October 16, 2024

Edwards Lifesciences
Daphney Germain-Kolawole
Director, Regulatory Affairs Program Management
One Edwards Way
Irvine, California 92614

Re: K240596
Trade/Device Name: Cerebral Autoregulation Index (CAI) Algorithm
Regulation Number: 21 CFR 870.2700
Regulation Name: Oximeter
Regulatory Class: Class II
Product Code: MUD, QEM
Dated: September 13, 2024
Received: September 16, 2024

Dear Daphney Germain-Kolawole:

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 (the 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 available 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.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

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 Part 803) for devices or postmarketing safety reporting (21 CFR Part 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 Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

All medical devices, including Class I and unclassified devices and combination product device constituent parts are required to be in compliance with the final Unique Device Identification System rule ("UDI Rule"). The UDI Rule requires, among other things, that a device bear a unique device identifier (UDI) on its label and package (21 CFR 801.20(a)) unless an exception or alternative applies (21 CFR 801.20(b)) and that the dates on the device label be formatted in accordance with 21 CFR 801.18. The UDI Rule (21 CFR 830.300(a) and 830.320(b)) also requires that certain information be submitted to the Global Unique Device Identification Database (GUDID) (21 CFR Part 830 Subpart E). For additional information on these requirements, please see the UDI System webpage at https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 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

for
Jay Gupta
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)*
K240596

Device Name
Cerebral Autoregulation Index (CAI) Algorithm

Indications for Use *(Describe)*
Cerebral Autoregulation Index (CAI) Algorithm is an informational index intended to represent a surrogate measurement of whether cerebral autoregulation is likely intact or is likely impaired as expressed by 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 Autoregulation 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.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

510(K) SUMMARY

Cerebral Autoregulation Index (CAI) Algorithm		
510(k) Submitter	Edwards Lifesciences LLC One Edwards Way, Irvine, CA 92614 (949) 250-5466	
Contact Person	Primary Contact Daphney Germain-Kolawole Director, RA Program Management Edwards Lifesciences LLC One Edwards Way, Irvine, CA USA, 92614 Tel.: (949) 250-5466 Email: daphney_germainkolawole@edwards.com	Secondary Contact Karen Clement Senior Director, Regulatory Affairs Edwards Lifesciences LLC One Edwards Way, Irvine, CA USA, 92614 Tel.: (949) 250-4746 Email: karen_clement@edwards.com
Date Prepared	September 13, 2024	
Trade Name	Cerebral Autoregulation Index (CAI) Algorithm	
Regulation Number / Name	21 CFR 870.2700 / Oximeter	
Product Code	MUD (21 CFR 870.2700), QEM (21 CFR 870.2700)	
Regulation Class	Class II	
Predicate Device	Cerebral Adaptive Index (CAI) Algorithm	
Device Description	The Cerebral Adaptive Index (CAI) Algorithm is being renamed to Cerebral Autoregulation Index (CAI) Algorithm. The originally cleared Cerebral Adaptive Index is in effect an index of cerebral autoregulation, and the renaming results in a labeling change. The evidence to support the proposed labeling change for the Cerebral Autoregulation Index algorithm demonstrates the capability of CAI to represent a surrogate measurement of whether cerebral autoregulation is likely intact or is likely impaired, as expressed by the level of coherence or lack thereof between MAP (as a surrogate of cerebral perfusion pressure) and cerebral StO_2 (as a surrogate of cerebral blood flow) of the patient. The Cerebral Autoregulation 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 represent a surrogate measurement of whether cerebral autoregulation is likely intact or is likely impaired as	

Cerebral Autoregulation Index (CAI) Algorithm	
	expressed by the level of coherence between MAP and cerebral StO_2. The output will be represented as an index value in a trend plot. 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). CAI will be continuously displayed at 20-second rate. The parameter will not have any alarm ranges and will be represented as a number with a range between 0 to 100. A high CAI value (CAI ≥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 because cerebral autoregulation is likely impaired. 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 because cerebral autoregulation is likely intact.
Indications for Use	Cerebral Autoregulation Index (CAI) Algorithm is an informational index intended to represent a surrogate measurement of whether cerebral autoregulation is likely intact or is likely impaired as expressed by 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 Autoregulation Index (CAI) Algorithm.
Intended Use	Cerebral Autoregulation 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 represent a surrogate measurement of whether cerebral autoregulation is likely intact or is likely impaired as expressed by the level of coherence or lack thereof between MAP and cerebral StO_2.
Comparative Analysis	The subject Cerebral Autoregulation Index (CAI) Algorithm is similar to the predicate Cerebral Adaptive Index (CAI) Algorithm in terms of the intended use and indications for use. The technological characteristics are identical (including design and principle of operation). Both the subject and predicate devices 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 predicate Cerebral Adaptive Index (CAI) Algorithm is being used to establish substantial equivalence for the subject Cerebral Autoregulation Index (CAI) Algorithm. The following table details the comparisons and differences between the subject and predicate devices.

Cerebral Autoregulation Index (CAI) Algorithm					
		Parameter	**Subject Device *Cerebral Autoregulation Index (CAI) Algorithm***	**Predicate Device *Cerebral Adaptive Index (CAI) Algorithm***	***Comparison***
		Trade Name	Cerebral Autoregulation Index (CAI) Algorithm	Cerebral Adaptive Index (CAI) Algorithm	Same + Autoregulation Device name has been modified to reference "Autoregulation" to distinguish this model from the predicate version.
		510(k) number	K240596	K223651	Not applicable
		Manufacturer	Edwards Lifesciences	Edwards Lifesciences	Same
		Device Classification	Class II	Class II	Same
		Regulation Number	21 CFR 870.2700	21 CFR 870.2700	Same
		Product Code – Device Classification Name	MUD – Oximeter, Tissue Saturation QEM – Cerebral Oximeter	MUD – Oximeter, Tissue Saturation QEM – Cerebral Oximeter	Same
		Intended Use	Cerebral Autoregulation Index (CAI) Algorithm is intended to be used by qualified personnel or trained clinicians in a critical care environment in a hospital	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	Same + Autoregulation Device name has been modified to reference "Autoregulation". The Cerebral Adaptive Index is in effect an index of cerebral

Cerebral Autoregulation Index (CAI) Algorithm						
			setting. CAI is intended to represent a surrogate measurement of whether cerebral autoregulation is likely intact or is likely impaired as expressed by the level of coherence or lack thereof between MAP and cerebral StO_2.	coherence between MAP and cerebral StO_2.	autoregulation. The evidence to support the proposed labeling change for the Cerebral Autoregulation Index algorithm demonstrates the capability of CAI to represent a surrogate measurement of whether cerebral autoregulation is likely intact or is likely impaired as expressed by the level of coherence or lack thereof between MAP and Cerebral StO_2 of the patient.	
		Indications for Use	Cerebral Autoregulation Index (CAI) Algorithm is an informational index intended to represent a surrogate measurement of whether cerebral autoregulation is likely intact or is likely impaired as expressed by the level of coherence or lack	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	Similar indications. Device name has been modified to reference "Autoregulation". The Cerebral Adaptive Index is in effect an index of cerebral autoregulation, which results in a labeling change. The evidence to support the proposed labeling change for the Cerebral	

Cerebral Autoregulation Index (CAI) Algorithm						
			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 Autoregulation Index (CAI) Algorithm.	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.	Autoregulation Index algorithm demonstrates the capability of CAI to represent a surrogate measurement of whether cerebral autoregulation is likely intact or is likely impaired as expressed by the level of coherence or lack thereof between MAP and Cerebral StO_2 of the patient.	
		Parameters	StO_2 MAP	StO_2 MAP	Same	

Cerebral Autoregulation Index (CAI) Algorithm						
			CAI	CAI		
		Method of Operation	The CAI algorithm calculates the level of coherence between obtained StO_2 measurement from NIRS waveforms and obtained MAP measurement from the pressure waveform. The CAI value is displayed to the user.	The CAI algorithm calculates the level of coherence between obtained StO_2 measurement from NIRS waveforms and obtained MAP measurement from the pressure waveform. The CAI value is displayed to the user.	Same	
Performance Data (Bench and/or Clinical)	The following verification activities were performed in support of a substantial equivalence determination for the subject Cerebral Autoregulation Index (CAI) Algorithm and Cerebral Adaptive Index (CAI) Algorithm and to ensure the safety and effectiveness of the Cerebral Autoregulation Index (CAI) Algorithm. **Software Verification** The Cerebral Autoregulation Index (CAI) Algorithm was tested at the algorithm level to verify the performance of the device. Algorithm verification testing was performed on the CAI algorithm in accordance with IEC 62304:2006/A1:2016 Medical device software - Software life cycle processes and FDA's Guidance for Industry and Food and Drug Administration Staff, the *Content of Premarket Submissions for Device Software Contained in Medical Devices Functions*. (issued June 14, 2023). The validation of the CAI Algorithm was performed as follows: 1. Validation using animal data 2. Validation using clinical data The algorithm passed all testing. **Clinical Performance Data** The following clinical performance data was submitted to support the indications for use of the subject device:					

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 and general surgery) whose StO2 and MAP were being monitored respectively via Foresight Sensors and Flotrac Sensors and whose cerebral blood flow velocity (CBFV) was being monitored via transcranial doppler ultrasound were randomly selected for the retrospective analysis.

Enrollment
The validation dataset was retrospectively obtained from 3 different clinical sites (Northwestern University, Chicago, US; UC Davis, Sacramento, US; Amsterdam UMC, Amsterdam, The Netherlands). A total of 50 subjects aged 18 or older were randomly selected for inclusion in the CAI Algorithm K240596 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 three sites.

Table 1-1 Summary of patient demographic information for the 3 sites used in the clinical data performance analysis. Data for Age, Height and Weight are Mean ± 1std and full range [min, max]

Site	Number of Patients	Age (years)	Gender	Height (cm)	Weight (kg)	Surgery Type
Northwestern University, Chicago, USA	18	66 ± 10 [46, 84]	4 Females 14 Males	173 ± 13 [155, 201]	89 ± 30 [53, 163]	Cardiac surgery (N = 12) General surgery (N = 6)
UC Davis, Sacramento, USA	9	61 ± 17 [32, 77]	4 Females 5 Males	169 ± 9 [158, 180]	79 ± 20 [50, 111]	General surgery (N=9)
Amsterdam UMC, Amsterdam, The Netherlands	23	58 ± 16 [20, 81]	7 Females 16 Males	180 ± 11 [157, 200]	83 ± 15 [56, 122]	Cardiac surgery (N = 16) General surgery (N =7)

Cerebral Autoregulation Index (CAI) Algorithm	
	General Summary The following is a summary of the validation procedure performed: MAP, StO2 and CBFV 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, individual patients' Lower Limit of Autoregulation (LLA) and Upper Limit of Autoregulation (ULA) were determined using a polynomial fit of the CBFV-MAP data. A ground-truth cerebral autoregulation status assessment, either Intact or Impaired, was then made based on the identified LLA and ULA according to the following general rule: • MAP ≤ LLA, autoregulation status = Impaired • MAP ≥ ULA, autoregulation status = Impaired • LLA < MAP < ULA, autoregulation status = Intact A Receiver Operating Characteristic (ROC) analysis was then performed to assess the performance of CAI to discriminate Intact vs Impaired cerebral autoregulation. *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; TP/P=TP/(TP+FN), where True Positives (TP) are defined as Impaired cerebral autoregulation data points with a corresponding CAI value greater than or equal to a given threshold, and False Negatives (FN) are defined as Impaired cerebral autoregulation data points with a corresponding CAI value less than a given threshold. • Specificity: The true negative rate; ratio of true negatives to total number of negative events; TN/N=TN/(TN+FP), where True Negatives (TN) are defined as Intact cerebral autoregulation data points with a corresponding CAI value less than a given threshold, and False Positives (FP) are defined as Intact cerebral autoregulation data points with a corresponding CAI value greater than or equal to 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.

Cerebral Autoregulation Index (CAI) Algorithm

Results of Clinical Performance Testing

The performances of CAI for the chosen threshold of 45 on the 50 subjects enrolled are reported in **Table 1-2** below.

Table 1-2 ROC analysis results for clinical data (N=50)

ROC AUC [95% confidence interval]	Sensitivity (%) [95% confidence interval]	Specificity (%) [95% confidence interval]	CAI Threshold
0.92 [0.89, 0.94]	82 [75, 88]	94 [91, 96]	45

Table 1-3 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

		Cerebral Autoregulation	
		Positive (Impaired Autoregulation)	**Negative (Intact Autoregulation)**
CAI	**Positive (CAI ≥ 45)**	1812 (TP)	493 (FP)
	Negative (CAI < 45)	392 (FN)	7851 (TN)

As shown in Table 1-2, at the chosen threshold of 45, CAI can accurately discriminate conditions of impaired cerebral autoregulation from conditions of intact autoregulation.

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, and 1-6 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 (N=9)

CAI Threshold	Sensitivity (%) [95% confidence interval]	Specificity (%) [95% confidence interval]	ROC AUC [95% confidence interval]
45	82 [66, 93]	89 [67, 98]	0.90 [0.77, 0.96]

<table>
<tr><th colspan="2">Cerebral Autoregulation Index (CAI) Algorithm</th></tr>
<tr><td></td><td>
Table 1-5 ROC analysis results for Northwestern University clinical data (N=18)
<table>
<tr><th>CAI Threshold</th><th>Sensitivity (%) [95% confidence interval]</th><th>Specificity (%) [95% confidence interval]</th><th>ROC AUC [95% confidence interval]</th></tr>
<tr><td>45</td><td>74
[61, 87]</td><td>93
[89, 98]</td><td>0.87
[0.79, 0.95]</td></tr>
</table>
Table 1-6 ROC analysis results for Amsterdam UMC clinical data (N=23)
<table>
<tr><th>CAI Threshold</th><th>Sensitivity (%) [95% confidence interval]</th><th>Specificity (%) [95% confidence interval]</th><th>ROC AUC [95% confidence interval]</th></tr>
<tr><td>45</td><td>84
[74, 89]</td><td>96
[94, 97]</td><td>0.93
[0.89, 0.96]</td></tr>
</table>
</td></tr>
<tr><td>Conclusion</td><td>The Cerebral Autoregulation 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 Autoregulation Index (CAI) Algorithm is substantially equivalent to its legally marketed predicate.</td></tr>
</table>