



NDA 21-290/S-015

Actelion Pharmaceuticals, Ltd.
Attention: Brian D. Schlag, MA, MS
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

SUPPLEMENT APPROVAL

Dear Mr. Schlag:

We refer to your supplemental New Drug Application (S-015) submitted December 23, 2008, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tracleer (bosentan) 62.5 and 125 mg Tablets.

We also acknowledge receipt of your submission dated January 15, 2009.

This supplemental new drug application provides for the following revisions to the Full Prescribing Information and the Medication Guide as agreed to per email correspondence dated March 17, 2009:

1. To add the following text to the **CONTRAINDICATIONS** section of the package insert:

Lopinavir/ritonavir or other ritonavir-containing HIV regimens: Co-administration of lopinavir/ritonavir and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of **TRACLEER®** and lopinavir/ritonavir or other ritonavir-containing HIV regimens is contraindicated (see **PRECAUTIONS/Drug Interactions**).

2. To modify the first paragraph in the **PRECAUTIONS/Drug Interactions** section of the package insert

FROM

Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these enzymes may increase the plasma concentration of bosentan (see ketoconazole). Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a CYP3A4 inhibitor (such as ketoconazole, itraconazole, or ritonavir) with bosentan will likely lead to large increases in plasma concentrations of bosentan. Co-administration of such combinations of a potent CYP2C9 inhibitor plus a CYP3A4 inhibitor with **TRACLEER®** is not recommended.

TO

Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these enzymes may increase the plasma concentration of bosentan (see ketoconazole). Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, ritonavir) or a moderate CYP3A4 inhibitor (e.g., amprenavir, erythromycin, fluconazole, diltiazem) with bosentan will likely lead to large increases in plasma concentrations of bosentan. Co-administration of such combinations of a CYP2C9 inhibitor plus a strong or moderate CYP3A4 inhibitor with **TRACLEER®** is not recommended.

3. To add the following text to the **PRECAUTIONS/Drug Interactions** section of the package insert:

Lopinavir/ritonavir or other ritonavir-containing HIV regimens: Co-administration of **TRACLEER®** in healthy subjects resulted in initial and steady state trough plasma concentrations of bosentan that were approximately 48-fold and 5-fold higher, respectively, than those measured after **TRACLEER®** administered alone. This is most likely explained by inhibition by ritonavir of OATP-mediated uptake into hepatocytes, but the potential for increased toxicity cannot be excluded. Co-administration of bosentan and lopinavir/ritonavir or other ritonavir-containing HIV regimens is contraindicated (see **CONTRAINDICATIONS**).

4. To modify the following text in the Medication Guide under “**Who should not take Tracleer?**”
Do not take Tracleer if:”

FROM

- **you are taking cyclosporine-A**, (used for psoriasis and rheumatoid arthritis, and to prevent rejection of heart or kidney transplants) **or glyburide** (used for diabetes)

TO

- **you are taking cyclosporine-A**, (used for psoriasis and rheumatoid arthritis, and to prevent rejection of heart or kidney transplants), **glyburide** (used for diabetes), or **lopinavir/ritonavir** or other **ritonavir-containing HIV regimens**.

5. To modify the following text in the Medication Guide under “Tell your doctor about **all** the medicines you use...”

FROM

- ritonavir (used to treat HIV).

TO

- lopinavir/ritonavir or other ritonavir-containing HIV regimens.

6. To modify the following text in the Medication Guide under “**What should I avoid while taking Tracleer?**”

FROM

- **Do not take cyclosporine-A**. This medicine can cause too much Tracleer in your blood and increase your chance of liver damage.

TO

- **Do not take cyclosporine-A**. This medicine can cause too much Tracleer in your blood

and increase your chance of side effects.

7. To add the following text in the Medication Guide under “**What should I avoid while taking Tracleer?**”

Do not take lopinavir/ritonavir or other ritonavir-containing HIV regimens. They can cause too much Tracleer in your blood and increase your chance of side effects.

We refer to previous labeling revisions approved on February 23, 2009 (S-014) regarding the following labeling changes that were also proposed in S-015:

- To add “Jaundice, Anemia requiring transfusion” to the **ADVERSE REACTIONS/Post-Marketing Experience** section of the package insert.
- To add the following text to the **OVERDOSAGE** section of the package insert:

In the postmarketing period, there was one reported overdose of 10,000 mg of bosentan taken by an adolescent male patient. He had symptoms of nausea, vomiting, hypotension, dizziness, sweating, and blurred vision. He recovered within 24 hours with blood pressure support.

Bosentan is unlikely to be effectively removed by dialysis due to the high molecular weight and extensive plasma protein binding.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved NDA 21-290/S-015.**”

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Dan Brum, PharmD, MBA, RAC, Regulatory Project Manager, at (301) 796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling text

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

/s/

Norman Stockbridge
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