DE NOVO CLASSIFICATION REQUEST FOR
CIPHEROX CRI TABLET

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Adjunctive cardiovascular status indicator.** The adjunctive cardiovascular status indicator is a prescription device based on sensor technology for the measurement of a physical parameter(s). 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 870.2200

CLASSIFICATION: Class II

PRODUCT CODE: PPW

BACKGROUND

DEVICE NAME: CipherOx CRI™ Tablet

SUBMISSION NUMBER: DEN160020

DATE OF DE NOVO: May 24, 2016

CONTACT: Flashback Technologies
1215 Spruce Street, Suite #101
Boulder, Colorado 80302

INDICATIONS FOR USE

The CipherOx CRI Tablet is indicated for continuous noninvasive monitoring of functional oxygen saturation of arterial hemoglobin (SpO2), pulse rate (measured by an SpO2 sensor), and the Compensatory Reserve Index (CRI), which trends changes in intravascular volume relative to the individual patient's response to hypovolemia.

For patients with a finger thickness of 0.3" to 1" in hospital and pre-hospital settings.

CRI trends with changes in intravascular volume relative to the individual patient's response to hypovolemia, and should only be used by qualified medical providers as an adjunct to rather than as a replacement for traditional hemodynamic measures. CRI is indicated for adults (19-36 years old) in the supine position under non-motion conditions and without cardiovascular disease. CRI has not been studied in trauma patients.

LIMITATIONS

The sale, distribution, and use of the CipherOx CRI Tablet are restricted to prescription use in accordance with 21 CFR 801.109.

The performance of CipherOx CRI Tablet has been validated using PPG data acquired from the Nonin Model 9560 Pulse Oximeter. The performance using data acquired from other pulse oximeters for which CipherOx CRI Tablet has not been validated is unknown, and therefore safety and effectiveness of its use has not been established.

Due to the possible variability in the CipherOx CRI Tablet results, the CRI values should be reviewed as one of several clinical vital signs to be used in conjunction with the patient's clinical history, symptoms and other diagnostic tests, as well as an appropriately trained clinician's clinical judgment, to evaluate the patient.

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

DEVICE DESCRIPTION

The CipherOx CRI Tablet consists of a Nonin Onyx II Model 9560 finger pulse oximeter (previously cleared under K081285) that communicates by Bluetooth with a Cybernet CyberMed T10 tablet PC. The CipherOx CRI Tablet is a continuous, multi-parameter monitor that displays SpO2, Heart Rate (HR), photoplethysmograph (PPG) waveform images, and the Compensatory Reserve Index (CRI) value and historical trend-line.

Nonin 9560 Pulse Oximeter **Cybernet CyberMed T10 Handheld Tablet**

CRI is an index related to the physiologic changes induced by intravascular fluid loss and ranges from 0 to 1, where 1 indicates a normal subject and 0 indicates a subject who has undergone significant physiological effects from loss of fluid volume.

SUMMARY OF NONCLINICAL/BENCH STUDIES

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The device is a software device that is installed on a dedicated tablet, the Cybernet CyberMed T10 tablet. The Cybernet tablet is intended for healthcare environments. Certifications were provided for IEC 60601-1:2005+ CORR. 1 (2006)+CORR. 2 (2007) 60601-1 and IEC 60601-1-2 Edition 3: 2007-03 that the Cybernet manufacturer has provided.

SOFTWARE

Software documentation as indicated by the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, issued 2005 was provided according to a moderate Level of Concern (LOC). This LOC was justified based on mitigating characteristics such as the intended population, lack of alarms or claims regarding CRI thresholds. Software verification and validation test plans and reports were provided including unit, integration and system level testing. The expected impact of various hardware features on performance was assessed and minimum specifications for acceptable PPG waveforms for analysis were specified. Stress testing and repeatability testing were also performed. Risks related to failure of various software components and their potential impact on patient reports and operator failures were also adequately addressed.

PERFORMANCE TESTING – BENCH

Wireless Connectivity and Coexistence

Wireless connectivity and coexistence test document was provided. This test addresses the types of radio frequency tests that were completed with the CipherOx CRI Tablet Software to confirm that the CipherOx CRI Tablet does not interfere with other devices nor do other devices obviously interfere with it. This testing was done ad hoc to identify issues of cross talk, electromagnetic incompatibility and disturbance, immunity, quality of service, and wireless coexistence. The sponsor based testing on the "Radio Frequency Wireless Technology in Medical Devices: Guidance for Industry and Food and Drug Administration Staff," the indications for use, and the hazard analysis.

Many devices of similar and differing frequencies were tested simultaneously to attempt to identify whether the CipherOx CRI Tablet software interfered with other wireless devices and frequencies or was compromised due to other wireless devices and frequencies. The tests were conducted with a multitude of wireless devices within close range of the CipherOx CRI Tablet device. No interference was observed.

Usability Assessment

A usability simulation study was conducted demonstrating that users were able to correctly interpret the CRI value in both hemorrhage and non-hemorrhage representative use scenarios using recorded data and assessing the ability to identify when an intervention is required. This study also helped demonstrate that the CRI

value could provide added utility beyond that provided by the traditional vital sign input parameters. This usability testing was considered adequate based on mitigating characteristics of the device such as the intended population, as well as lack of alarms or claims regarding CRI thresholds.

SUMMARY OF CLINICAL INFORMATION

Three clinical tests were performed during the development and testing phases of the CipherOx CRI Tablet:

1. A lower body negative pressure (LBNP) study was performed to gather reference data used as a training dataset during the development of the CRI algorithm.

   CRI was developed by collecting reference PPG signals on 230 healthy human volunteers undergoing lower body negative pressure (LBNP) to the point of presyncope (defined as systolic blood pressure below 80 mmHg). LBNP reduces the pressure around the lower extremities of a subject, shifting blood volume to the legs. This model has been shown to mimic effects of central hypovolemia. Step decreases in LBNP were applied during the study until the stopping criteria of systolic blood pressure of less than 80 mmHg or a minimum LBNP of -100 mmHg was reached. Reference CRI values were then defined as CRI = 1 – LBNPcurrent / LBNPcollapse, where LBNPcollapse refers to the LBNP pressure level at the point a subject either had a precipitous fall in systolic blood pressure below 80 mmHg and/or voluntary subject termination due to discomfort or expression of presyncopal symptoms such as sweating, nausea, grey-out, or dizziness (or until completion of -100 mmHg), at which time the LBNP was discontinued.

2. An additional LBNP study was performed to verify that the software implementation of the CRI algorithm correctly calculates CRI levels as specified by the Software Requirements Specification and Software Design Specification.
   The verification study included 20 healthy participants undergoing LBNP in the same manner as was used to develop the training set. The verification study was used to verify that subjects with known CRI values (computed based on the LBNP levels in the same manner as was used to develop the training data) have CRI estimated accurately using the device algorithm. Four CipherOx CRI Tablets were applied to each subject during the study. The results of this study showed the root-mean-squared error between the estimated CRI and reference CRI according to the LBNP level to be less than 0.1.
   In addition, it was verified that
   1. Turning the CipherOx CRI Tablets on and off during the study had no significant effect on CRI estimates.
   2. Each of four CipherOx CRI Tablets gave statistically similar CRI estimates.

3. A blood draw study was performed to validate that the CRI algorithm specifications that were developed and verified using LBNP data conform to the user needs and intended use of the device. The validation study included 42 healthy participants (ages 19 to 36) undergoing blood withdrawal of ~20% intravascular blood volume (15 ml/kg male; 13 ml/kg female) followed by replacement of all blood removed. Blood was removed in 2-4 steps. PPG recordings were taken and CRI calculated and recorded for analysis. Three

subjects' data were lost during the study. Seven subjects had symptoms (e.g., a systolic blood pressure of <80 mmHg or a 30% drop in mean arterial pressure) during blood loss resulting in early termination of blood withdrawal. These subjects are grouped together as 'symptomatic' in the study analysis and used to examine CRI for subjects reaching the point of hemodynamic decompensation. The remaining 32 subjects were analyzed for the relationship between CRI and volume of blood removed. These two groups represent the differences in individual tolerance to central hypovolemia. It was shown that there was a high correlation between CRI and volume of blood removed, and that the change in CRI varied between individuals. The symptomatic group of subjects reached much lower CRI values than those who completed the blood removal without symptoms.

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

Labeling includes the following essential elements:

1. Description of the algorithm, input sensor data and output measures with associated assumptions;
2. Identification of the patient population that was validated in the clinical testing;
3. A description of the clinical validation testing including summary of the clinical trial procedures, patient population, and results with confidence intervals. This summary includes prominent warnings regarding interpretation of the output as well as a representation of average error observed in the clinical data for various ranges of CRI measurement;
4. Guidance for interpretation of the CRI measurement, and clinical use considerations such as factors that affect the signals;
5. Identification of all limitations that were identified and included as part of the clinical study;
6. All applicable warnings and precautions regarding the CRI measurement and associated sensor and its operation, which include:
    a. Identification of data acquisition and clinical factors that may impact CRI results,
    b. Requirement to be used as an adjunct measurement to other clinical signs and symptoms as part of patient assessment;

RISKS TO HEALTH

Table 1 identifies the risks to health that may be associated with use of the adjunctive cardiovascular status indicator and the measures necessary to mitigate these risks.

Table 1– Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
Delayed or incorrect treatment due to erroneous output as a result of 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	Usability assessment Labeling

SPECIAL CONTROLS:

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

1. Software description and verification & validation based on comprehensive hazard analysis must be provided including:
    a. Full characterization of technical parameters of the software, including any proprietary algorithm(s);
    b. Description of the expected impact of all applicable sensor acquisition hardware characteristics on performance and any associated hardware specifications;
    c. Specification of acceptable incoming sensor data quality control measures; and
    d. Mitigation of impact of user error or failure of any subsystem components (signal detection and analysis, data display, and storage), on accuracy of patient reports.

2. Scientific justification for the validity of the status indicator algorithm(s) must be provided. Verification of algorithm calculations and validation testing of the algorithm using a separate data set separate from the training data must demonstrate the validity of modeling.

3. Usability assessment must be provided to demonstrate that risk of misinterpretation of the status indicator is appropriately mitigated.

4. Clinical data must be provided in support of the proposed intended use and include the following:
    a. Output measure(s) must be compared to an acceptable reference method to demonstrate that it/they represent(s) the predictive measure(s) that the device provides in an accurate and reproducible manner.
    b. The data set must be representative of the intended use population for the device. Any selection criteria or limitations of the samples must be fully described and justified.
    c. Agreement of the measure(s) with the reference measure(s) must be assessed across the full measurement range.
    d. Data must be provided within the clinical validation study or using equivalent datasets to demonstrate the consistency of the output and be representative of the

range of data sources and data quality likely to be encountered in the intended use population and relevant use conditions in the intended use environment.

5. Device labeling must include the following:
    a. The type of sensor data used, including specification of compatible sensors for data acquisition;
    b. A description of what the device measures and outputs to the user;
    c. Warnings identifying sensor reading acquisition factors that may impact measurement results;
    d. Guidance for interpretation of the measurements, including warning(s) specifying adjunctive use of the measurements;
    e. Key assumptions made in the calculation and determination of measurements;
    f. The measurement performance of the device for all presented parameters, with appropriate confidence intervals, and the supporting evidence for this performance; and
    g. A detailed description of the patients studied in the clinical validation (e.g., age, gender, race/ethnicity, clinical stability) as well as procedural details of the clinical study.

BENEFIT/RISK DETERMINATION

The primary risks associated with using the CipherOx CRI Tablet are a false or misinterpreted CRI output. In case of false positive, i.e., incorrectly low CRI value, the risk is unnecessary clinical interventions and mobilization of resources. In the case of a false negative, i.e., false high CRI value, the identification of unrecognized bleeding and resultant monitoring of patients at risk of impending hypotension due to blood loss could be delayed, which could lead to delay in treatment.

The probable benefits of the device are based on data collected in clinical studies as described above. The use of CipherOx CRI Tablet may provide adjunctive information to traditional vital sign monitoring about changes in blood volume and hemodynamic status. This may aid in the identification of unrecognized bleeding and monitoring of patients at risk of impending hypotension due to blood loss. The use of CipherOx CRI Tablet trending information may improve recognition of changes in patient status to allow clinical reassessment and more timely interventions as needed.

Patient Perspectives

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

Benefit/Risk Conclusion

In conclusion, given the available information the data supports that the use of CipherOx CRI Tablet as an adjunct to traditional vital signs monitoring will aid in the identification of unrecognized bleeding and monitoring of patients at risk of impending hypotension due to blood

loss in the population studied. The risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the CipherOx CRI Tablet is granted and the device is classified under the following:

Product Code: PPW
Device Type: Adjunctive cardiovascular status indicator
Class: II
Regulation: 21 CFR 870.2200