DE NOVO CLASSIFICATION REQUEST FOR ACUMEN HYPOTENSION PREDICTION INDEX FEATURE SOFTWARE

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Adjunctive predictive cardiovascular indicator.** The adjunctive predictive cardiovascular indicator is a prescription device that uses software algorithms to analyze cardiovascular vital signs and predict future cardiovascular status or events. This device is intended for adjunctive use with other physical vital sign parameters and patient information and is not intended to independently direct therapy.

NEW REGULATION NUMBER: 21 CFR 870.2210

CLASSIFICATION: II

PRODUCT CODE: QAQ

BACKGROUND

DEVICE NAME: Acumen Hypotension Prediction Index (HPI) Feature Software

SUBMISSION NUMBER: DEN160044

DATE OF DE NOVO: September 26, 2016

CONTACT: Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614

INDICATIONS FOR USE

The Edwards Lifesciences Acumen Hypotension Prediction Index (HPI) feature provides the clinician with physiological insight into a patient's likelihood of future hypotensive events (defined as mean arterial pressure < 65 mmHg for at least one minute in duration) and the associated hemodynamics. The Acumen HPI feature is intended for use in operating room (OR) patients receiving advanced hemodynamic monitoring. The Acumen HPI feature is considered to be additional quantitative information regarding the patient's physiological condition for reference only and no therapeutic decisions should be made based solely on the Hypotension Prediction Index (HPI) parameter.

LIMITATIONS

The sale, distribution, and use of the Acumen Hypotension Prediction Index Feature are restricted to prescription use in accordance with 21 CFR § 801.109.

Inaccurate FloTrac/Cardiac Output (FT-CO) measurements can be caused by factors such as:

- Improperly zeroed and/or leveled sensor/transducer
- Over- or under-damped pressure lines
- Excessive variations in blood pressure. Some conditions that cause BP variations include, but are not limited to:
    - Intra-aortic balloon pumps
- Any clinical situation where the arterial pressure is deemed inaccurate or not representative of aortic pressure, including but not limited to:
    - Extreme peripheral vasoconstriction which results in a compromised radial arterial pressure waveform
    - Hyperdynamic conditions as seen in post liver transplant
- Excessive patient movement
- Electrocautery or electrosurgical unit interference
- Aortic valve regurgitation may cause an over estimation of Stroke Volume / Cardiac Output calculated depending on the amount of valvular disease and the volume lost back into the left ventricle.

The Hypotension Prediction Index, HPI, should not be used exclusively to treat the patients. A review of the patient's hemodynamics is recommended prior to initiating treatment.

Exercise caution when using dP/dt in patients with severe aortic stenosis, since the stenosis may reduce the coupling between the left ventricle and the afterload.

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

DEVICE DESCRIPTION

The Acumen Hypotension Prediction Index Feature ("the device") consists of software running on the Edwards Lifesciences EV1000 Platform (previously cleared under K100709, K110597, K131892, K140312, and K160552) paired with the FloTrac IQ extravascular blood pressure transducer (K152980) and a radial arterial catheter. The device includes the Hypotension Prediction Index (HPI), the Dynamic Arterial Elastance Parameter (Ea_{dyn}), the Left Ventricular Contractility Parameter (dP/dt), and additional graphical user interface features.

HPI is an index related to the likelihood of a patient experiencing a hypotensive event (defined as mean arterial pressure (MAP) <65 mmHg for one minute in duration) within fifteen minutes, where zero (0) indicates low likelihood and one hundred (100) indicates high likelihood. The EV1000 Platform initiates a high priority alarm (red) when HPI exceeds 85. The Hypotension Prediction Index, HPI, should not be used exclusively to treat the patients. A review of the patient's hemodynamics is recommended prior to initiating treatment.

HPI is not defined by a single equation. HPI uses features extracted from FloTrac IQ measurements, some compared to an initial base value determined over the first 10 minutes of the patient monitoring session, to a data-driven model developed from retrospective analysis of an arterial waveform database collected from ICU and OR patients containing annotated hypotensive (defined as MAP <65 mmHG for at least 1 minute) and non-hypotensive events. The sensitivity, specificity, and area under the receiver operating characteristic for the first database of 52 subjects were 83.7%, 99.8%, and 0.95 respectively. The sensitivity, specificity, and area under the receiver operating characteristic for the second database of 204 subjects were 65.8%, 99.4%, and 0.88 respectively.

The accuracy of the presented measurements are based on several factors: the arterial line is reliable (not damped), the pressure sensor is well aligned and the arterial line zeroed properly is connected to the device, and patient demographics (age, gender, height, and weight) have been entered into the device. Usability testing demonstrated that users recognize that HPI is an adjunctive parameter.

Ea_{dyn} is a physiologic parameter related to left ventricular afterload relative to the left ventricular elastance. It is calculated by dividing Pulse Pressure Variation (PPV) by Stroke Volume Variation (SVV), or Ea_{dyn} = PPV/SVV.

dP/dt is a physiologic parameter related to the change in contractility of the left ventricle. It is calculated as the maximal first derivative of the arterial pressure waveform with respect to time.

Additional graphical user interface features include the HPI High Alert Popup, which displays when HPI exceeds 85 for two consecutive 20-second updates or reaches 100 at any time, and the HPI Secondary Screen, which consolidates hemodynamic parameters into a single screen.

Figure 1: (top, left) HPI displayed as a Key Parameter; (bottom, left) HPI High Alert Popup; (right) HPI Secondary Screen

SUMMARY OF NONCLINICAL/BENCH STUDIES

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The device is a software feature installed on the EV1000 Platform. The EV1000 Platform conforms with FDA-recognized standards for basic safety and essential performance of Medical Electrical Equipment. These standards include:

- IEC 60601-1:2005 + CORR. 1 (2006) + CORR. 2 (2007) with report of US National Differences - Medical Electrical Equipment, Part 1: General requirements for basic safety and essential performance

- IEC 60601-1-2:2007 - Medical Electrical Equipment, Part 1-2: General requirements for safety – Collateral Standard: Electromagnetic compatibility – Requirements and tests.

- IEC 60601-1-6:2010 - Medical Electrical Equipment, Part 1-6: General requirements for safety and essential performance – Collateral Standard: Usability.

- IEC 62366:2007 - Medical Devices – Application of usability engineering to medical devices.

- IEC 60601-1-8:2006 - Medical Electrical Equipment, Part 1-8: General requirements

for basic safety and essential performance – Collateral Standard: General requirements, tests, and guidance for alarm systems in medical electrical equipment and medical electrical systems.

- IEC 60601-2-49:2011 - Medical electrical equipment Part 2-49: Particular requirements for the basic safety and essential performance of multifunction patient monitoring equipment

- IEC 60068-2-13:1985 - Basic environmental testing procedures - Part 2-13: Tests - Test M: Low air pressure

Electromagnetic compatibility information was provided in accordance with the FDA Guidance Document, "Information to Support a Claim of Electromagnetic Compatibility (EMC) of Electrically-Powered Medical Devices – Guidance for Industry and Food and Drug Administration Staff" (issued July 11, 2016).

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 other patient vital signs.

Regression testing was performed to demonstrate that the device software does not adversely impact the performance of the cleared EV1000 Platform.

Translation testing was performed to demonstrate that movement of the device software from the development environment to the EV1000 Platform does not adversely impact the intended performance of the EV1000 Platform.

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

Cybersecurity information was provided in accordance with the FDA Guidance Document, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices – Guidance for Industry and Food and Drug Administration Staff" (issued October 02, 2014).

USABILITY TESTING

Usability testing was necessary to mitigate the risk of delayed or incorrect treatment due

to user misinterpretation or overreliance on the indicator. Test reports were 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). Fifteen (15) clinical participants, including anesthesiologists, intensivists, Certified Registered Nurse Anesthetists (CRNAs), and Intensive Care Unit (ICU) nurses participated in the testing. Testing was performed in a simulated use environment using a sequence of tasks, including monitoring initiation, configuration of the screen, response to high alert, and end of case. Specifically, users were assessed for the understanding that after a high HPI result, other physiologic parameters should be considered before taking clinical action. Interview questions were administered to assess user understanding of the monitor features and the meaning of a different HPI values. At least 80% of participants met the acceptance criteria of agree or strongly agree for all items, including when separating subjects by clinical profession and years of experience.

PERFORMANCE TESTING – ANIMAL

Device performance was evaluated in five swine using a hemorrhagic model and a vasodilation model. In the hemorrhagic model, swine were bled by venous catheter insertion at 5-20 cc/min after baseline stabilization was established, then held at a MAP of 60 mm/hg for 15 minutes. In the vasodilation model, swine at a MAP of 85 mm/hg were slowly administered nitroprusside (NTP) to reduce MAP to less than 65 mm/hg for 15 minutes. Device outputs (HPI, Ea_{dyn}, and dP/dt) were recorded during execution of both models. The device outputs were compared to animal status and proposed Indications for Use.

SUMMARY OF CLINICAL INFORMATION

Clinical validation of the HPI index used both publicly and privately collected data. Data utilized in the validation of the HPI Algorithm originated from two databases. The first database, the Edwards Lifesciences database, has archived data that were all collected via prospective, IRB/EC approved clinical protocols with informed consent for each patient. This database archive contains acute care OR patients (N=52) with wide ranges of procedures and with various acute conditions collected from global clinical sites. The patient data used for validation were all collected via prospective protocols. The second database came from a university hospital and included OR patients (n=204). The sensitivity, specificity, and area under the receiver operating characteristic for the first database were 83.7%, 99.8%, and 0.95 respectively. The sensitivity, specificity, and area under the receiver operating characteristic for the second database were 65.8%, 99.4%, and 0.88 respectively.

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

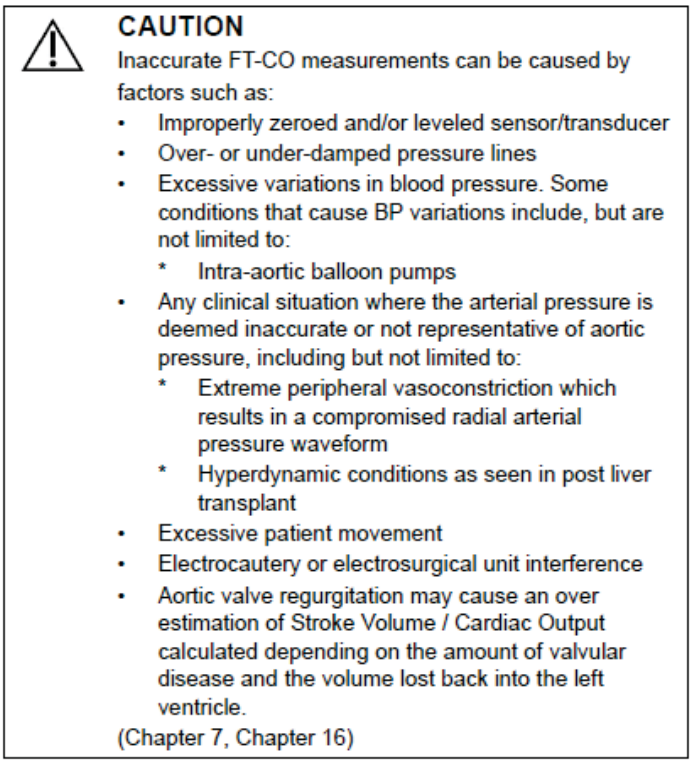
The labeling includes the following elements:

a. A description of what the device measures and outputs to the user;

   "Acumen Hypotension Prediction Index (HPI) software, when active and when using a FloTrac IQ sensor, connected to a radial arterial catheter, provides the clinician with information regarding the likelihood of a patient trending toward a hypotensive vent, defined as mean arterial pressure (MAP) < 65 mmHg for at least one minute."

   "HPI uses features extracted from FloTrac IQ measurements, some compared to an initial base value determined over the first 10 minutes of the patient monitoring session, to a data-driven model developed from retrospective analysis of an arterial waveform database collected from ICU and OR patients containing annotated hypotensive (defined as MAP <65 mmHG for at least 1 minute) and non-hypotensive events. HPI is displayed as an integer value between 0 and 100."

b. Warnings identifying sensor acquisition factors that may impact measurement results;



CAUTION

Inaccurate FT-CO measurements can be caused by factors such as:

- Improperly zeroed and/or leveled sensor/transducer
- Over- or under-damped pressure lines
- Excessive variations in blood pressure. Some conditions that cause BP variations include, but are not limited to:
  - Intra-aortic balloon pumps
- Any clinical situation where the arterial pressure is deemed inaccurate or not representative of aortic pressure, including but not limited to:
  - Extreme peripheral vasoconstriction which results in a compromised radial arterial pressure waveform
  - Hyperdynamic conditions as seen in post liver transplant
- Excessive patient movement
- Electrocautery or electrosurgical unit interference
- Aortic valve regurgitation may cause an over estimation of Stroke Volume / Cardiac Output calculated depending on the amount of valvular disease and the volume lost back into the left ventricle.

(Chapter 7, Chapter 16)

"The accuracy of the presented measurements are based on several factors: the arterial line is reliable (not damped), the pressure sensor is well aligned and the arterial line zeroed properly is connected to the device, and patient demographics (age, gender, height, and weight) have been entered into the device."

c. Guidance for interpretation of the measurements, including a statement that the output is adjunctive to other physical vital sign parameters and patient information;

Table 16-2 HPI Value Graphical and Audible Display Elements

HPI Value	Graphical Display Elements	Audible	General Interpretation	User Action
HPI ≤ 85	White	None	Patient hemodynamics indicate that there is a low to moderate likelihood of a hypotensive event occurring. A low HPI value does not exclude a hypotensive event from occurring in the next 5-15 minutes regardless of MAP value	Continue monitoring patient hemodynamics. Remain vigilant with respect to changing patient hemodynamics using the primary monitoring screen, HPI secondary screen, HPI, and trends in parameters and vital signs
HPI > 85	Red (Flashing)	High Priority Alarm Tone	Patient has a high likelihood of experiencing a hypotensive event within 15 minutes	Check patient hemodynamics using the secondary screen and other primary screen parameters in order to investigate the potential cause of the high likelihood of hypotension in order to inform a potential course of action
HPI > 85 and persists for 2 continuous readings (40 seconds)	Red (Flashing) Popup	High Priority Alarm Tone	Patient has a high likelihood of experiencing a hypotensive event within 15 minutes	Acknowledge popup by chosen method Check patient hemodynamics using the secondary screen and other primary screen parameters in order to investigate the potential cause of the high likelihood of hypotension in order to inform a potential course of action
HPI = 100	Red (Flashing) Popup	High Priority Alarm Tone	Patient is hypotensive	Acknowledge popup by chosen method Check patient hemodynamics using the secondary screen and other primary screen parameters in order to investigate the potential cause of the hypotension in order to inform a potential course of action

Note: If HPI is displayed in the Information Bar, the graphical display element changes will not change color nor alarm. Instead, the user will only be notified when HPI exceeds 85 for consecutive updates by displaying the HPI High Alert Popup.

"The Hypotension Prediction Index, HPI, should not be used exclusively to treat the patients. A review of the patient's hemodynamics is recommended prior to initiating treatment."

"The Acumen HPI feature is considered to be additional quantitative information regarding the patient's physiological condition for reference only and no therapeutic decisions should be made based solely on the Hypotension Prediction Index (HPI) parameter."

d. A specific time or a range of times before the predicted patient status or clinical event occurs, accounting for differences in patient condition and environment;

"Patient has a high likelihood of experiencing a hypotensive event within 15 minutes"

e. Key assumptions made during calculation of the output;

"The HPI parameter uses data from the first ten minutes of monitoring to establish a 'base value'. Device performance during these first ten minutes may differ as a result."

f. The type(s) of sensor data used, including specification of compatible sensors for data acquisition;

"Acumen Hypotension Prediction Index (HPI) software, when active and when using a FloTrac IQ sensor, connected to a radial arterial catheter, provides the clinician with information regarding the likelihood of a patient trending toward a hypotensive vent, defined as mean arterial pressure (MAP) < 65 mmHg for at least one minute."

g. The expected performance of the device for all intended use populations and environments; and

Table 16-8 Clinical Validation (N=52)

HPI Range	Event Rate (%)	Time-to-Event in minutes: Median [10th percentile, 90th percentile]
10-14	14.2	8.0 [4.7, 12.7]
15-19	16.6	6.7 [3.3, 12.6]
20-24	15.4	7.0 [3.3, 14.0]
25-29	16.9	7.8 [3.7, 13.4]
30-34	22.5	9.0 [3.7, 14.0]
35-39	27.4	8.0 [3.3, 13.3]
40-44	31.8	8.3 [3.0, 13.7]
45-49	40.4	8.3 [3.3, 13.7]
50-54	43.4	7.7 [2.7, 13.3]
55-59	44.3	7.3 [3.0, 13.1]
60-64	57.0	6.7 [2.7, 12.8]
65-69	56.8	5.7 [2.3, 12.3]
70-74	67.2	5.7 [2.0, 11.7]
75-79	81.0	4.7 [2.0, 11.0]
80-84	84.2	5.0 [1.7, 12.3]
85-89	92.9	4.0 [1.7, 10.3]
90-94	95.8	3.7 [1.3, 10.0]
95-99	97.6	1.3 [0.3, 8.0]

"The Acumen HPI feature is intended for use in OR patients receiving advanced hemodynamic monitoring."

h. Relevant characteristics of the patients studied in the clinical validation (e.g., age, gender, race/ethnicity, patient condition) and a summary of validation results

Table 16-6 Patient Demographics

Type	Clinical Validation Study (N=52)	Clinical Validation Study (N=204)
# of Patients	52	204
Gender (Male)	29	100
Age	58.3±11.3	56.7±14.4
BSA	1.8±0.2	1.9±0.3

Table 16-7 Clinical Validation Studies*

Clinical Validation Study	HPI Threshold	PPV [confidence interval]	NPV [confidence interval]	Specificity (%) [95% confidence interval]	# True negative/ # nonevents	Sensitivity (%) [95% confidence interval]	# True positive/ # events	AUC
(N=52)	85	99.9 (=886/887) [99.7, 100.0]	75.1 (=520/692) [71.9, 78.4]	99.8 [99.4, 100.0]	520/521	83.7 [81.5, 86.0]	886/1058	0.95
(N=204)	85	98.3 (=1265/1287) [97.6, 99.0]	84.9 (=3709/4367) [83.9, 86.0]	99.4 [99.2, 99.7]	3709/3731	65.8 [63.7, 67.9]	1265/1923	0.88

*Data on File at Edwards Lifesciences

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the adjunctive predictive cardiovascular indicator and the measures necessary to mitigate these risks.

Identified Risk	Mitigation Measures
Delayed or incorrect treatment due to erroneous device output resulting from software malfunction or algorithm error	Software verification, validation, and hazard analysis Non-clinical performance testing Clinical performance testing Labeling
Delayed or incorrect treatment due to user misinterpretation or overreliance on indicator	Usability assessment Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the adjunctive predictive cardiovascular indicator is subject to the following special controls:

1. A software description and the results of verification and validation testing based on a comprehensive hazard analysis and risk assessment must be provided, including:

    a. A full characterization of the software technical parameters, including algorithms;
    b. A description of the expected impact of all applicable sensor acquisition hardware characteristics and associated hardware specifications;
    c. A description of sensor data quality control measures;
    d. A description of all mitigations for user error or failure of any subsystem components (including signal detection, signal analysis, data display, and storage) on output accuracy;
    e. A description of the expected time to patient status or clinical event for all expected outputs, accounting for differences in patient condition and environment; and
    f. The sensitivity, specificity, positive predictive value, and negative predictive value in both percentage and number form.

2. A scientific justification for the validity of the predictive cardiovascular indicator algorithm(s) must be provided. This justification must include verification of the algorithm calculations and validation using an independent data set.

3. A human factors and usability engineering assessment must be provided that evaluates the risk of misinterpretation of device output.

4. A clinical data assessment must be provided. This assessment must fulfill the following:

    a. The assessment must include a summary of the clinical data used, including source, patient demographics, and any techniques used for annotating and separating the data.
    b. The clinical data must be representative of the intended use population for the device. Any selection criteria or sample limitations must be fully described and justified.
    c. The assessment must demonstrate output consistency using the expected range of data sources and data quality encountered in the intended use population and environment.
    d. The assessment must evaluate how the device output correlates with the predicted event or status.

5. Labeling must include:

    a. A description of what the device measures and outputs to the user;
    b. Warnings identifying sensor acquisition factors that may impact measurement results;
    c. Guidance for interpretation of the measurements, including a statement that the output is adjunctive to other physical vital sign parameters and patient information;
    d. A specific time or a range of times before the predicted patient status or clinical event occurs, accounting for differences in patient condition and environment;
    e. Key assumptions made during calculation of the output;
    f. The type(s) of sensor data used, including specification of compatible sensors for data acquisition;
    g. The expected performance of the device for all intended use populations and environments; and
    h. Relevant characteristics of the patients studied in the clinical validation (including age, gender, race or ethnicity, and patient condition) and a summary of validation results.

BENEFIT/RISK DETERMINATION

The risks of the device are based on nonclinical laboratory and animal studies, as well as retrospective clinical data as described above. The primary risk would be fluid overload or subsequent treatment with vasopressor based on a false positive HPI reading when the anesthesiologist is only relying on that single reading.

The probable benefits of the device are also based on nonclinical laboratory and animal studies, as well as retrospective clinical data as described above. The primary benefit of the HPI software is that it provides the physician with a predictive score that the patient may be trending toward a hypotensive event (defined as Mean Arterial Pressure < 65 mmHg for at least one minute in duration). For most patients, increased awareness to the increased risk for a hypotensive event

may help prevent a hemodynamic deterioration by first diagnosing the underlying dysfunction and then treating it.

Patient Perspectives

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

Benefit/Risk Conclusion

In conclusion, given the available information summarized above, the data support that for the intended use specified above, the probable benefits outweigh the probable risks for the Acumen Hypotension Prediction Index Feature Software. 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 Acumen Hypotension Prediction Index Feature Software is granted and the device is classified under the following:

Product Code: QAQ
Device Type: Adjunctive predictive cardiovascular indicator
Class: II
Regulation: 21 CFR 870.2210