DE NOVO CLASSIFICATION REQUEST FOR KERASAVE

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Corneal storage medium with preservatives including antifungals. Corneal storage medium with preservatives including antifungals is a device that is used to temporarily preserve human cornea tissue between harvesting and implantation.

NEW REGULATION NUMBER: 21 CFR 886.4320

CLASSIFICATION: Class II

PRODUCT CODE: QCW

BACKGROUND

DEVICE NAME: Kerasave

SUBMISSION NUMBER: DEN200063

DATE DE NOVO RECEIVED: November 10, 2020

SPONSOR INFORMATION:

AL.CHI.MI.A. S.r.l.
Viale Austria 14
Ponte San Nicolo, Province of Padua 35020
ITALY

INDICATIONS FOR USE

Kerasave is indicated for storage of human corneas at 2-8°C for up to 14 days. It is intended for prescription (Rx) use by physicians or highly skilled personnel, such as Eye Bank operators.

LIMITATIONS

The sale, distribution, and use of Kerasave are restricted to prescription use in accordance with 21 CFR 801.109.

Prior to distribution for surgical use, the cornea should be evaluated for suitable use as there may be reduced corneal clarity during storage due to the addition of Amphotericin B.

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

DEVICE DESCRIPTION

Kerasave is made of a buffered corneal storage medium, which provides basic nutrients for cell maintenance during storage of donor corneas at 2-8°C for up to 14 days, at physiological pH. The device also includes antimicrobial agents. The antibiotics are dissolved in the solution and an antifungal agent is formulated as a tablet for stability reason and constitutes integral part of the device; it shall be dissolved in the medium prior to use.

The product specifications and ingredients for the Kerasave are presented in Table 1 and Table 2, respectively, below.

Table 1: Kerasave product summary

Parameter	Product
Form	Liquid
Appearance	Clear orange-red solution
Volume/Weight	20 mL
Sterilization	Filtration
Contents	12 vials and 12 tablets of Amphotericin B
Storage temperature	2-8ºC
Shelf-life	24 months
Temperature of actual use	2-8 ºC
Use-life	14 days
Number of uses	Single-use

Table 2: Kerasave ingredients and their functions

Ingredient	Category	Function
(b)(4) and (b)(4) salt solution (including (b)(4) amino acids, (b)(4) and (b)(4)	Base medium	Provides basic nutrients for cell maintenance, maintains pH, and a color indicator for pH indication
Sodium bicarbonate	Buffer	Maintains pH
Gentamicin sulfate	Antibiotic	Reduces bacterial growth
Streptomycin sulfate	Antibiotic	Reduces bacterial growth
Amphotericin B	Antifungal	Reduces Fungal Growth
Dextran (b)(4)	Osmotic agent	Prevents swelling, preserves corneal thickness
Sodium pyruvate	ATP precursor	Provides energy for pumping function
(b)(4)		
(b)(4)		
(b)(4)		

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY

Kerasave is a surface device with prolonged (> (b) h to 30 days) contact with breached/compromised surface. The biocompatibility assessment summarized below in Table 3 was conducted in accordance with FDA's Biocompatibility Guidance Document titled "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process", as well as other relevant parts of standard ISO 10993- Biological evaluation of medical devices. This assessment demonstrated that the device is biocompatible for its intended use.

Table 3: Summary of Biocompatibility Assessment

Biocompatibility assessment	Assessment outcome
Cytotoxicity (MEM extraction method) (ISO 10993-5)	Non-cytotoxic
Sensitization (Guinea pig maximization test) (ISO 10993-10)	Non-sensitizer
Ocular irritation (ISO 10993-10)	Non-irritant
Acute systemic toxicity (FDA Biocompatibility Guidance)	Non-toxic
Material mediated pyrogenicity (FDA Biocompatibility Guidance)	Non-pyrogenic
Subacute/Subchronic systemic toxicity (FDA Biocompatibility Guidance)	Non-toxic
Biocompatibility Assessment of Primary Packaging (FDA Biocompatibility Guidance)	Biocompatible

CHEMICAL CHARACTERIZATION

Analysis of critical properties of Amphotericin B through chemical characterization were performed through multiple assessments. Identification by (b)(4) (b)(4) indicated that the Amphotericin B in Kerasave is the same as the reference Amphotericin B CRS (Chemical Reference Substance). Further testing of the Amphotericin B tablet included an impurity profile that met limits based on US Pharmacopeia (UP) and European Pharmacopoeia; a heavy metals tests that met the acceptance criterion of (b)ppm, and a light degradation assessment which demonstrated that the Amphotericin B concentration was above (b)% after (b) hours of light exposure and indicated Amphotericin B was stable after (b)(hours of light exposure. Testing performed after dissolution of the tablet in solution indicated that there was a uniform distribution of the Amphotericin B and that the osmolality and pH stayed within acceptance limits 14 days after dissolving amphotericin B tablet in the solution.

SHELF-LIFE/STERILITY

Device sterility is achieved using multiple methods of sterilization, including filter sterilization of the corneal storage medium, a combination of dry heat and gamma irradiation of the device primary packaging, and gamma irradiation of the Amphotericin B tablets. The dry heat and gamma irradiation sterilization methods were demonstrated to achieve a Sterility Assurance Level of 10^{-6} (e.g., a reduction of at least 10^{6} microorganisms). The filter sterilization method was validated to reproducibly remove viable microorganisms from the aseptic manufacturing process. Bacterial endotoxin testing demonstrated levels below recommended limits.

A shelf-life of 24 months has been established for Kerasave corneal storage media when stored at the recommended storage temperature of 2-8°C in its primary packaging. A shelf-life of (b)(months has been established for Amphotericin B tablets when stored at the recommended storage temperature of 4°C in its primary packaging. These claims are supported by demonstration of Kerasave corneal storage media and Amphotericin B tablet sterility and stability in both real-time and accelerated aging studies, as well as after short term storage at high temperatures.

Relevant standards followed include: Sterilizing Filtration of Liquids (PDA TR 26-2008-), Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration (ASTM F838)-, Sterilization of health care products (ISO 11137-1 and ISO 11137-2, and ISO 20857), Bacterial Endotoxins (USP<85>).

PERFORMANCE TESTING - BENCH

The performance characteristics of Kerasave were assessed to ensure that the cornea was preserved while in storage. The assessment for the preservation of the cornea included the viability of the endothelial cell layer, corneal clarity, and cornea central thickness.

CORNEAL ENDOTHELIAL CELL LAYER PRESERVATION

The performance characteristics of Kerasave were assessed in comparison with Optisol-GS, a US FDA-cleared corneal storage medium as control in preserving the corneal endothelial cell layer using a Konan specular microscope. The specular microscopy outcomes measured were:

- Endothelial cell density (ECD)
- Endothelial cell morphology (pleomorphism): Hexagonality (HEX)
- Endothelial cell morphology (polymegathism): Coefficient of variation (%CV)

Twenty-seven (27) paired donor corneas were included in the study. For each paired corneas, one cornea was stored in Kerasave and the contralateral cornea in Optisol-GS. Tissue and media assignments were performed randomly. The storage was performed at 2-8°C for 14 days and each cornea was tested at Day 1 and Day 14. The study demonstrated that, using a (b)(4)% non-inferiority margin, the corneas stored in Kerasave were non-inferior to those stored in Optisol-GS at Day 14 in terms of ECD (Table 4) and HEX (Table 5). The study failed to statistically clear the (b)(4)% non-inferiority margin between Kerasave and Optisol-GS at Day 14 in terms of %CV (Table 6). However, an exploratory analysis that excluded an outlier datapoint (CV%=(b)(4)) for Kerasave (identified as a protocol deviation), showed that Kerasave was non-inferior to the Optisol-GS in terms of Coefficient of variation (Table 7).

Table 4: Endothelial Cell Density (ECD) Results Obtained in Corneas Stored in Kerasave or Optisol-Gs at Day 1 and Day 14

	Kerasave		Optisol-GS	
	ECD Day 1	ECD Day 14	ECD Day 1	ECD Day 14
Mean (cells/mm)	(b)(4)			
SD (cells/mm)				
Median (cells/mm)				
Minimum (cells/mm)				
Maximum(cells/mm)				
Coefficient of variation (%)				
d, non-inferiority limit (10% of the mean ECD in Optisol-GS day 14)				
The null hypothesis μs: the mean Optisol-GS treatment μe: the mean Kerasave treatment				
Alternative hypothesis				
Statistical analysis and conclusion				

Table 5: Pleomorphism (hexagonality, HEX) results obtained in corneas stored in Kerasave or Optisol-Gs at Day 1 and Day 14 of storage

	Kerasave		Optisol-GS	
	HEX Day 1	**HEX Day 14**	**HEX Day 1**	**HEX Day 14**
Mean	(b)(4)			
SD				
Median				
Minimum				
Maximum				
Coefficient of variation (%)				
d, non-inferiority limit (10% of the mean HEX in Optisol- GS day 14)				
Null hypothesis μs: the mean Optisol-GS treatment μe: the mean Kerasave treatment				
Alternative hypothesis				
Statistical analysis and conclusion				

Table 6: Statistical evaluation of polymegathism (%CV) results based on pre-specified analysis obtained in corneas stored in Kerasave or Optisol-Gs at Day 1 and Day 14 of storage

	Kerasave		Optisol-GS	
	Day 1	Day 14	Day 1	Day 14
Mean	(b)(4)			
SD				
Median				
Minimum				
Maximum				
Coefficient of variation				
d, non-inferiority limit (10% of the mean CV% in Optisol- GS day 14)				
Null hypothesis μs: the mean Optisol-GS treatment μe: the mean Kerasave treatment				
Alternative hypothesis				
Statistical analysis and conclusion				

Table 7: Exploratory Analysis of polymegathism (%CV) results obtained in corneas stored in Kerasave or Optisol-Gs at Day 1 and Day 14 of storage

	Kerasave		Optisol-GS	
	Day 1	Day 14	Day 1	Day 14
Mean	(b)(4)			
SD				
Median				
Minimum				
Maximum				
Coefficient of variation				
d, non-inferiority limit (10% of the mean CV% in Optisol- GS day 14)				
Exploratory analysis μs: the mean Optisol-GS treatment μe: the mean Kerasave treatment				

EVALUATION OF PERFORMANCE CHARACTERISTICS ON CORNEA

Corneal clarity and central corneal thickness (CCT) were evaluated at Day 1 and Day 14. The 27 paired donor corneas used in the specular microscopy measurements were also used to determine the CCT and corneal clarity through optical coherence

tomography and slit lamp examination, respectively. The results demonstrated that the CCT changes were similar between the Kerasave and Optisol-GS arms and had no statistical difference (Table 8).

Table 8: Statistical evaluation of Corneal central thickness (CCT) by OCT obtained in corneas stored in Kerasave or Optisol-GS at Day 1 and Day 14 of storage

	Kerasave			Optisol-GS		
	CCT Day 1	CCT Day 14	Change in CCT (Day14 - Day1)	CCT Day 1	CCT Day 14	Change in CCT (Day14 - Day1)
Mean (µm)	(b)(4)					
SD (µm)						
Median (µm)						
Minimum (µm)						
Maximum (µm)						
Coefficient of variation(%)						
p value (Kerasave vs Optisol-GS)						

In the assessment for corneal clarity, a statistical difference was not observed for the clarity scores on the Day 14 between Kerasave and the comparator arm, Optisol-GS (Table 9). It should be noted that Kerasave had 7 out of the 27 corneas that progressed from a score of '1' (mild) on Day 1 to a score of '2' (moderate) on Day 14 demonstrating an increase in opacity. Whereas the control arm had 2 out of 27 corneas that had increased opacity from Day 1 to Day 14. Additionally, increased edema and fold/striae were observed in the corneas that progressed.

Table 9: Statistical evaluation of corneal transparency scores obtained in corneas stored in Kerasave or Optisol- GS at Day 1 and Day 14 of storage

	Transparency score Kerasave		Transparency score Optisol-GS	
	Day 1	Day 14	Day 1	Day 14
Median	(b)(4)			
Minimum				
Maximum				
p value[1] (Kerasave vs Optisol-GS)				

[1]Day 1 (p=1.0000, Mann-Whitney test) and Day 14 (p=0.1651, Mann-Whitney test)

ANTIMICROBIAL EVALUATION

An analysis of antimicrobial presence and activity were provided. FDA determined that the concentrations of streptomycin, gentamicin, and Amphotericin B in the Kerasave device were unlikely to contribute to antimicrobial resistance emergence, or the spread of resistant microorganisms.

Ex-vivo testing and preservative testing were provided to evaluate effectiveness of the instructions for use in reducing antimicrobial presence prior to implantation to reduce unnecessary exposure, as well as the antimicrobial effectiveness of the antimicrobial components of the device, respectively.

EX VIVO TESTING

Assessment of Amphotericin B accumulation on the cornea grafts was performed to determine the residual concentration of the antifungal after storage. (b)(4) corneal grafts (n=(b)) were stored in Kerasave device at 2-8°C for 14 days. The grafts (with or without rinsing in (b)(mL of (b)(4)) were (b)(4) and evaluated by (b)(4)) for the presence of Amphotericin B. Amphotericin B was below detection limit in rinsed corneas and between (b)(4) - (b)(4) mg/cornea in corneas that were not rinsed.

PRESERVATIVE TESTING

Kerasave with streptomycin and gentamicin (antibacterials) and Amphotericin B (antifungal) were tested at appropriate concentrations in the final solution. Testing was conducted to evaluate the microbial log reduction of laboratory strains, specifically (b)(4) , (b)(4) (b)(4) and (b)(4) (b)(4)) after incubation in Kerasave. Testing was performed at (b)(4) (e.g., the temperature range for product storage), and conducted in accordance with standard ISO 18259 (Contact lens care products). (b)(4) in the device arm was compared to microbial growth the control arm, which involved (b)(4) (b)(4) . The results indicate that the combination of streptomycin and gentamicin in Kerasave inhibited the growth of all (b)(4) tested in comparison to the respective controls and reduced the number of (b)(4) with known susceptibility. With the addition of Amphotericin B to the storage solution, the (b)(4) (b)(4) population was reduced by (b)(4) (+/- SE), while the spore-forming filamentous fungi (*Fusarium* sp.) population was reduced by (-log (+/- SE). These results demonstrate that the device adequately inhibited the growth of laboratory microorganisms over the 14-Day storage time.

LABELING

Device labeling satisfies the requirements of 21 CFR § 801.109 for prescription devices. The device labeling provides product description, Indications for Use, and instructions for how to use the device by the end user. The labeling also provides a summary of the cornea viability after storage. The labeling includes warnings and precautions describing limitations and risks of the device.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of corneal storage medium with preservatives including antifungals and the measures necessary to mitigate these risks.

Table 10: Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Infection	Sterilization validation Non-clinical performance testing Labeling Shelf life testing
Adverse tissue reaction	Biocompatibility evaluation Non-clinical performance testing
Antimicrobial resistance	Antimicrobial resistance analysis Non-clinical performance testing Labeling
Worsening prognosis that may need recurring or more invasive surgery due to damage to cornea tissue while in storage	Non-clinical performance testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the corneal storage medium with preservatives including antifungals 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.

(i) The following performance characteristics of the cornea following storage in the device must be demonstrated:

(A) Endothelial cell density;

(B) Endothelial cell morphology;

(C) Corneal transparency; and

(D) Central corneal thickness.

(ii) Antimicrobial activity of the device must be demonstrated at the initial and maximum labeled storage time.

(iii) Characterization of all preservatives, including antifungals, must include the following:

(A) Characterization of impurities, heavy metal analysis, concentration, and dissolution; and

(B) Chemical activity of all preservatives over the labeled use life of the device.

(2) Performance data must demonstrate the sterility of the device.

(3) The device must be demonstrated to be biocompatible and non-pyrogenic.

(4) Performance data must support the claimed shelf life by demonstrating continued sterility, controlled bioburden, package integrity, and device functionality over the intended shelf life.

(5) The device and each of its components (e.g., antifungal, antibiotic, medium) must be demonstrated to be compatible with their respective commercial container closure system/packaging.

(6) An analysis must be provided that identifies and evaluates any contribution to the development and spread of antimicrobial resistance.

(7) Labeling must include the following instructions:

(i) Rinsing of cornea prior to transplantation; and

(ii) Complete dissolution of all preservatives.

BENEFIT-RISK DETERMINATION

The risks of the device are based on the non-clinical performance testing data collected. The data demonstrated that corneal clarity decreased with increased edema and folds/striae in some of the corneas stored in the device for 14 days. Device labeling will help ensure that the end users clearly understand the device description, indications, contraindications, precautions, warnings, and instructions for use. Specifically, the device labeling informs the end user to check the suitability of the cornea prior to distribution.

The probable benefits of the device are based on the non-clinical performance testing data collected. The non-clinical study demonstrated inhibition in the growth of microbials in the presence of preservatives, including an antifungal in the device. The endothelial cell layer was preserved in the corneas stored in the device for 14 days.

Although it is unknown whether reduced corneal clarity may occur after transplantation, the overall probable benefits of limiting infection of the cornea tissue stored in the device that includes an antifungal agent to minimize microbial growth outweighs the probable risks of decreased corneal clarity.

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.

Patient Perspectives

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

BENEFIT/RISK CONCLUSION

In conclusion, given the available information above, for the following indication statement:

> Kerasave is indicated for storage of human corneas at 2-8°C for up to 14 days. It is intended for prescription (Rx) use by physicians or highly skilled personnel, such as Eye Bank operators.

The probable benefits outweigh the probable risks for the Kerasave device. 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 Kerasave is granted and the device is classified as follows:

> Product Code: QCW
> Device Type: Corneal storage medium with preservatives including antifungals
> Regulation Number: 21 CFR 886.4320
> Class: II