Initial REMS Approval: 04/2010
Most Recent Modification: 11/2011

NDA 21-560

ZORTRESS® (everolimus)

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936 -1080
(862)778-0981

Risk Evaluation and Mitigation Strategy (REMS)

1 Goals

The goal of the ZORTRESS REMS is:

- 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 REMS Elements

2.1 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 A) and a Dear Pharmacist letter (see Attachment B).

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:

- American Society of Nephrology (ASN)
- American Society of Transplantation (AST)
- American Society of Transplant Surgeons (ASTS)
- National Foundation for Transplants
- American Nephrology Nurses Association (ANNA)
- National Kidney Foundation (NKF)
- European Society of Organ Transplantation (ESOT)
- International Transplant Nurses Society
- The Transplantation Society
- North American Transplant Coordinators Organization (NATCO)
- American Society of Health System Pharmacists
- American College of Clinical Pharmacy
- American Pharmacists Association

3 Timetable for Assessments

Novartis will submit REMS Assessments to the FDA 18 months, 3 years, and 7 years from the initial approval date of the REMS (April 20, 2010). 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.

ATTACHMENT A. DEAR HEALTHCARE / PROFESSIONAL ASSOCIATION LETTER

ZORTRESS Logo & Branding

IMPORTANT DRUG WARNING

Dear [Healthcare Professional/Professional Association]:

This letter informs you of important safety information for ZORTRESS® (everolimus) TABLETS, which have been approved by the US Food and Drug Administration for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant.

Important Information about the Risks of ZORTRESS

In addition to the Boxed Warning about malignancy, serious infections, and other established risks of immunosuppression, Novartis Pharmaceuticals Corporation (Novartis) is implementing a Risk Evaluation and Mitigation Strategy (REMS) to inform health care providers and patients about the following additional risks of ZORTRESS:

- **Delayed or Impaired Wound Healing**

ZORTRESS delays wound healing and increases the occurrence of wound dehiscence, wound infection, incisional hernia, lymphocele and seroma which may require surgical intervention. Lymphoedema and other types of localized fluid collection, such as pericardial and pleural effusions and ascites have also been reported.

- **Hyperlipidemia**

It may not be possible to normalize ZORTRESS-associated hyperlipidemia, despite anti-lipid therapy. Patients on a HMG-CoA reductase inhibitor and/or fibrate should be monitored for rhabdomyolysis and other adverse effects as per labeling for these lipid lowering agents. Due to an interaction with cyclosporine, use of the HMG-CoA reductase inhibitors simvastatin and lovastatin was discouraged in the everolimus clinical trials.

- **Proteinuria**

ZORTRESS is associated with increased proteinuria. This risk increases with higher everolimus whole blood trough concentrations in kidney transplant patients receiving ZORTRESS with cyclosporine.

- **Renal Allograft Thrombosis**

An increased risk of kidney arterial and venous thrombosis, resulting in graft loss, has been reported, mostly within the first 30 days post-transplantation.

- **Nephrotoxicity with Standard Dose Cyclosporine**

ZORTRESS with standard dose cyclosporine increases the risk of renal dysfunction which is manifested by lowered glomerular filtration rate. Lower cyclosporine doses are required in combination with everolimus to reduce renal dysfunction.

Additional Information

- ZORTRESS is administered in combination with basiliximab induction and concurrently with reduced doses of cyclosporine and corticosteroids.
- Therapeutic drug monitoring of everolimus and cyclosporine is recommended for all patients receiving these products.
- In patients at high immunologic risk, the safety and efficacy of everolimus has not been established.
- Use of everolimus for the prophylaxis of organ rejection in transplanted organs other than kidney has not been established.

Please review the FDA approved **Medication Guide** with your patients.

Adverse event reporting: Healthcare providers should report all suspected adverse events associated with the use of ZORTRESS. Please contact Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1-888-669-6682) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the accompanying complete Prescribing Information. For more information regarding ZORTRESS, please contact Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1-888-669-6682) or visit www.zortress.com.

Sincerely,

Felix Geissler, MD, PhD

Medical Director

Novartis Pharmaceuticals Corporation

ATTACHMENT B. DEAR PHARMACIST LETTER

ZORTRESS Logo & Branding

IMPORTANT DRUG WARNING

Dear Pharmacist:

This letter informs you of important safety information for ZORTRESS® (everolimus) TABLETS, which have been approved by the US Food and Drug Administration for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant.

Important Information about the Risks of ZORTRESS

In addition to the Boxed Warning about malignancy, serious infections, and other established risks of immunosuppression, Novartis Pharmaceuticals Corporation (Novartis) is implementing a Risk Evaluation and Mitigation Strategy (REMS) to inform health care providers and patients about the following additional risks of ZORTRESS:

- **Delayed or Impaired Wound Healing**

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- **Hyperlipidemia**

It may not be possible to normalize ZORTRESS-associated hyperlipidemia despite anti-lipid therapy. Patients on a HMG-CoA reductase inhibitor and/or fibrate should be monitored for rhabdomyolysis and other adverse effects as per labeling for lipid lowering agents. Due to an interaction with cyclosporine, use of the HMG-CoA reductase inhibitors simvastatin and lovastatin was discouraged in the everolimus clinical trials.

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- **Renal Allograft Thrombosis**

An increased risk of kidney arterial and venous thrombosis, resulting in graft loss, has been reported, mostly within the first 30 days post-transplantation.

- **Nephrotoxicity with Standard Dose Cyclosporine**

ZORTRESS with standard dose cyclosporine increases the risk of renal dysfunction which is manifested by lowered glomerular filtration rate. Lower cyclosporine doses are required in combination with ZORTRESS to reduce renal dysfunction. Refer to the complete Prescribing Information for dosing and monitoring, including section *2.3 Therapeutic Drug Monitoring-Cyclosporine*

Additional Information

- ZORTRESS is administered in combination with basiliximab induction and concurrently with reduced doses of cyclosporine and corticosteroids.
- Therapeutic drug monitoring of everolimus and cyclosporine is recommended for all patients receiving these products.
- In patients at high immunologic risk, the safety and efficacy of everolimus has not been established.
- Use of everolimus for the prophylaxis of organ rejection in transplanted organs other than kidney has not been established.

Dispensing Information

Each carton of ZORTRESS includes the **Medication Guide**. It is important that patients receive the Medication Guide with each new ZORTRESS prescription that you fill and with each refill as there may be new information. For additional copies of the Medication Guide, please contact Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1- 888-669-6682) or visit www.zortress.com.

Carton and Container labels for ZORTRESS include the required statement to alert dispenser to provide the Medication Guide.

ZORTRESS is available as 0.25 mg, 0.5 mg, and 0.75 mg tablets

Adverse event reporting: Healthcare providers should report all suspected adverse events associated with the use of ZORTRESS. Please contact Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1-888-669-6682) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the accompanying complete Prescribing Information. For more information regarding ZORTRESS, please contact Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1-888-669-6682) or visit www.zortress.com.

Sincerely,

Felix Geissler, MD, PhD
Medical Director
Novartis Pharmaceuticals Corporation

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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11/21/2011