K994137

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510(k) SUMMARY OF SAFETY AND EFFECTIVENESS
ATRISORB®-D FreeFlow™ Bioabsorbable Guided Tissue Regeneration (GTR) Barrier with 4% Doxycycline

1 General Information

Manufacturer:	Atrix Laboratories, Inc. 2579 Midpoint Drive Fort Collins, CO 80525 Telephone: (970) 482 - 5868 Fax: (970) 482 - 9735
Contact:	Amy Taylor Regulatory Affairs Manager
Date Prepared:	December 3, 1999
Proprietary Name:	ATRISORB®-D FreeFlow™ Bioabsorbable Guided Tissue Regeneration (GTR) Barrier with 4% Doxycycline
Common Name:	Bioabsorbable Guided Tissue Regeneration Barrier with Doxycycline
Classification Name:	Bone Filling Augmentation Material
510(k) Clearance Number:	K_____
Predicate Device:	ATRISORB® Bioabsorbable Guided Tissue Regeneration (GTR) Barrier K955838 and K982865

2 Device Description

2.1 Formulation

The polymer formulation used in the ATRISORB®-D FreeFlow™ Bioabsorbable Guided Tissue Regeneration (GTR) Barrier with 4% Doxycycline (hereafter referred to as the ATRISORB®-D FreeFlow™ Barrier) exists as a sterile, synthetic flowable polymeric solution. It is mixed with doxycycline hyclate prior to formation to give a 4% doxycycline concentration in the formulation prior to barrier placement. The barrier precipitates to a firm consistency upon contact with water and

bioabsorbs over time. The polymer formulation is composed of poly(DL-lactide) (PLA) dissolved in *N*-methyl-2-pyrrolidone (NMP).

2.2 Device

One sterile ATRISORB®-D FreeFlow™ Barrier unit consists of:

- A large pouch containing a pouched syringe with 715 mg of the ATRISORB® polymer formulation and a syringe with 35 mg doxycycline hyclate;
- A blunt tip cannula, and;
- A product insert containing instructions for use.

The ATRISORB®-D FreeFlow™ Barrier package contains three product units.

2.3 Mechanics

The ATRISORB®-D FreeFlow™ Barrier functions as a guided tissue regeneration barrier by isolating the regenerative surgical site from the adjacent gingival connective tissue and epithelium. This facilitates population of the surgical site with cells from the periodontal ligament and adjacent alveolar bone that lead to regeneration. The doxycycline hyclate in the barrier serves to reduce bacterial colonization of the barrier and the surgical site.

To prepare the barrier, the user couples the two syringes and mixes the contents together by passing the contents between syringes. Then, the user fills the periodontal defect with bone grafting material and applies the ATRISORB®-D FreeFlow™ Barrier directly over the defect area. To precipitate the barrier, the user sprays it with a fine mist of sterile water and then sutures the surgical flap closed over the barrier and site.

Once placed, the ATRISORB®-D FreeFlow™ Barrier precludes the migration of epithelial or connective tissue cells through it, while isolating the periodontal compartment and promoting regeneration. The barrier bioabsorbs through hydrolysis over several months. However, the ATRISORB®-D FreeFlow™ Barrier does remain at the site, intact, during the critical period when periodontal regenerative cells are proliferating during the wound-healing cascade from adjacent periodontal sources.

3 Intended Use

The ATRISORB®-D FreeFlow™ Barrier is intended for use in the surgical treatment of periodontal defects to aid in the regeneration and integration of tissue components in guided tissue regeneration procedures. ATRISORB®-D FreeFlow™ Barrier has been shown to reduce bacterial colonization of the barrier.

The indications for the ATRISORB®-D FreeFlow™ Barrier are equivalent to the predicate device, the ATRISORB® GTR Barrier. The difference is the additional

indication for reducing the bacterial colonization of the barrier through the incorporation of doxycycline hyclate to the barrier.

4 Summary of Technological Characteristics

The ATRISORB®-D FreeFlow™ Barrier is substantially equivalent to the predicate ATRISORB® GTR Barrier (K955838) and a variation of the device (K982865). Both are legally marketed products. The polymer formulation is the same in both the ATRISORB®-D FreeFlow™ Barrier and the ATRISORB® GTR Barrier. The only difference between the ATRISORB®-D FreeFlow™ Barrier and its predicate is the addition of doxycycline hyclate to the polymer formulation prior to barrier formation. The doxycycline is intended to reduce the bacterial colonization of the barrier.

5 Summary of In Vitro Studies

5.1 Pyrogenicity

A *Limulus* amebocyte lysate test (LAL) estimated the concentration of bacterial endotoxins in an extract of the ATRISORB®-D FreeFlow™ Barrier. The results indicated that the ATRISORB®-D FreeFlow™ Barrier is non-pyrogenic.

5.2 Sterilization

The ATRISORB®-D FreeFlow™ Barrier is terminally sterilized by Cobalt-60 gamma irradiation.

5.3 In Vitro Characterization of the ATRISORB®-D FreeFlow™ Barrier

The ATRISORB®-D FreeFlow™ Barrier was characterized in a simulated use test to demonstrate that the molecular weight specification for the ATRISORB®-D FreeFlow™ Barrier is appropriate and to determine the thickness of the directly applied barrier. The molecular weight of the polymer is a key factor in influencing the viscosity and precipitation behavior of the formulation.

In the experiment, ATRISORB®-D FreeFlow™ Barrier formulations with four different PLA molecular weights (21, 25, 41, and 64 kiloDaltons) were evaluated for handling properties and barrier thickness. Results were compared to previous data generated for the directly applied version of the predicate ATRISORB® GTR Barrier.

All ATRISORB®-D FreeFlow™ Barriers passed the simulated use test criteria, verifying that the ATRISORB®-D FreeFlow™ Barrier molecular weight limit (21 kiloDaltons) is appropriate. Thickness comparisons demonstrated that the average thickness of the ATRISORB®-D FreeFlow™ Barrier (0.474-3.584 mm) is slightly less than the average thickness of the

directly applied version of the ATRISORB® GTR Barrier (0.729-3.178 mm). These data support that the ATRISORB®-D FreeFlow™ Barrier is suitable for its intended use.

5.4 Irradiation of Doxycycline Hyclate

Experiments were performed to demonstrate that gamma irradiation has no detrimental effects on the doxycycline hyclate present in the barrier, as this is how the device is rendered sterile. Investigators detected a color change from bright yellow to a yellow-brown after irradiation. Attempting to determine if the heat of irradiation produced this effect, investigators heated doxycycline hyclate, but observed no color change.

Additional doxycycline analysis detected three impurities not present in unirradiated doxycycline hyclate. However, the levels of these impurities were less than 0.1% and, therefore, considered insignificant.

Bioassay results also indicated that the potency of doxycycline irradiated at levels of up to 110.9 kGy remained unchanged after irradiation. Further, clinically usable barriers were formed using irradiated doxycycline hyclate.

Collectively these results indicate that the use of gamma irradiation at levels up to 39.4 kGy do not significantly alter the chemical structure, potency, and/or the ability of the doxycycline hyclate to be incorporated into clinically acceptable barriers.

5.5 In Vitro Release of Doxycycline

Atrix has conducted in vitro doxycycline release studies with ATRISORB®-D Barriers containing varying levels of doxycycline (between 1.0% and 10%) formed extraorally in barrier-forming cases. Results demonstrated greater than 90% cumulative release of doxycycline from the barriers into water at 24 hours.

5.6 In Vitro Bioactivity

Time kill assay and agar diffusion techniques were used to demonstrate that an ATRISORB®-D Barrier with 5% doxycycline exhibited bioactivity against periodontal pathogens in vitro. The growth of both *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* were inhibited when exposed to various sizes of ATRISORB®-D Barriers with 5% doxycycline in these assays. This study supports the in vitro bioactivity of the ATRISORB®-D FreeFlow™ Barrier.

6 Summary of In Vivo Implantation Studies

Results from two nonclinical studies performed with the ATRISORB®-D FreeFlow™ Barrier in the dog demonstrated no significant tissue irritation. In addition, extensive biocompatibility, implantation and degradation studies performed

previously on the predicate ATRISORB® GTR Barrier and ATRISORB®-D Barriers with varying concentrations of doxycycline (between 2.5% and 10%) support that the ATRISORB®-D FreeFlow™ Barrier is safe for its intended use.

7 Clinical Performance Data

Atrix performed a six-month clinical study to compare reduction of microorganisms and clinical outcomes following the treatment of Class II furcation defects with either ATRISORB®-D FreeFlow™ Barrier applied directly over decalcified freeze-dried bone allograft (DFDBA) versus ATRISORB® GTR Barrier applied over DFDBA. It was conducted at three different centers.

The study's primary objective was to demonstrate that sites treated with the ATRISORB®-D FreeFlow™ Barrier applied directly over bone graft material had significantly greater microbial reductions than sites treated with the case-formed ATRISORB® GTR Barrier applied over the same graft material. Researchers compared reductions in total anaerobic bacterial counts and specific counts of periodontal pathogens at evaluated timepoints through Week 6 and met the objective. The ATRISORB®-D FreeFlow™ Barrier treatment group demonstrated significantly greater reductions for total anaerobes and counts of *P. intermedia/P. nigrescens* when compared to the ATRISORB® GTR Barrier control. Reductions approaching significant levels in favor of the ATRISORB®-D FreeFlow™ Barrier were also observed for counts of *F. nucleatum.*

The study's secondary objective was to evaluate efficacy endpoints (change from baseline for the following clinical parameters: horizontal attachment level, vertical attachment level, probing depth, and percent defect closure) at Month 6. These data will be reported later.

Finally, levels of doxycycline achieved in the gingival crevicular fluid at surgical sites in all subjects were consistently higher than the minimum inhibitory concentrations of commonly isolated periodontal pathogens.

8 Conclusions

The claims for the ATRISORB®-D FreeFlow™ Barrier are equivalent to the ATRISORB® GTR Barrier. Additionally, the ATRISORB®-D FreeFlow™ Barrier also claims to reduce bacterial colonization of the barrier.

A human clinical trial has demonstrated that the ATRISORB®-D FreeFlow™ Barrier is superior to the predicate ATRISORB® GTR Barrier as an implantable barrier intended to aid in the healing of periodontal defects.

In vitro, animal, and clinical studies have demonstrated that the ATRISORB®-D FreeFlow™ Barrier is safe and effective for its stated indications (treatment of periodontal disease and reducing bacterial colonization of the ATRISORB®-D

FreeFlow™ Barrier) and is substantially equivalent to the predicate device, the ATRISORB® GTR Barrier.

The ATRISORB®-D FreeFlow™ Barrier is non-pyrogenic and biocompatible.

The ATRISORB®-D FreeFlow™ Barrier is bioabsorbed, eliminating the need for a second surgical procedure to remove the barrier.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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Rockville MD 20850

SEP 13 2000

Ms. Amy Taylor
Regulatory Affairs Manager
Atrix Laboratories, Incorporated
2579 Midpoint Drive
Fort Collins, Colorado 80525-4417

Re: K994137
Trade Name: Atrisorb-D FreeFlow Bioabsorbable Guided Tissue Regeneration (GTR) Barrier with 4% Doxycycline
Regulatory Class: Unclassified
Product Code: LYC
Dated: August 29, 2000
Received: August 30, 2000

Dear Ms. Taylor:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4692. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Timothy A. Ulatowski
Director
Division of Dental, Infection Control
and General Hospital Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

INDICATIONS FOR USE

510(k) Number (if known): K994137

Device Name: ATRISORB®-D FreeFlow™ Bioabsorbable Guided Tissue Regeneration (GTR) Barrier with 4% Doxycycline

Indications For Use:

ATRISORB®-D FreeFlow™ Barrier is indicated for the surgical treatment of periodontal defects to aid in the regeneration and integration of tissue components in guided tissue regeneration procedures. ATRISORB®-D FreeFlow™ Barrier has been shown to reduce bacterial colonization of the barrier.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ OR Over-The-Counter Use _____
(Per 2.1 CFR 801.109)

Susan Runner

(Division Sign-Off)
Division of Dental, Infection Control,
and General Hospital Devices
510(k) Number K994137