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RESEARCH**

APPLICATION NUMBER:

21-560

REMS

NDA 21-560 ZORTRESS® (everolimus)

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Risk Evaluation and Mitigation Strategy (REMS)

GOALS

The goals of the ZORTRESS REMS are:

- 1) To inform healthcare providers about the following serious risks associated with ZORTRESS: wound-healing complications, hyperlipidemia, proteinuria, graft thrombosis, as well as nephrotoxicity when ZORTRESS is co-administered with standard doses of cyclosporine.
- 2) To inform patients about the serious risks associated with ZORTRESS.

REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed as part of the Package Insert with each prescription for ZORTRESS. The product is supplied as 0.25 mg, 0.5 mg, and 0.75 mg tablets. Each strength is available in boxes of 60 (6 blister strips of 10 tablets each), approximately a one-month supply of ZORTRESS per box. One copy of the ZORTRESS Medication Guide will be enclosed in each box of ZORTRESS. The Medication Guide will be available for distribution to patients with each prescription that is dispensed. A reminder to pharmacists to provide the Medication Guide each time ZORTRESS is dispensed will be printed on each box.

In compliance with 21 Code of Federal Regulation (CFR) 208.24, the Sponsor will institute the following measures:

- * The Medication Guide will be enclosed in all ZORTRESS packaging.
- * Retail pharmacies will be instructed to provide the Medication Guide with each ZORTRESS prescription. Novartis will conduct ongoing surveys to assess distribution and understanding of the Medication Guide by healthcare professionals and patients.

The Medication Guide will also be available from the Novartis ZORTRESS Web Site (www.zortress.com) and by request through the Sponsor's toll-free information phone number 1-888-NOW-NOVA (1-888-669-6682).

See Attachment A.

B. Communication Plan

Novartis will institute a Communication Plan to educate healthcare professionals on the goals of the ZORTRESS REMS. Materials that will be utilized are the US Package Insert, a Dear Healthcare Professional/Professional Association letter (see Attachment B) and a Dear Pharmacist letter (see Attachment C).

At the time of ZORTRESS launch, Novartis will distribute the letters to key stakeholder healthcare professionals within 60 days of REMS approval and/or in conjunction with product launch, whichever is sooner. The FDA-approved DHCP letters will be available via a prominent (single click) link on the homepage of the ZORTRESS product website.

The following healthcare professionals will be targeted for communication:

1. transplant surgeons
2. transplant medical physicians
3. professionals who act as physician extenders for transplant surgeons and transplant medical physicians
4. pharmacists (in-hospital and community-based)

The following professional associations will be targeted for communication:

1. American Society of Nephrology (ASN)
2. American Society of Transplantation (AST)
3. American Society of Transplant Surgeons (AST)
4. National Foundation for Transplants
5. American Nephrology Nurses Association (ANNA)
6. National Kidney Foundation (NKF)
7. European Society of Organ Transplantation (ESOT)
8. International Transplant Nurses Society
9. The Transplantation Society
10. North American Transplant Coordinators Organization (NATCO)
11. American Society of Health System Pharmacists
12. American College of Clinical Pharmacy
13. American Pharmacists Association

C. Elements To Assure Safe Use

The ZORTRESS REMS can be approved without elements to assure safe use.

D. Implementation System

Because the REMS for ZORTRESS does not include elements to assure safe use, an implementation system is not required.

E. Timetable for Assessments

Novartis will submit REMS Assessments to the FDA by 18 months, by 3 years, and in the 7th year from the date of approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Novartis will submit each assessment so that it will be received by the FDA on or before the due date.