DE NOVO CLASSIFICATION REQUEST FOR THE COORAL SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Intraoral cooling device: An intraoral cooling device is a prescription device that is intended to cool the mouth for patients to reduce the likelihood of oral mucositis. The device consists of a removable mouthpiece that cools the oral mucosal surfaces.

NEW REGULATION NUMBER: 21 CFR 872.5590

CLASSIFICATION: Class II

PRODUCT CODE: QUA

BACKGROUND

DEVICE NAME: The Cooral System

SUBMISSION NUMBER: DEN210027

DATE OF DE NOVO: January 18, 2022

CONTACT: BrainCool AB
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INDICATIONS FOR USE

The Cooral Device is intended to cool the oral mucosa during chemotherapy treatments to reduce the likelihood and severity of chemotherapy induced Oral Mucositis in adult patients.

LIMITATIONS

Prescription use only.
The device is only to be used only on patients undergoing chemotherapy treatment.

Warnings

- The Cooral System is intended for single use only. After treatment, the complete Cooral Mouth device shall be disposed of per hospital regulations.
- Do not use any coolant fluid other than sterile water in the ECU 200..

- Do not use The Cooral System in the presence of flammable agents because an explosion and/or fire might result.
- Leakage test shall be performed if sanitization is performed.

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

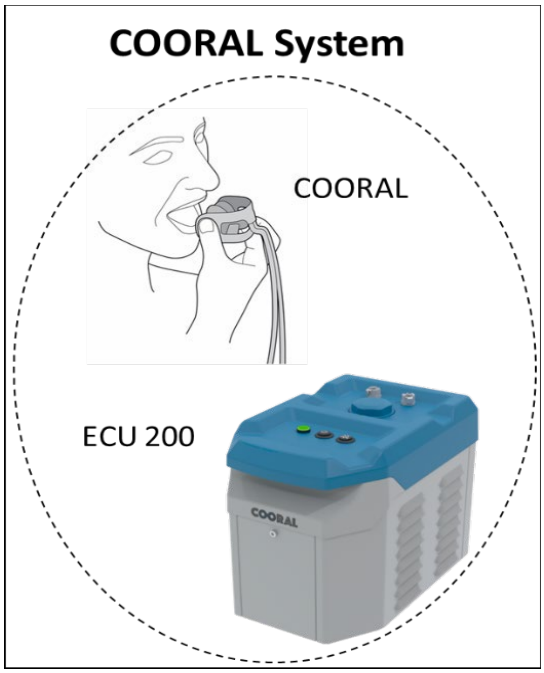
DEVICE DESCRIPTION

The Cooral System is an intraoral mouthpiece that cools the oral mucosa using a water coolant which circulates internally through the mouthpiece for patients undergoing chemotherapy treatment to reduce the likelihood and severity of oral mucositis. Oral mucositis is one of the most common, debilitating complications of cancer treatment. The device consists of an energy control unit with a computerized control system to which an intraoral mouthpiece is connected via plastic tubing. Liquid coolant (sterile water) is circulated from the tank through the plastic tubes of the intraoral mouthpiece and is designed to specifically cool the areas where the major arteries enter the oral cavity. The cooling is initiated 30 minutes prior to start of chemotherapy infusion and continues 30 minutes after termination of the infusion. The infusion time can vary between 15 min to 3 hours based on the half-life of the chemotherapeutics.

The Cooral System pushes temperature-controlled coolant which results in heat exchange between the Cooral System, and the patient's oral mucosa. The coolant temperature is controlled by a thermostat and its temperature probe. The Cooral System maintains a controlled coolant temperature at 8°C during the entire treatment period.
The device is intended to use is intended to reduce the severity and likelihood of oral mucositis in patients undergoing chemotherapy treatment. The device is a system made out of different components.

The device consists of three components:

1) Computerized Control System (ECU 200 - refrigeration and control unit)
2) Plastic tubing connecting the ECU to the mouthpiece
3) Intraoral Mouthpiece



SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The biocompatibility evaluation for The Cooral System was conducted in accordance with the International Standard ISO 10993-1 :2009 "*Biological Evaluation of Medical Devices Part-1: Evaluation and Testing Within a Risk Management Process.*" Assessment of the device included the following tests which were deemed acceptable according to the guidance acceptance criteria:

- Cytotoxicity (ISO 10993-5:2009)
- Sensitization Test (ISO 10993-10:2010)
- Intracutaneous Reactivity (ISO 10993-10:2010)

REPROCESSING/STERILITY

The Cooral System is not provided sterile and is not intended to be sterilized prior to use. The device is a single patient single use device (mouthpiece and tubing) and instructions have been provided to dispose of the mouthpiece and tubing portions of the device after each use. A validation of the sanitization procedure of the ECU 200 was conducted by placing a disinfectant in the coolant tank, letting it rest for 15 minutes, and then removing the disinfectant by flushing the tank with sterile water three times. The testing met the acceptance criteria of +/- 1% residual alcohol content..

ELECTROMAGNETIC COMPATIBILITY, WIRELESS AND ELECTRICAL SAFETY

The following testing standards were used to demonstrate the electrical safety for The Cooral System:

- IEC 60601-1 Part 1: General requirements for basic safety and essential performance
- IEC 60601-1-8 Collateral standard: General requirements, tests, and guidance for alarm systems in medical electrical equipment and medical electrical systems
- IEC 60601-1-2 Part1-2: General Requirements for Basic Safety and Essential Performance Collateral Standard: Electromagnetic Compatibility
- IEC 60601-1-2 Part1-2 US Voltage Collateral Standard: Electromagnetic Disturbances – Requirements and Tests
- IEC 60601-1-6 Medical Electrical Equipment Part 1-6 General Requirements for Safety – Collateral Standard: Usability

The following tests were conducted to support electrical safety of their system. These tests include:

- Power Input
- Leakage Currents and patient auxiliary currents
- Dielectric Strength
- Creepage distances and air clearances
- Single Fault Conditions
- Alarms
- Ingress Protection
- Excessive Temperatures
- Limitation of Voltage, Current and Power
- Expected Service Life of 5 years
- The equipment produces a sound level of maximum 60.4dBA and 69.7dBA during alarm condition.
- NiHM batteries used as backup, Battery pack certified to IEC 62133:2002.
- Power supply – an alarm is triggered if the power is cut.

Electromagnetic Compatibility (EMC) according to the Agency recognized standard IEC 60601-1-2:2014 was also conducted. The following tests were performed and passed:

- Electrostatic Discharge
- Radiate RF Electromagnetic Fields
- Electrical Fast Transients and Bursts
- Surges
- Conducted Disturbances, Induced by RF Fields
- Voltage Dips, Interruptions and Variations
- Power-Frequency Magnetic Field

SOFTWARE

The De Novo request provided adequate software documentation consistent with a "Moderate" level of software concern as discussed in the FDA Guidance Document "Guidance for the Content of Premarket Submissions for Software Contained in Medical

Devices," issued May 11, 2005.

Software validation and verification testing demonstrated that the device met its design, implementation, and cybersecurity requirements.

PHYSICAL PROPERTIES TESTING

The sponsor provided the following physical properties of the material as listed below:

Physical Properties	Method
Melt Flow Index	ISO 1133
Density	ISO 1183
Tensile Strength	ISO 527
Tensile Modulus	ISO 527
Elongation at Break	ISO 527
Shore Hardness	ISO 868

In addition, hose pull force, burst pressure, welding strength, and hose pull force destructive test was also performed.

THERMAL TESTING

Climactic testing was done according to IEC 60068-78:2013 for the ECU cooling tank for temperature and humidity for a duration of two hours at varying temperatures. No damage or deterioration was caused from the exposure.

Cooling distribution testing was also conducted to demonstrate temperature differences and the cooling distribution before using The Cooral System and after 60 minutes of use. Before and after imaging was provided.

SUMMARY OF CLINICAL INFORMATION

HUMAN FACTORS

A human factors assessment was conducted for The Cooral System and a Use Related Risk Analysis (URRA) was submitted in consideration of the FDA Guidance Document "*Applying Human Factors and Usability Engineering to Medical Devices*" issued February 3, 2016 and aligned with the IEC 62366-1 Usability Engineering Standard. The intended users for the testing were Registered Nurses (RNs) and Licensed Nurse Practitioners (LPNs) responsible for the patient during chemotherapy. The critical tasks included proper placement of The Cooral System within the oral cavity. A use-related risk analysis was provided to ensure that all potential risks involved in using the device for its intended use by its intended users in the intended use environments were considered and adequately mitigated. The use related risk analysis included analysis of

the risks of specific use errors related to the steps needed to successfully set up the device as follows:

- •Fill with the correct type of water
- •Place the device in the patient's mouth
- •Monitor that the device functions as needed during treatment

The residual risks were found to be acceptable in consideration of the prescription status of the device as well as the clinical data provided.

CLINICAL TESTING

Study Design: The study was conducted on patients who received myeloablative therapy prior to hematopoietic stem cell transplantation. The study was conducted in five hospital sites in Sweden where patients were randomized to ice or the Cooral System in a 1:1 proportion. The primary variable was analyzed in a multiple linear regression model and the significance level used was 5%.

Objective: To compare Cooral and ice cooling with regards to efficacy and tolerability.

The primary objective was to study patients with myeloma or lymphoma undergoing autologous hematopoietic stem cell transplantation (ASCT), to evaluate whether cooling with Cooral compared with ice cubes/crushed ice or ice pop succeeds in reducing the degree of oral mucositis (OM) according to the Oral Mucositis Assessment Scale, a validated assessment scale to measure oral mucositis (OMAS total). For OMAS, the degree of OM was assessed at eight intraoral locations, graded 0–3 for ulceration and 0–2 for erythema. Zero corresponded to 'normal' while 3 and 2 are 'sore >3 cm^2' and 'severe erythema,' respectively. The assessment generated both an average for OMAS ulceration (0–3) and OMAS erythema (0–2) and a total average OMAS (0–5), which was the mean of both ulceration and erythema. The study design also assessed subjective questionnaires including ratings of pain conducted with a Numeric Pain Rating by a treating nurse as well as assessing the tolerability of the cooling methods with the aid of a questionnaire to identify discomforts or side effects associated with the treatments. Patients assessed their perception of oral problems daily with the aid of specific questions in an online diary.

The secondary objectives were to evaluate OMAS total divided according to OMAS ulceration, OMAS erythema, degree of OM according to WHO, tolerability of either cooling method, subjective experience of OM, rating of general quality of life and oral pain, number of days with total parenteral nutrition (TPN), number of hospital days, total dose of opioids and C reactive protein (CRP) during time in care.

The tertiary objectives were to evaluate weight loss, leucocyte plasma concentration (LPC), number of days until bone marrow response, S-albumin and body temperature.

Trial Design: An open randomized controlled trial with blinded evaluation of OM of the dental staff in charge of assessing the oral mucositis and the statistician.

Eligibility criteria- Inclusion criteria

1. Patients aged 16 or over diagnosed with myeloma or lymphoma
2. Able to communicate in Swedish
3. Treated with melphalan (myeloma), BEAM/BEAC (lymphoma), before ASCT

Eligibility criteria- Exclusion criteria

1. Patients who do not understand oral and written information in Swedish
2. The patient is taking part in another study which, in the doctor's judgement, can affect the result of this study
3. The patient is receiving post-treatment care at a different hospital than where the stem cell transplant took place and follow-up is not possible
4. The doctor judges that the patient is for some reason not suitable for the study

Sample Size: A total of 183 participants were randomized to either Cooral Device (N=90) or Ice (N=93). Of those 183 participants, 26 were diagnosed with Lymphoma, and 157 with Myeloma.

Interventions - Ice: Patients were provided with ice cubes/crushed ice or ice pop 30 min prior to the start of chemotherapy. The procedure was repeated until 30 min after the termination of the cytostatic infusion.

Cooling continued throughout conditioning with cytostatics in the treatment schema melphalan (myeloma) and BEAM/BEAC (lymphoma). The patient was provided with ice cubes/crushed ice or ice pop for 30 min every 4 hours during the infusion. The patient ended with 30 min cooling of the oral mucous membrane after each completed cytostatic administration.

Interventions - Cooral: Prior to treatment, the patient received clear oral instructions and a demonstration on the use of Cooral. When the patient was able to administer the intraoral component until it felt comfortable, the device was checked to ensure that it has good contact with the oral mucosal membrane. Cooling began 30 min before the start of chemotherapy and continued until 30 min after the termination of the cytostatic infusion. The patient ended with 30 min cooling of the oral mucous membrane after each completed cytostatic administration.

Participant Timeline: Total cooling time for myeloma was 1.5 hours and for lymphoma was 3–6 hours. All patients were followed beginning at admission and continued until discharge or until day +28.

Blinding: The dental staff in charge of assessing OM and the statistician were blinded to the interventions. Data collection, management and analysis were done by two independent contract research organizations.

Results

Though not achieving statistical significance in the primary endpoint, the trial did point to a clinical benefit for use of The Cooral System in regards to tolerability of The Cooral System compared to ice chips. In addition, the use of The Cooral System reduced Oral Mucositis symptoms and occurrence in the subgroup of subjects undergoing lymphoma treatment as compared with ice chips. Based on the lymphoma subgroup results, subjects treated with The Cooral System experienced a statistically significant, higher percentage of freedom from severe OM which is represented by peak OMAS score of ≥3. Significant difference was found within the lymphoma subgroup between the ice chips (IC) and the Cooral (ICD) ($\bar{x}$ ± SD; 3.08 ± 1.50 for IC vs. 1.77 ± 1.59 for ICD; p=0.047). The corresponding figures for myeloma subgroup were ($\bar{x}$ ± SD; 0.92 ± 1.41 for IC vs. 0.85 ± 1.41 for ICD; p=0.734).

In terms of tolerability for the entire population in the group using The Cooral System, 5.0% (n = 4/80) reported discomfort, whereas the comparable score for the subjects randomized to IC was 16.1% (n = 14/87). This difference reached statistical significance (odds ratio (OR) = 0.274 [95% CI 0.086–0.873]; p = 0.028).

Table 1:

The results in Tables 1 below show comparable performance between the OMAS scores of The Cooral System as compared to Ice:

Difference in Peak OMAS Total Score Between Treatment Arms Full Analysis Set

Category	Coral Device (N=90)		Ice (N=93)
Peak OMAS Total Score			
N	84		88
mean	**0.988**		**1.239**
Std	1.4685		1.6117
median	0.000		0.000
Min	0.00		0.00
Max	5.00		5.00
Mean Difference		-0.251	
p-value		0.3518	

- Max=Maximum; Min=Minimum; OMAS=Oral Mucositis Assessment Scale; std=Standard Deviation. p-value computed using a Mann-Whitney U Test

Table 2:

The results in the Table 2 below shows less discomfort using The Cooral System as compared to ice:

Rate of Patients Reporting Discomfort by Treatment Arm Full Analysis Set

Category	Cooral Device (N=90)	Ice (N=93)
Patients who experienced discomfort, n/Nsub (%)	**4/80 (5.00)**	**14/87 (16.09)**
Odds Ratio	0.274	
Confidence Intervals	[0.086 - 0.873]	
p-value	**0.0285**	

- Note: n is the number of patients who experienced discomfort, i.e., reported the cooling of the oral mucosa as "rather painful" and "painful". Nsub is the number of patients who completed the assessment.
- Note: The odds ratio was computed using a logistic regression model using treatment arm and diagnosis as predictors.

Table 3

The results in the table below show a subset analysis of the lymphoma treatment group OMAS score as compared to ice:

Difference in Peak OMAS Score between Treatment Arms in Patients with Lymphoma Full Analysis Set

Category	Cooral Device (N=13)	Ice (N=13)
Peak OMAS Score		
n	13	13
mean	**1.769**	**3.077**
std	1.5892	1.4979
median	2.000	3.000
min	0.00	0.00
max	4.00	5.00
Mean Difference	-1.308	
p-value	**0.0499**	

Max=Maximum; Min=Minimum; OMAS=Oral Mucositis Assessment Scale; std=Standard Deviation. p-value computed using a Mann-Whitney U Test

Adverse Events

Table 1
Incidence of Adverse Events
Full Analysis Set

	Ice chips (N = 93)	Intraoral cooling device (ICD = 90)	All Participants (N=183)
Number Subjects Reporting Adverse Event (n) [%]			
Chills	24 [25.81%]	13 [14.44%]	37 [20.22%]
Numbness	9 [9.68%]	2 [2.22%]	11 [6.01%]
Bad taste	6 [6.45%]	2 [2.22%]	8 [4.37%]
Headache	2 [2.15%]	2 [2.22%]	4 [2.19%]
Teeth hypersensitivity	17 [18.28%]	5 [5.56%]	22 [12.02%]
Oral soreness	8 [8.60%]	5 [5.56%]	13 [7.10%]
Poor fit ICD	0 [-]	16 [17.78%]	16 [8.74%]
Nausea	11 [11.83%]	3 [3.33%]	14 [7.65%]
Vomiting sensation	5 [5.38%]	6 [6.67%]	11 [6.01%]
Difficulties swallowing	2 [2.15%]	16 [17.78%]	18 [9.84%]
Rubbing discomfort ICD	0 [-]	24 [26.67%]	24 [13.11%]
Other discomforts	12 [12.90%]	17 [18.89%]	29 [15.85%]

Table 2
Incidence of Serious Adverse Events
Full Analysis Set

	Ice chips (N = 93)	Intraoral cooling device (ICD = 90)	All Participants (N=183)
Number of Subjects Reporting Serious Adverse Events, (n) [%]			
No Subjects met this criteria	0 [-]	0 [-]	0 [-]

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 (User Instructions) meets the requirements of 21 CFR Part 801.109 for prescription devices.

The User Guide instructions for use includes the following:

a. Complete instructions on device components, set-up, use instructions, and cleaning
b. The User Profile is described as the following:
    - As a clinician/nurse who will be responsible for overseeing the device during patient use in a hospital or clinic setting
    - As patients who will be using the prescription device to assist in the reduction of the likelihood and severity of oral mucositis during chemotherapy treatment
c. Device specifications
d. Warnings and Cautions

e. A description of error messages and alarms

The following warnings and cautions are included in the IFU to advise the user on safe and appropriate use.

Warnings – The Cooral System should only be used:

- With the appropriate electrical outlet, voltage, and frequency
- After appropriate sanitation methods and leakage testing
- With sterile water as the coolant fluid

Cautions:

- The Cooral System should be used for single use for the mouthpiece and tubing. After treatment, the mouthpiece and tubing should be disposed of
- The coolant tank should be emptied after each treatment to avoid bacterial growth in the sterile water

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the intraoral cooling and the measures necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Thermal tissue damage	Non-clinical performance testing Software verification, validation & hazard analysis
Electrical shock, or device failure due to electromagnetic interference	Electromagnetic compatibility (EMC) testing Electrical safety testing
Adverse tissue reaction	Biocompatibility evaluation
Discomfort	Labeling
Obstruction or device leakage	Non-clinical performance testing

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the intraoral cooling device is subject to the following special controls:

(1) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use and must include:
   (i) Thermal testing to evaluate cooling consistency and performance; and
   (ii) Physical Testing of the device to demonstrate material integrity.

(2) Electromagnetic compatibility (EMC) and electrical safety testing must be performed for any electrical components.

(3) Software verification, validation, and hazard analysis must be performed for any software components of the device.

(4) The patient contacting components of the device must be demonstrated to be biocompatible.

(5) Labeling must include the following:

(i) A summary of the device specifications, including temperature cooling range and duration of cooling; and
(ii) Instructions to stop the use of the device if skin irritation or sensitivities develop, or if the device leaks or does not maintain its material integrity.

BENEFIT/RISK DETERMINATION

The known probable risks of the device are based on the data collected in the clinical study described above. The adverse events that occurred were temporary and had complete resolution. No device-related serious adverse events were observed. The device exhibited an acceptable safety profile in the clinical studies which were conducted.

The Cooral System consists of a mouthpiece, a cooling unit, and plastic tubing connecting the two. The mouthpiece and tubing is to be disposed of after each use. The device is to be prescribed and dispensed by a healthcare professional and to be used in a hospital or clinic setting. Risks of a harmful event would be related to improper use or device malfunction that may cause thermal tissue damage, electrical shock, or device discomfort during use. Of these risks, only device discomfort was seen in the clinical study. No serious adverse events such as thermal injury, electrical injury, adverse tissue reaction, or device failure were noted and the probability of these harmful events with the use of this device is low. Any adverse events reported were temporary and transient in nature. If patients cannot tolerate The Cooral System, they may simply remove it from their mouth and opt for traditional treatment methods such as use of ice chips which is the current standard of care.

The probable benefits of the device are also based on the data collected in the clinical study described above. The benefit of this device is that it provides patients with a more comfortable way to cool the oral mucosa when undergoing chemotherapy treatment as compared to cryotherapy (ice chips) and without the use of drugs. Study subjects found the device more comfortable and tolerable than the traditional cryotherapy standard of care and the device is easily placed and removed. The use of the device is overseen by a licensed professional during treatment, provides a consistent cooling temperature, and may have less potential for infection. Based on the study results, use of this device is likely to lead to a more comfortable and tolerable experience for patients undergoing chemotherapy treatment who are at risk of oral mucositis.

Patient Perspectives

The Cooral System offers patients the following advantages over palifermin, which is the only FDA approved drug for the management of treatment-induced oral mucositis in cancer patients. Palifermin is administered via intravenous bolus injection in a hospital setting three days before, and three days after chemotherapy treatments:

- The Cooral System offers patients a non-drug alternative with fewer side effects and no drug interactions.

- The Cooral System is administered concurrently with cancer therapy, which allows patients to avoid making additional hospital visits, whereas Palifermin requires additional hospital visits for the patient, as it cannot be administered within 24 hours of the actual chemotherapy process.

- The study design utilized ratings of pain conducted with a Numeric Pain Rating conducted with a nurse. Patients were also requested to access the tolerability of the cooling methods with the aid of a questionnaire to identify discomforts or side effects associated with the treatments. Patients assessed their perception of oral problems daily with the aid of specific questions in an online diary.

- The ease of use of the Cooral System may increase compliance and improve the patient experience due to increased tolerability, compliance, and consistency of dosing due to a standardized mouthpiece, temperature control, and device design.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data provide support for increased patient tolerability and comfort for patients at risk for oral mucositis through the use of The Cooral System. The data demonstrate that the probable benefits outweigh the probable risks for The Cooral System. The risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for The Cooral System is granted and the device is classified under the following:

Product Code: QUA
Device Type: Intraoral cooling device
Class: II
Regulation: 21 CFR 872.5590