March 1, 2006

RE: IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

We are writing to inform you of changes to the Tracleer (bosentan) product labeling and to remind you of the importance of continued monthly liver function testing in patients receiving Tracleer.

As you know, your patients receive Tracleer® through the Tracleer® Access Program (T.A.P). The most important feature of T.A.P. is that each patient is called by the distributor each month to remind him/her of the need for monthly liver function tests (LFT) and, if a woman of childbearing potential, to have a pregnancy test done, prior to the monthly refill shipment of Tracleer®. In cases where the patient says that he/she has not had an LFT/Pregnancy test in the preceding month, or does not remember if he/she had such a test(s), the Tracleer® distributor calls the prescribing physician to inform them of the patient's response.

The labeling changes are based on rare cases of hepatotoxicity that were reported to Actelion (and thus to the FDA). In one case, a female patient, treated for P.A.H since childhood, with multiple co-morbidities and on multiple drug therapies was treated with Tracleer® for 21 months at the recommended dosage. After her first year of treatment, her LFTs (aminotransferases, alkaline phosphatase, and total bilirubin) remained near her baseline values, but about one year after starting Tracleer® her ALT gradually rose from baseline (2-4x baseline) but stayed within normal limits. After another nine months of treatment, marked elevations in aminotransferase and bilirubin levels were noted and Tracleer® was discontinued. After discontinuation of Tracleer®, AST and ALT remained elevated and bilirubin continued to rise. In this period, she was hospitalized for an i.v. catheter line infection. The patient developed liver failure and biopsy-confirmed cirrhosis. A contribution of Tracleer to the development of liver failure could not be ruled out. Eventually, her liver failure abated and her LFTs recovered about seven months after discontinuation of Tracleer®.

This case underscores the need to continue monthly monitoring for the duration of Tracleer® treatment. It also emphasizes the need to adhere to the recommended dosage adjustment and monitoring guidelines described below and in the product labeling.

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Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5 x ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).
> 5 and ≤ 8 x ULN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
> 8 x ULN	Treatment should be stopped and re-introduction of **TRACLEER®** should not be considered. There is no experience with re-introduction of **TRACLEER®** in these circumstances.

Actelion strongly encourages you to submit a report of any serious adverse events that occur with the use of Tracleer® to 1-888-835-5445 or to the FDA's MedWatch Adverse Event Reporting program online [at www.fda.gov/MedWatch/report.htm], by phone [1-800-FDA-1088], or by returning the postage-paid FDA form 3500 [which may be downloaded from www.fda.gov/MedWatch/getforms.htm] by mail [to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787] or fax [1-800-FDA-0178].

If you have any questions or comments, please feel free to contact me.

Sincerely,

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