



NDA 021290/S-027; S-029

SUPPLEMENT APPROVAL

Actelion Pharmaceuticals Ltd.
Attention: Frances Duffy-Warren, PhD.
Associate Director, Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Dr. Duffy-Warren:

Please refer to your Supplemental New Drug Application (sNDA) dated and received June 11, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tracleer (bosentan) 62.5 mg and 125 mg Tablets.

We acknowledge receipt of your amendments dated August 1, and December 23, 2014, and July 1, and November 24, 2015.

This supplemental new drug application provides for proposed modifications to the approved Tracleer risk evaluation and mitigation strategy (REMS), the Tracleer Package Insert, and the Tracleer Medication Guide.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text. The following changes were made to the Package Insert and the Medication Guide:

In the Package Insert:

1. In **HIGHLIGHTS/BOXED WARNING**, the following information was added/deleted:

**WARNING: RISKS OF HEPATOTOXICITY and
TERATOGENICITY~~EMBRYO-FETAL TOXICITY~~**
See full prescribing information for complete boxed warning.

Tracleer is available only through a restricted distribution program called the Tracleer **REMS Program** ~~Access Program (T.A.P.)~~ because of these risks (5.2):

Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer (5.1).

- Measure liver aminotransferases prior to initiation of treatment and then monthly (5.1).
- Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin $\geq 2 \times$ ULN (2.2, 5.1).

Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy (4.1, 8.1).

- Must exclude pregnancy before and during treatment (4.1, 8.1).
- To prevent pregnancy, females of ~~childbearing~~ reproductive potential must use two reliable forms of contraception during treatment and for one month after stopping Tracleer (4.1, 8.1).

2. In **HIGHLIGHTS**, the following text was added/deleted:

Recent Major Changes

<u>Boxed Warning</u>	12/2014
<u>Dosage and Administration (2.3)</u>	12/2014
<u>Warnings and Precautions (5.2)</u>	12/2014
Dosage and Administration: Use in Females of Childbearing Potential (2.4)	10/2012
Warnings and Precautions (5.2, 5.6, 5.7)	10/2012

3. In **FULL PRESCRIBING INFORMATION**, the Boxed Warning was updated:

**WARNING: RISKS OF HEPATOTOXICITY and
TERATOGENICITY~~EMBRYO-FETAL TOXICITY~~**

Because of the risks of hepatotoxicity and birth defects, Tracleer is available only through a restricted program called the Tracleer ~~Access~~ **REMS Program (T.A.P.). The Tracleer **REMS Program T.A.P.** is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). Under the Tracleer REMS, prescribers, patients, and pharmacies must enroll in the program. [see *Warnings and Precautions (5.2)*].**

Hepatotoxicity

In clinical studies, Tracleer caused at least 3-fold upper limit of normal (ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious hepatotoxicity, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.1)*]. In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with Tracleer in patients with multiple comorbidities and drug therapies. There have also been reports of liver failure. The contribution of Tracleer in these cases could not be excluded.

In at least one case, the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of Tracleer. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping Tracleer with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction [see *Dosage and Administration (2.2)*].

Elevations in aminotransferases require close attention [see *Dosage and Administration (2.2)*]. Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring for hepatotoxicity may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment with Tracleer should be stopped. There is no experience with the reintroduction of Tracleer in these circumstances.

Teratogenicity/Embryo-Fetal Toxicity

Tracleer is likely to cause major birth defects if used by pregnant females based on animal data [see *Use in Specific Populations (8.1)*]. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of ~~childbearing~~reproductive potential must use two reliable methods of contraception unless the patient has an intrauterine devices (IUD), or tubal sterilization, ~~tubal sterilization or Copper T 380A IUD or LNG 20 IUS inserted~~, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer [see *Drug Interactions (7.2)*]. Obtain monthly pregnancy tests.

4. Under **DOSAGE AND ADMINISTRATION**, the following text was added/deleted:

Healthcare professionals who prescribe Tracleer must enroll in the Tracleer Access REMS Program (~~T.A.P.~~) and must comply with the required monitoring to minimize the risks associated with Tracleer [see *Warnings and Precautions (5.2)*].

2.3 Pregnancy Testing in Females of Reproductive Potential

Initiate treatment with Tracleer in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy test during treatment [see Use in Specific Populations (8.1)].

5. Under **CONTRAINDICATIONS**, the following text was added/deleted:

4.1 Pregnancy

Use of Tracleer is contraindicated in females who are or may become pregnant. To prevent pregnancy, females of ~~childbearing~~ reproductive potential must use two reliable forms of contraception during treatment and for one month after stopping Tracleer. [see *Boxed Warning, Warnings and Precautions (5.2), Drug Interactions (7.2), Use in Specific Populations (8.1)*].

6. Under **WARNINGS AND PRECAUTIONS**, the following information was added/deleted:

5.2 Prescribing and Distribution Program for Tracleer

Because of the risks of hepatotoxicity and birth defects, Tracleer is available only through a restricted program called the Tracleer ~~Access~~REMS Program (~~T.A.P.~~). As a component of the Tracleer REMS, prescribers, patients, and pharmacies must enroll in the program. [see *Boxed Warning and Contraindications (4.1)*].

Required components of the Tracleer REMS are:

- Healthcare professionals who prescribe Tracleer must review the prescriber educational materials, enroll in the ~~T.A.P.~~Tracleer REMS Program and comply with its requirements.
- Healthcare professionals must (1) review serum aminotransferases (ALT/AST) and bilirubin, and agree to order and monitor these tests monthly; and (2) for females of ~~childbearing~~ reproductive potential, confirm that the patient is not pregnant, and agree to order and monitor pregnancy tests monthly.
- To receive Tracleer, all patients must understand the risks and benefits, complete a patient enrollment form ~~and be re-enrolled annually by their prescriber~~.
- Pharmacies that dispense Tracleer must enroll in the program and agree to comply with the ~~T.A.P.~~Tracleer REMS Program requirements.

Further information about Tracleer and ~~T.A.P.~~the Tracleer REMS Program is available at www.Tracleerrem.com or 1-866-228-3546.

7. Under **ADVERSE REACTIONS/ Postmarketing Experience**, the following term was added to the list after the second paragraph:

Nasal congestion

8. Under **USE IN SPECIFIC POPULATIONS**, the following text was added/deleted:

8.1 Pregnancy

Pregnancy Category X: Teratogenic Effects [*see Contraindications (4.1)*]

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well-controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. Bosentan caused teratogenic effects in animals including malformations of the head, mouth, face, and large blood vessels. If Tracleer is used during pregnancy or if a patient becomes pregnant while taking Tracleer, the patient should be apprised of the potential hazard to the fetus.

Females of ~~childbearing~~childbearing reproductive potential should have a negative pregnancy test before starting treatment with Tracleer. The prescriber should not dispense a prescription for Tracleer without documenting a negative urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly in females of ~~childbearing~~childbearing reproductive potential taking Tracleer. The patient should contact her physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to her, the pregnancy, and the fetus.

Contraception: Drug interaction studies show that bosentan reduces serum levels of the estrogen and progestin in oral contraceptives. Based on these findings, hormonal contraceptives (including oral, injectable, transdermal, and implantable contraceptives) may be less effective for preventing pregnancy in patients using Tracleer and should not be used as a patient's only contraceptive method [*see Drug Interactions (7.2)*]. Females of ~~childbearing~~childbearing reproductive potential using Tracleer must use ~~two reliable~~two reliable ~~forms~~acceptable methods of contraception ~~unless she has a~~during treatment with Tracleer and for 1 month after treatment with Tracleer. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), or tubal sterilization or has a Copper T 380A IUD) or LNG-20 IUS. In these cases, no additional contraception a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is needed the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [*see Boxed Warning*].

Contraception should be continued until one month after completing Tracleer therapy. Females of ~~childbearing~~childbearing reproductive potential using Tracleer should seek contraception counseling from a gynecologist or other expert as needed.

Bosentan was teratogenic in rats given oral doses two times the maximum recommended human dose [MRHD] (on a mg/ m² basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses 2 and 10 times the MRHD (on a mg/m² basis). Although birth defects were not observed in rabbits given oral doses of up to the equivalent of 10.5 g/day in a 70 kg person, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that ~~teratogenicity~~embryo-fetal toxicity is a class effect of these drugs [*see Nonclinical Toxicology (13.1)*].

9. Under **PATIENT COUNSELING INFORMATION**, the following information was added/deleted:

Advise the patient that Tracleer is only available through a restricted access program called the Tracleer ~~Access~~ REMS Program (~~T.A.P.~~).

As a component of the Tracleer REMS, prescribers must review the contents of the Tracleer Medication Guide with the patient before initiating Tracleer.

Instruct patients that the risks associated with Tracleer include:

- **Hepatotoxicity**

Discuss with the patient the requirement to measure serum aminotransferases monthly.

- ~~Serious birth defects if used by pregnant women~~ **Embryo-fetal toxicity**

Educate and counsel female patients of ~~childbearing~~childbearing reproductive potential about the need to use reliable methods of contraception during treatment with Tracleer and for one month after treatment discontinuation. Females of ~~childbearing~~childbearing reproductive potential must have monthly pregnancy tests and must use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer [*see Use in Specific Populations (8.1)*].

Females who have intrauterine devices (IUD), or tubal sterilization ~~a tubal ligation or a Copper T 380A IUD or LNG 20 IUS can use these contraceptive methods alone~~. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant. Patients should seek additional contraceptive advice from a gynecologist or similar expert as needed.

Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.

Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Advise patients to contact their gynecologist or healthcare provider if they want to change the form of birth control which is used to ensure that another acceptable form of birth control is selected.

Advise the patient that Tracleer is available only from specialty pharmacies that are enrolled in Tracleer ~~Aceess~~REMS Program.

Patients must sign the ~~Tracleer Enrollment for Patients and Prescribers form~~ Tracleer Patient Enrollment and Consent Form to confirm that they understand the risks of Tracleer.

~~Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the Tracleer REMS.~~

10. The revision date and version number were updated.

In the Medication Guide

1. Under **What is the most important information I should know about Tracleer?**, the following information was added:

Tracleer can cause serious birth defects if taken during pregnancy. You must not be pregnant when you start taking Tracleer or during Tracleer treatment. Serious birth defects from Tracleer can happen early in pregnancy. Females who are able to get pregnant must have a negative pregnancy test before starting treatment with Tracleer, and each month during treatment with Tracleer, treatment and 1 month after stopping treatment with Tracleer.

- Talk to your healthcare provider about your menstrual cycle. Your healthcare provider will decide when to do a pregnancy test and will order a pregnancy test for you depending on your menstrual cycle.
 - Females who **are able** to get pregnant are females who:
 - have entered puberty, even if they have not started their menstrual period, and
 - have a uterus, and
 - have not gone through menopause. Menopause means that you have not had a menstrual period for at least 12 months for natural reasons, or that you have had your ovaries removed.
 - Females who are **not able** to get pregnant are females who:
 - have not yet entered puberty, or
 - do not have a uterus, or

- have gone through menopause. Menopause means that you have not had a menstrual period for at least 12 months for natural reasons, or that you have had your ovaries removed or
- are infertile for other medical reasons and this infertility is permanent and cannot be reversed.
- **Females who are able to get pregnant must use two acceptable forms of birth control during treatment with Tracleer, and for one month after stopping Tracleer because the medicine may still be in the body.**
 - If you have had a tubal sterilization or have an IUD (intrauterine device), these methods can be used alone and no other form of birth control is needed.
 - Talk with your healthcare provider or gynecologist (a doctor who specializes in female reproduction) to find out about how options for acceptable birth control that you may use to prevent pregnancy. during treatment with Tracleer.
 - If you decide that you want to change the form of birth control that you use, talk with your healthcare provider or gynecologist to be sure that you choose another acceptable form of birth control.

See the chart below for Acceptable Birth Control Options during treatment with Tracleer.

- **Do not have unprotected sex. Talk to your healthcare provider or pharmacist right away if you have unprotected sex or if you think your birth control has failed. Your healthcare provider may talk with you about using emergency birth control.**
- **Tell your healthcare provider right away if you miss a menstrual period or think you may be pregnant.**

If you are the parent or caregiver of a female child who are able to get pregnant must use two forms of birth control (contraception) during Tracleer treatment because there is a possibility of birth defects- started taking Tracleer before reaching puberty, you should check your child regularly to see if she is developing signs of puberty. Tell your healthcare provider right away if you notice that she is developing breast buds or any pubic hair. Your healthcare provider may recommend that you use a different method of birth control to help lower your risk of problems with should decide if your pulmonary arterial hypertension. See the end of this Medication Guide for more information about reliable methods of contraception during treatment with Tracleer. child has reached puberty. **Your child may reach puberty before having her first menstrual period.**

2. The chart of Acceptable Birth Control Options, was revised from:

Reliable methods of contraception during treatment with Tracleer		
Methods to use alone	Hormone (choose 1 and use with a barrier method)	Barrier (use both OR choose 1 and use with hormone method)
<ul style="list-style-type: none"> • Intrauterine devices (IUDs) <ul style="list-style-type: none"> — Copper T 380A IUD — LNG-20 IUS (progesterone IUD) • Tubal sterilization 	<ul style="list-style-type: none"> • Estrogen and progesterone <ul style="list-style-type: none"> — Oral contraceptives — Transdermal patch — Vaginal ring • Progesterone only <ul style="list-style-type: none"> — Injection — Implant 	<ul style="list-style-type: none"> • Male condom with spermicide • Diaphragm with spermicide <p>OR</p> <ul style="list-style-type: none"> • Cervical cap with spermicide
A partner's vasectomy still requires 1 additional method of contraception.		

To:

Option 1 One method from this list:	Option 2 One method from this list:	Option 3 One method from this list:	Option 4 One method from this list:
<p>Standard intrauterine device (Copper T 380A IUD)</p> <p>Intrauterine system (LNg 20 IUS: progesterone IUS)</p> <p>Tubal sterilization</p>	<p>Estrogen and progesterone oral contraceptives (“the pill”)</p> <p>Estrogen and progesterone transdermal patch</p> <p>Vaginal ring</p> <p>Progesterone injection</p> <p><u>Progesterone implant</u></p>	<p>Diaphragm with spermicide</p> <p>Cervical cap with spermicide</p> <p>PLUS One method from this list:</p> <p>Male condom</p>	<p>Partner’s vasectomy</p> <p>PLUS One method from this list:</p> <p>Male condom</p> <p>Diaphragm with spermicide</p> <p>Cervical cap with spermicide</p> <p>Estrogen and progesterone oral contraceptives (“the pill”)</p> <p>Estrogen and progesterone transdermal patch</p> <p>Vaginal ring</p> <p>Progesterone injection</p> <p><u>Progesterone implant</u></p>
	<p>PLUS One method from this list:</p> <p>Male condom</p> <p>Diaphragm with spermicide</p> <p>Cervical cap with spermicide</p>		

3. Under **What is Tracleer?**, the following text was added/deleted:

Tracleer is only:

Prescribed by healthcare providers who are enrolled in ~~T.A.P.~~ the Tracleer REMS Program.

~~available~~ Available to people who understand and agree to enroll in ~~T.A.P.~~ the Tracleer REMS Program.

4. Under **Who should not take Tracleer?**, the following text was added/deleted:

- take ~~any one~~ of these medicines:
 - cyclosporine A used to ~~treat~~ for psoriasis and rheumatoid arthritis, and to prevent rejection of heart, ~~liver,~~ and ~~for~~ kidney transplants

- glyburide used to treat ~~for~~ diabetes
- you are allergic to bosentan or any of the ingredients in Tracleer. See the end of this Medication Guide for a complete list of the ingredients in Tracleer. If you have a rash, hives or your lips swell after taking Tracleer, it may be a sign of allergy. You should stop taking your Tracleer and talk to your healthcare provider.

5. Under **What should I tell my healthcare provider before taking Tracleer?**, the following was added/deleted:

Tell your healthcare provider about all the medicines you take, including prescription and ~~nonprescription~~ ~~over-the-counter~~ medicines, vitamins, and herbal supplements. Tracleer and other medicines may affect how each other works and cause side effects. Especially tell your healthcare provider if you take:

- hormone-based birth control, such as pills, shots, patches, and implants. These birth control
- methods may not work as well when taken with Tracleer.
- simvastatin or other “-statin” medicines used to lower cholesterol
- rifampin used for tuberculosis
- tacrolimus used to prevent rejection of liver or kidney transplant
- ketoconazole, fluconazole, itraconazole, or voriconazole used for fungal infections
- warfarin sodium used to prevent blood clots
- ritonavir used to treat HIV

6. The **How should I take Tracleer?** and the **What are the possible side effects of Tracleer?**, sections were re-bulleted.

7. The **How should I store Tracleer?** section was revised to read:

Store Tracleer at room temperature between 68°F to 77°F (20°C to 25°C).

8. The following statement was relocated in the Medication Guide in accordance with 21 CFR 208.20(b)(8)(iv).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

9. There are several editorial changes noted throughout the label and the Medication Guide, (i.e. the Table of Contents was updated, the sections in Dosage and Administration were re-numbered, the words “embryo fetal toxicity” replace the word “teratogenicity” throughout the label, the word “reproductive” replaces the word “childbearing” throughout the label, the words “Tracleer REMS Access Program (T.A.P.S.)” is replaced by the words “Tracleer REMS Program”, Tracleer replaces TRACLEER)

10. The revision date and version number were updated.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Tracleer (bosentan) was originally approved on August 7, 2009, and the most recent modification was approved on July 1, 2013. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of:

- Change of REMS program name to “the Tracleer REMS Program” from “Tracleer Access Program”
- Replacement of the "Tracleer Renewal Form" with the "Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form"
- Replacement of Hospital Certification with Inpatient Pharmacy Certification and addition of an Inpatient Pharmacy Enrollment Form
- Changes to the roles and responsibilities of the inpatient and outpatient pharmacy authorized representatives
- Removal of the monthly wallet reminder card
- Removal of form FRM-549-COP-US that was required for patients to receive Tracleer when traveling outside of the United States
- Addition of a new female of non-reproductive potential subcategory (“Other medical reasons for permanent, irreversible infertility”) to all relevant sections of the REMS document and related forms

Your proposed modified REMS, submitted on November 24, 2015, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on February 19, 2010.

There are no changes to the REMS assessment plan described in our May 5, 2014 letter.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary; the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021290 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 021290 REMS ASSESSMENT

**NEW SUPPLEMENT FOR 021290/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 021290/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 021290/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021290/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 021290

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REPORTING REQUIREMENTS

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:

Lori Anne Wachter RN, BSN, RAC
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
REMS

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

/s/

MARY R SOUTHWORTH
12/04/2015