitivity** | **Specificity** | **CAI Threshold** |
| 0.88 [0.85,0.90] | **0.84 [0.78,0.88]** | **0.80 [0.76,0.85]** | **45** |

**Table 1-3** below provides the confusion matrix that was used to calculate sensitivity/specificity for CAI threshold of 45.

**Table 1-3 Confusion matrix for CAI at the chosen threshold of 45**

| | | Corr | |
|---|---|---|---|
| | | **Positive** (Corr ≥ 0.7) | **Negative** (0 ≤ Corr < 0.7) |
| **CAI** | **Positive** (CAI ≥ 45) | 3176 (TP) | 18235 (FP) |
| | **Negative** (CAI < 45) | 625 (FN) | 74110 (TN) |

As shown in Table 1-2, at the chosen threshold of 45, CAI can accurately discriminate conditions where MAP-$StO_2$ association is strong from conditions where MAP-$StO_2$ association is weak/moderate.

In order to evaluate potential site effects on CAI performance, the ROC analysis was also repeated for each site individually. The results are summarized in Table **1-4**,**1-5**,**1-6** and **1-7** below. The results demonstrate that CAI performance is consistent across different sites, as shown by the almost identical AUCs. The confidence intervals of AUCs and the sensitivity and specificity vary across sites due to different number of patients enrolled in different sites, and different number of positive events and/or negative events in these patients.

**Table 1-4 ROC analysis results for UC Davis Clinical Data**

| ROC Analysis - UCD Clinical Data | | | |
|---|---|---|---|
| **AUC** | **Sens** | **Spec** | **Threshold (%)** |
| **0.87 [0.82,0.92]** | 0.86 [0.76,0.93] | 0.73 [0.65,0.80] | 45 |

**Table 1-5 ROC analysis results for Northwestern University Clinical Data**

| ROC Analysis - NWU Clinical Data | | | |
|---|---|---|---|
| **AUC** | **Sens** | **Spec** | **Threshold (%)** |
| **0.87 [0.84,0.91]** | 0.90 [0.83,0.94] | 0.71 [0.63,0.78] | 45 |

**Table 1-6 ROC analysis results for University of Minnesota Clinical Data**

| ROC Analysis - UoM Clinical Data | | | |
|---|---|---|---|
| **AUC** | **Sens** | **Spec** | **Threshold (%)** |
| **0.89 [0.85, 0.92]** | 0.65 [0.53, 0.76] | 0.93 [0.92, 0.95] | 45 |

**Table 1-7 ROC analysis results for Stanford University Clinical Data**

| ROC Analysis - SU Clinical Data | | | |
|---|---|---|---|
| **AUC** | **Sens** | **Spec** | **Threshold (%)** |
| **0.87 [0.70, 0.98]** | 0.96 [0.90, 0.99] | 0.75 [0.52, 0.92] | 45 |

**Benefit-Risk Analysis**

There was no exclusion of data across the spectrum of weak, moderate, and strong MAP-StO2 association states in the post-hoc statistical analysis. All patient conditions were included in the analysis.

CAI quantifies the dynamic relationship between two existing hemodynamic parameters, MAP and $StO_2$ in the cerebral tissue, to show the level of coherence between the two parameters. The ROC analysis against Corr demonstrates that

CAI can accurately differentiate weak/moderately MAP-$StO_2$ association from strong MAP-$StO_2$ association states at the chosen threshold of 45. Although the agreement between CAI and Corr is strong but not perfect, the benefits outweigh the risks, as CAI can enhance clinician's understanding of the underlying hemodynamic changes behind cerebral desaturation events that may not be easily identifiable if just visually looking at MAP and $StO_2$ values individually (which is the current clinical practice). Additionally, CAI is continuously calculated and displayed, enabling clinicians to continuously assess the underlying hemodynamic changes instead of visually/mentally calculating the relationship which is more susceptible to error and subjective judgement.

While CAI will be shown on the monitor as an index value and a trended graph, both $StO_2$ and MAP trends will still be individually displayed on the monitor for review by the clinician and to aid them make treatment decisions based on these individual values.

**Conclusions**

**Overall Conclusion:**

The Cerebral Adaptive Index (CAI) Algorithm has successfully passed functional and performance testing, including software verification and validation, bench, and clinical analysis. Completion of all performance verification and validation activities demonstrated that the subject device meets its predetermined design and performance specifications. Verification activities performed confirmed that the differences in the features and design did not adversely affect the safety and effectiveness of the subject device. Note that the lower bound CI performance goal was not pre-specified, but the observed results demonstrate safety and effectiveness. The testing performed demonstrates that the Cerebral Adaptive Index (CAI) Algorithm is substantially equivalent to its legally marketed predicate.