DE NOVO CLASSIFICATION REQUEST FOR ELEOSx™ LIMB SALVAGE SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Limb and joint salvage device with quaternary ammonium compound coating. A limb and joint salvage device with quaternary ammonium compound coating is a metallic implant with or without polymer bearing for bone and joint replacement. Implants are for resection and replacement of an extremity bone (including the entire bone, epiphyseal bone, metaphyseal bone, or diaphyseal bone), or an extremity bone and the surrounding joint(s) in a skeletally mature patient. The device includes a quaternary ammonium compound coating that is covalently bonded to the device. Where applied, the coating is intended to reduce microbial contamination on the surface of the device prior to implantation. The device does not contain antimicrobial agents that act within or on the body and this device type does not include combination products.

NEW REGULATION NUMBER: 21 CFR 888.3900

CLASSIFICATION: Class II

PRODUCT CODE: QZZ

BACKGROUND

DEVICE NAME: ELEOSx™ Limb Salvage System

SUBMISSION NUMBER: DEN210058

DATE DE NOVO RECEIVED: January 4, 2022

SPONSOR INFORMATION:

Onkos Surgical
77 East Halsey Rd
Parsippany, NJ 07054

INDICATIONS FOR USE

The ELEOS™/ELEOSx™ Limb Salvage System is indicated for resection and replacement of the proximal femur, intercalary portion of the femur, total femur, distal femur, and proximal tibia in skeletally mature patients with the following conditions:
1) Non-inflammatory degenerative joint disease such as osteoarthritis, traumatic arthritis, avascular necrosis, ankylosis, protrusion acetabuli, and painful hip dysplasia;
2) Inflammatory degenerative joint disease such as rheumatoid arthritis;
3) Correction of functional deformity

4) Revision procedures where other treatments or devices have failed; and,
5) Treatment of fractures that are unmanageable using other techniques.

The ELEOS™/ELEOSx™ Limb Salvage System is also indicated for procedures where resection and replacement of the proximal femur, intercalary portion of the femur, total femur, distal femur, and proximal tibia is required with the following conditions:
1) Patients suffering from severe arthropathy of the hip and/or knee that does not respond to any conservative therapy or better alternative surgical treatment;
2) Surgical intervention for severe trauma, revision hip or knee arthroplasties, and/or Oncology indications.
3) Metastatic diseases

The ELEOSx™ MDPB coating, where applied, is intended to reduce bacterial contamination prior to implantation resulting from deposition in the operating room on the surface of the device components. The clinical impact associated with the MDPB coating, including prevention of infection or reduction of infection risk in patients, has not been evaluated in human clinical trials. The MDPB coating is not intended to treat existing infections and does not act within or on the body.

LIMITATIONS

The sale, distribution, and use of the ELEOSx™ Limb Salvage System are restricted to prescription use in accordance with 21 CFR 801.109.

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

DEVICE DESCRIPTION

Implant Description

The Onkos Surgical ELEOSx™ Limb Salvage System consists of components that are used in the reconstruction of the lower limb. The systems include components manufactured from cobalt-chrome alloy (CoCr), titanium alloy (TAV), and ultra-high molecular weight polyethylene (UHMWPE). Non-articulating CoCr component surfaces are coated with 12-Methacryloyloxydodecyl Pyridinium Bromide (MDPB), which is intended to reduce bacterial contamination on the surface of the device components prior to implantation resulting from deposition in the operating room. Based on in vitro testing, this coating may result in immobilization and/or lysis of some challenge organisms. The MDPB coated CoCr stems are for cemented use in the reconstruction/replacement of the lower limb. The reconstruction applications are proximal femur, intercalary portion of the femur, distal femur, total femur, proximal tibia, and hinged knee. The ELEOS™ Limb Salvage components are femoral head, proximal femur, female stem, mid-section, stem, distal femur, tibial hinge component, axial pin, tibial poly spacer, tibial baseplate, male-male mid-section, resurfacing femur, proximal tibia, tapered screws, patella, stem

extension, tibial wedges, and augments.

Proximal Femur	Intercalary	Distal Femur	Total Femur	Proximal Tibia	Hinged Knee
					

Components	Material	Reconstruction Applications and Assemblies					
		Proximal Femur	Intercalary	Distal Femur	Total Femur	Proximal Tibia	Hinged Knee
Femoral head	CoCr	X			X		
Proximal Femur	TAV	X			X		
Female Stem[2]	CoCr		X				
Mid-Section[2]	CoCr	X	X	X	X	X	
Segmental Stem[2]	CoCr or TAV	X	X	X		X	
Modular Collar	TAV	X		X		X	
Distal Femur	CoCr			X	X		
Tibial Hinge Component	CoCr and UHWMPE			X	X	X	X
Axial Pin	CoCr and UHWMPE			X	X	X	X
Tibial Poly Spacer	UHWMPE			X	X	X	X
Tibial Baseplate	TAV			X	X		X
Male-Male Mid-Section[2]	CoCr or TAV				X		
Resurfacing Femur	CoCr					X	X
Proximal Tibia	TAV					X	
Tapered Screw[1]	TAV			X	X	X	X
Patella[1]	UHWMPE			X	X	X	X
Wedges and Augments[1]	TAV			X	X		X
Stem Extensions[1]	TAV			X	X	X	X

1 - These implants are optional for each procedure. The surgeon shall use his/her medical judgement to determine if these implants are necessary based on factor such as patient bone quality, joint stability, and pathology.

2 - These implants are available with the ELEOSx™ antibacterial coating (MDPB).

Instrument Description

Instruments included in the Onkos ELEOSx™ Limb Salvage System are used in implantation and removal of the system components.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The non-articulating CoCr alloy components of the Onkos ELEOSx™ Limb Salvage System include a MDPB surface coating.

Biocompatibility evaluation of the subject implant device has been completed according

to FDA's Guidance, "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.'" Biocompatibility testing for the permanent implant included cytotoxicity (ISO 10993-5), intracutaneous reactivity (ISO 10993-10), sensitization (ISO 10993-10), material-mediated pyrogenicity (ISO 10993-11), acute systemic toxicity (ISO 10993-11), genotoxicity (ISO 10993-3; bacterial reverse mutation assay, mouse lymphoma assay). All test methods and results were found acceptable.

A 52-week ovine study was conducted to evaluate systemic toxicity per ISO 10993-11:2017 and local implantation per ISO 10993-6:2016. An additional 13-week rabbit study was conducted (intramuscular and epicondylar) to supplement the ovine study and address local implantation per ISO 10993-6:2016. The totality of the implantation data supports that the test articles did not produce systemic toxicological effects and resulted in minimal local tissue reactivity, similar to the control article (uncoated metal).

Chemical characterization with exhaustive extraction in polar (neutral pH of 7 and acidic pH of 4), mid-polar, non-polar conditions was performed per ISO 10993-18 with toxicological risk assessment per ISO 10993-17 to evaluate the reported extractables.

The Ti6Al4V (TAV) and UHMWPE components (without MDPB coating) were adequately evaluated for biocompatibility in prior marketing submissions.

The instruments included in the Onkos ELEOSx™ Limb Salvage System are made from various materials with limited (≤ 24h) contact to tissue/bone. The instruments were adequately evaluated for biocompatibility in prior marketing submissions.

STERILIZATION/PACKAGING AND SHELF-LIFE/PYROGENICITY

Sterilization

The ELEOSx™ Limb Salvage System is a single-use device provided clean and sterile to the end user. Gamma sterilization of the device has been validated to provide a Sterility Assurance Level (SAL) of 10^{-6} based on the VDMax^{25} method as recommended by FDA Recognized Consensus Standard series ANSI/AAMI/ISO 11137-1 ("Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices")/-2 ("Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose").

Packaging and Shelf-life

Implants are packaged within a (b)(4) mil urethane sleeve, followed by an inner nylon/(b)(4) pouch, an outer nylon/(b)(4) pouch, a retention insert, and a shrink-wrapped shelf box. Non-clinical performance testing established a shelf-life of 3 months. Antibacterial performance testing supported device performance over the proposed shelf-life. Packaging was validated using ANSI/AAMI/ISO 11607-1 ("Packaging for terminally

sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems").

Pyrogenicity

Bacterial endotoxins testing (BET) was performed to determine whether the total endotoxin value for the device met pyrogen limit specifications. All tested devices passed with a reported value of less than or equal to 20 EU/device, meeting the recommended endotoxin limits per ANSI/AAMI ST72:2019 ("Bacterial endotoxins - Test methods, routine monitoring, and alternatives to batch testing").

PERFORMANCE TESTING – BENCH

Some previous device information and performance data for the uncoated implant configurations are considered to demonstrate acceptable device-specific performance due to insignificant effect of the MDPB coating on those construct mechanical tests. A summary of those special control performance data, including evaluation of static and dynamic strength, range of motion, articulating bearing wear and bearing material, and implant disassembly as well as validation information for the reprocessing instructions for the reusable instrumentation of the device is identified in Onkos's cleared marketing applications (K211677, K203815, K203588, K203090, K180130, K161520). Additional non-clinical performance testing is provided to address the device performance due to the addition of the MDPB coating and a summary of these additional non-clinical mechanical performance evaluations is provided in **Table 1:**

Table 1: Summary of Non-clinical Mechanical Performance Evaluations

Test	Purpose	Method	Performance Criteria	Results
Evaluation of MDPB Coating Integrity	To demonstrate that MDPB coating does not shear off or delaminate from the subject device through handling and implantation.	Follow the surgical technique protocol for proximal femoral replacement, and verify pre-assembly and post-assembly, using optical microscopy, that the MDPB coating remains intact on the device.	N/A – this is a characterization of the effect of surgical assembly on the MDPB-coated device.	No evidence of damage or removal of the MDPB coating from the device observed.
Range of Motion (ROM)	To assess the risk of MDPB coating contact with any of the ELEOSx system articulating surfaces.	Computer simulated hip and knee joint movement performed throughout entire ROM until impingement contact.	No impingement contact of MDPB-coated components.	No contact with MDPB-coated components under maximum ROM; ROM equivalent to the currently available non-MDPB coated limb salvage device.

Cement interface Pull-out	To evaluate the pull-out strength of the stem/cement interface	Stems were inserted into cylinders surrounded by bone cement. Once cured, stems were pulled axially until failure.	MDPB-coated group to have equivalent or higher pull-out strength compared to un-coated group.	MDPB-coated group had higher pull-out strength compared to un-coated group.
Fretting and Corrosion	To demonstrate that the addition of the MDPB coating does not compromise the mechanical integrity of the limb salvage assembly.	Proximal femurs (with maximum mid-section modularity) were distally potted and proximally loaded. The device was fatigue tested in saline at (b)(4) N for (b)(4) cycles at a frequency of (b)(4) Hz. Components were optically inspected for fretting and corrosion damage after testing.	The MDPB-coated proximal femurs to have comparable performance to the control device (un-coated proximal femurs).	Similar fretting corrosion was observed in the MDPB-coated proximal femurs and the controls.

Antimicrobial Performance

The subject device's MDPB coating was evaluated for its antimicrobial performance based on a simulated use *in vitro* test method that demonstrated antibacterial activity. The subject device's MDPB coating was also evaluated for its antimicrobial resistance risk profile.

Information was provided establishing reasonable evidence to support the understanding that the antimicrobial action of the MDPB coating is neutralized in the body and would not be expected to have meaningful antimicrobial activity within or on the body following implantation.

MDPB Coating Physicochemical Characterization

The subject device's MDPB coating was characterized and evaluated for assessment of coating physicochemical properties such as coating chemistry, thickness, density, and uniformity. Information to establish these characteristics included a detailed description of the substrate morphology and coating process, a validated fluorescein method to determine the MDPB coating density on the surface of the subject device, micro-imaging and spectroscopy techniques to determine the coating thickness and elemental compositions, appropriate visual inspections to demonstrate sufficient uniformity of the MDPB coating on the surface of the subject device, and a final product release strategy containing appropriately established product specification and sampling plan. The sponsor demonstrated that the biocompatibility and antibacterial performance testing are representative of worst-case performance of the subject device based on the coating characterization.

LABELING

The labeling consists of the following: device description, indications for use, instructions for use including surgical steps (e.g., device selection and placement), principles of device operation, identification of device materials, contraindications, warnings, precautions, and a list of potential adverse effects. Furthermore, the sterile packaging includes a shelf-life for the device. The labeling meets the requirements of 21 CFR 801.109 for prescription devices.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a limb and joint salvage device with quaternary ammonium compound coating and the measures necessary to mitigate these risks.

Risks to Health	Mitigation Measures
Antimicrobial resistance	Antimicrobial resistance analysis
Loss of implant integrity and function leading to revision	Non-clinical performance testing Shelf life testing Labeling
Adverse tissue reaction	Animal performance testing Biocompatibility evaluation Non-clinical performance testing Pyrogenicity testing
Infection	Non-clinical performance testing Sterilization validation Shelf life testing Reprocessing validation Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the limb and joint salvage device with quaternary ammonium compound coating is subject to the following special controls:

(1) Animal performance testing must demonstrate that the device performs as intended under anticipated conditions of use. Animal testing must include imaging, histology, and histomorphometry to assess bone formation, healing, and tissue response at relevant timepoints over the course of healing.

(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use and include the following:
   (i) Evaluation of the static and dynamic performance of the implant;
   (ii) Evaluation of coated implant initial fixation;
   (iii) Evaluation of coating integrity;
   (iv) Evaluation of range of motion;
   (v) Evaluation of articulating bearing wear and bearing material;

(vi) Evaluation of implant disassembly;
(vii) Evaluation of fretting and corrosion;
(viii) Evaluation of antimicrobial performance with clinically relevant microbial species; and
(ix) Coating characterization, including a detailed description of the substrate morphology and coating process and an evaluation of coating physicochemical properties such as density, thickness, chemistry, and uniformity.

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

(4) An analysis or information must be provided to support that the antimicrobial does not act within or on the body.

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

(6) Performance data must support the sterility and pyrogenicity of the device components intended to be provided sterile.

(7) Performance data must validate the reprocessing instructions for the reusable instrumentation to be used with the device.

(8) Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

(9) Labeling must include the following:
(i) Identification of device materials;
(ii) A shelf life; and
(iii) Instructions for removal/revision procedures.

BENEFIT-RISK DETERMINATION

The target populations for the ELEOSx™ Limb Salvage System are high-risk patients due to associated medical co-morbidities, the magnitude of the types of surgical procedures, and the high risk of device-related and procedure-related adverse events including infection.

The sponsor has collected adequate data to assess the safety profile of the subject device and has identified that there are benefits from the use of the device. Mechanical evaluations demonstrated restoration of function, while the antimicrobial performance testing demonstrated a reduction of *in vitro* bacterial contamination. The risks to health, which include antimicrobial resistance, loss of implant integrity and function leading to revision, adverse tissue reaction, and infection have been mitigated by an animal safety study and other non-clinical studies as described above. A list of warnings and potential adverse effects is provided in the labeling. In conclusion, the benefits of using the subject device for its intended use/indications for use outweigh the risks to health.

Benefits: The probable benefits of the subject device with the MDPB coating, as demonstrated by the non-clinical evaluations described above, include limb salvage and restoration of function, and reduced bacterial contamination on the surface of the device prior to implantation in a high-risk patient group.

Risks: The risks of the subject device, as listed in the Risks to Health section above, are antimicrobial resistance, loss of implant integrity and function leading to revision, adverse tissue reaction, and infection. These risks have been mitigated by the listed Mitigation Measures above, which include non-clinical performance testing, biocompatibility evaluation, pyrogenicity testing, sterilization validation, shelf-life validation, reprocessing validation, and labeling.

To address potential safety concerns related to the MDPB coating stability and effect in humans, a 522 Order for a Postmarket Surveillance Study will be issued for this device.

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:

> The ELEOS™/ELEOSx™ Limb Salvage System is indicated for resection and replacement of the proximal femur, intercalary portion of the femur, total femur, distal femur, and proximal tibia in skeletally mature patients with the following conditions:
> 1) Non-inflammatory degenerative joint disease such as osteoarthritis, traumatic arthritis, avascular necrosis, ankylosis, protrusion acetabuli, and painful hip dysplasia;
> 2) Inflammatory degenerative joint disease such as rheumatoid arthritis;
> 3) Correction of functional deformity
> 4) Revision procedures where other treatments or devices have failed; and,
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> The ELEOS™/ELEOSx™ Limb Salvage System is also indicated for procedures where resection and replacement of the proximal femur, intercalary portion of the femur, total femur, distal femur, and proximal tibia is required with the following conditions:
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> The ELEOSx™ MDPB coating, where applied, is intended to reduce bacterial contamination prior to implantation resulting from deposition in the operating room on the surface of the device components. The clinical impact associated with the MDPB coating, including prevention of infection or reduction of infection risk in patients, has

not been evaluated in human clinical trials. The MDPB coating is not intended to treat existing infections and does not act within or on the body.

The probable benefits outweigh the probable risks for the ELEOSx™ Limb Salvage System. 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 Onkos Surgical ELEOSx™ Limb Salvage System is granted and the device is classified as follows:

Product Code: QZZ
Device Type: Limb and joint salvage device with quaternary ammonium compound coating
Regulation Number: 21 CFR 888.3900
Class: II