DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22081/S-033

SUPPLEMENT APPROVAL

POSTMARKETING COMMITMENT NOT FULFILLED

Gilead Sciences, Inc.
Attention: Saima Malik, M.Sc.
Senior Associate, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Malik:

Please refer to your Supplemental New Drug Application (sNDA) dated December 5, 2014, received December 5, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Letairis (ambrisentan) 5 and 10 mg tablets.

We acknowledge receipt of your amendments dated January 19, February 16 and 18, March 20, April 21 and 24, July 9, 13, 15, 17, 28, and 29, August 5, 11, 13, 25, and September 4, 23, 24, 28, and October 1, 2015, and your risk evaluation and mitigation strategy (REMS) assessment dated December 5, 2014.

This "Prior Approval" supplemental new drug application proposes to revise the indication to include language about the benefits of using Letairis in combination with tadalafil to reduce the risk of disease progression and hospitalization for worsening PAH, and to improve exercise ability, based on the AMBITION study, and proposes modification to the approved risk evaluation and mitigation strategy (REMS) to incorporate the revised indication. In addition, the supplement provides data intended to fulfill an open postmarketing commitment.

The following changes were made to the Package Insert (additions are noted in Underline text and deletions are noted in Strikethrough text):

In the HIGHLIGHTS:

In the **RECENT MAJOR CHANGES** section:

FROM:

- Boxed Warning 08/2013
- Dosage and Administration (2.2) 08/2013

- Warnings and Precautions, Embryo-fetal Toxicity (5.1) 08/2013
- Warnings and Precautions, Letairis REMS Program (5.2) 08/2013

TO:
- Indications and Usage (1) 10/2015
- Dosage and Administration (2.1) 10/2015
- Warnings and Precautions (5.3) 10/2015

In the **INDICATIONS AND USAGE** section:
FROM:
Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%) (1).

TO:
Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):
- To improve exercise ability and delay clinical worsening.
- In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

Studies establishing effectiveness included trials predominantly in patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) ~~(64%)~~ or PAH associated with connective tissue diseases (34%) ~~(32%)~~ (1).

In the **DOSAGE AND ADMINISTRATION** section:
FROM:
- Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated (2.1).
- Tablets should not be split, crushed, or chewed (2.1).

TO:
- Initiate treatment at 5 mg once daily (2.1).
- May be started with tadalafil (2.1).
- Titrate at 4-week intervals as needed and tolerated (2.1).
- Do not split, crush, or chew tablets (2.1).

In the **ADVERSE REACTIONS** section:
FROM:
Most common adverse reactions (>3% compared to placebo) are peripheral edema, nasal congestion, sinusitis, and flushing (6.1).

TO:

- Most common adverse reactions (>3% compared to placebo) are peripheral edema, nasal congestion, sinusitis, and flushing (6.1).
- When used in combination with tadalafil, most common adverse reactions (>5% compared with either monotherapy) are peripheral edema, headache, nasal congestion, cough, anemia, dyspepsia, and bronchitis (6.1).

In the Full Prescribing Information:

In the **INDICATIONS AND USAGE** section:

FROM:
Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%) (1).

TO:
Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- To improve exercise ability and delay clinical worsening.
- In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

Studies establishing effectiveness included trials predominantly in patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) ~~(64%)~~ or PAH associated with connective tissue diseases (34%) ~~(32%)~~ (1).

In the **DOSAGE AND ADMINISTRATION** section, subsection 2.1 **Adult Dosage:**:

FROM:
Initiate treatment at 5 mg once daily, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated.

Tablets may be administered with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in patients with pulmonary arterial hypertension (PAH).

TO:
Initiate treatment at 5 mg once daily, with or without tadalafil 20 mg once daily~~, and consider increasing the dose to 10 mg oncedaily if 5 mg is tolerated~~.. At 4-week intervals, either the dose of Letairis or tadalafil can be increased, as needed and tolerated, to Letairis 10 mg or tadalafil 40 mg.

~~Tablets may be administered with or without food. Tablets should not be~~ Do not split, crush~~ed~~, or chew~~ed~~ tablets. ~~. Doses higher than 10 mg once daily have not been studied in patients with~~

~~pulmonary arterial hypertension (PAH).~~

In the **WARNINGS AND PRECAUTIONS** section, subsection 5.3 **Fluid Retention:**:

FROM:
Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg Letairis compared to placebo [see Adverse Reactions (6.1)]. Most edema was mild to moderate in severity, and it occurred with greater frequency and severity in elderly patients.

In addition, there have been postmarketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting Letairis. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Letairis or underlying heart failure, and the possible need for specific treatment or discontinuation of Letairis therapy.

TO:
Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg Letairis compared to placebo [see Adverse Reactions (6.1)]. Most edema was mild to moderate in severity ~~in elderly patients~~.

In addition, there have been postmarketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting Letairis. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Letairis or underlying heart failure, and the possible need for specific treatment or discontinuation of Letairis therapy.

<u>Peripheral edema/fluid retention is more common with Letairis plus tadalafil than with Letairis or tadalafil alone.</u>

In the **ADVERSE REACTIONS** section, subsection 6.1 :

FROM:

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data for Letairis were obtained from two 12-week, placebo-controlled studies in patients with pulmonary arterial hypertension (PAH) (ARIES-1 and ARIES-2) and four nonplacebo-controlled studies in 483 patients with PAH who were treated with doses of 1, 2.5, 5, or 10 mg once daily. The exposure to Letairis in these studies ranged from 1 day to 4 years (N = 418 for at least 6 months and N = 343 for at least 1 year).

In ARIES-1 and ARIES-2, a total of 261 patients received Letairis at doses of 2.5, 5, or 10 mg once daily and 132 patients received placebo. The adverse reactions that occurred in >3% more patients receiving Letairis than receiving placebo are shown in Table 1.

Table 1 Adverse Reactions with Placebo-Adjusted Rates >3%

	Placebo (N = 132)	**Letairis (N =**	
Adverse Reaction	**n**	**n**	**Placebo-adjusted**
Peripheral edema	14 (11)	45 (17)	6
Nasal congestion	2 (2)	15 (6)	4
Sinusitis	0 (0)	8 (3)	3
Flushing	1 (1)	10 (4)	3

Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent.

Few notable differences in the incidence of adverse reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving Letairis (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥65 years) receiving Letairis (29%; 16/56) compared to placebo (4%; 1/28). The results of such subgroup analyses must be interpreted cautiously.

The incidence of treatment discontinuations due to adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for Letairis (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for placebo (7%; 9/132 patients) and for Letairis (5%; 13/261 patients).

During 12-week controlled clinical trials, the incidence of aminotransferase elevations >3 x upper limit of normal (ULN) were 0% on Letairis and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause.

Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Serum Liver Enzyme Abnormalities

In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to aminotransferase elevations >3 x ULN were treated with Letairis. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5 x ULN, but 9 patients had elevations >8 x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of aminotransferase abnormalities that

required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8 x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on Letairis 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients increasing the dose of Letairis median follow-up of 13 months and with 50% of patients increasing the dose of Letairis to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs or show that Letairis led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that Letairis may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

TO:

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data for Letairis ~~were obtained~~ are presented from two 12-week, placebo-controlled studies (ARIES-1 and ARIES-2) in patients with pulmonary arterial hypertension (PAH) ~~(ARIES-1 and ARIES-2) and four nonplacebo-controlled studies~~ and one randomized, double-blind, active-controlled trial in ~~483~~ 605 patients with PAH (AMBITION) ~~who were treated with doses of~~

~~1, 2.5, 5~~ comparing Letairis plus tadalafil to Letairis or tadalafil alone. The exposure to Letairis in these studies ranged from 1 day to 4 years (N=357 ~~418~~ for at least 6 months and N=279 ~~343~~ for at least 1 year).

In ARIES-1 and ARIES-2, a total of 261 patients received Letairis at doses of 2.5, 5, or 10 mg once daily and 132 patients received placebo. The adverse reactions that occurred in >3% more patients receiving Letairis than receiving placebo are shown in Table 1.

Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent.

Few notable differences in the incidence of adverse reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving Letairis (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥65 years) receiving Letairis (29%; 16/56) compared to placebo (4%; 1/28). The results of such subgroup analyses must be interpreted cautiously.

The incidence of treatment discontinuations due to adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for Letairis (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for placebo (7%; 9/132 patients) and for Letairis (5%; 13/261 patients).

During 12-week controlled clinical trials, the incidence of aminotransferase elevations >3 x upper limit of normal (ULN) were 0% on Letairis and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause.

Combination Use with Tadalafil

The mean exposure to Letairis + tadalafil in the AMBITION study was 78.7 weeks. The adverse reactions that occurred in >5% more patients receiving Letairis + tadalafil than receiving Letairis or tadalafil monotherapy in AMBITION are shown in Table 2.

Table 2 Adverse Reactions Reported More Commonly (>5%) on Letairis + Tadalafil than on Letairis or Tadalafil Monotherapy (ITT) in AMBITION

Adverse Reactions	Letairis + Tadalafil Combination Therapy (N=302) n (%)	Letairis Monotherapy (N=152) n (%)	Tadalafil Monotherapy (N=151) n (%)
Peripheral edema	135 (45%)	58 (38%)	43 (28%)
Headache	125 (41%)	51 (34%)	53 (35%)
Nasal congestion	58 (19%)	25 (16%)	17 (11%)
Cough	53 (18%)	20 (13%)	24 (16%)
Anemia	44 (15%)	11 (7%)	17 (11%)
Dyspepsia	32 (11%)	5 (3%)	18 (12%)
Bronchitis	31 (10%)	6 (4%)	13 (9%)

Peripheral edema was more frequent on combination therapy; however, there was no notable difference observed in the incidence of peripheral edema in elderly patients (≥65 years) versus younger patients (<65 years) on combination therapy (44% vs. 45%) or Letairis monotherapy (37% vs. 39%) in AMBITION.

Treatment discontinuations due to adverse events while on randomized treatment were similar across treatment groups: 16% for Letairis + tadalafil, 14% for Letairis alone, and 13% for tadalafil alone.

Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Serum Liver Enzyme Abnormalities

In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to aminotransferase elevations >3 x ULN were treated with Letairis. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5 x ULN, but 9 patients had elevations >8 x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8 x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on Letairis 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients increasing the dose of Letairis to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs or show that Letairis led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that Letairis may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

In the **ADVERSE REACTIONS** section, subsection 6.2 **Postmarketing Experience**:

FROM:
6.2 Postmarketing Experience

The following adverse reactions were identified during postapproval use of Letairis. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate reliably the frequency or to establish a causal relationship to drug exposure: anemia *[see Warnings and Precautions (5.6)]*, asthenia, dizziness, fatigue, fluid retention *[see Warnings and Precautions (5.3)]*, heart failure (associated with fluid retention), hypersensitivity (eg, angioedema, rash), nausea, and vomiting.

Elevations of liver aminotransferases (ALT, AST) have been reported with Letairis use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). Other endothelin receptor antagonists have been associated with elevations of aminotransferases, hepatotoxicity, and cases of liver failure *[see Adverse Reactions (6.1)]*.

TO:
6.2 Postmarketing Experience

The following adverse reactions were identified during post-approval use of Letairis. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate reliably the frequency or to establish a causal relationship to drug exposure: anemia

requiring transfusion [see Warnings and Precautions (5.6)] ~~asthenia, dizziness, fatigue, fluid retention [see Warnings and Precautions (5.3)]~~, heart failure (associated with fluid retention), symptomatic hypotension, and hypersensitivity (e.g., angioedema, rash)~~, nausea and vomiting~~.

Elevations of liver aminotransferases (ALT, AST) have been reported with Letairis use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). Other endothelin receptor antagonists have been associated with elevations of aminotransferases, hepatotoxicity, and cases of liver failure [see Adverse Reactions (6.1)].

In the **USE IN SPECIFIC POPULATIONS** section, subsection 8.1 **Pregnancy, Animal Data:**

FROM:
Animal Data

Letairis was teratogenic at oral doses of ≥15 mg/kg/day (AUC 51.7 h•µg/mL) in rats and ≥7 mg/kg/day (24.7 h•µg/mL) in rabbits; it was not studied at lower doses. These doses are of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day (14.8 h•µg/mL) based on AUC. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid.

A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testicle size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 17 x, 51 x, and 170 x (on a mg/kg:mg/m^2 basis) the maximum oral human dose of 10 mg and an average adult body weight of 70 kg.

TO:
Letairis was teratogenic at oral ~~doses~~ dosages of ≥15 mg/kg/day (AUC 51.7 h•µg/mL) in rats and ≥7
mg/kg/day (24.7 h•µg/mL) in rabbits; it was not studied at lower ~~doses~~ dosages. These ~~doses~~ ~~dosages~~ are of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day (14.8 h•µg/mL) based on AUC. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid.

A preclinical study in rats has shown decreased survival of newborn pups (mid and high dosages) and effects on testicle size and fertility of pups (high ~~dose~~ dosage) following maternal treatment with ambrisentan from late gestation through weaning. ~~Doses tested~~ The mid and high dosages were 51 x, and 170 x (on a ~~mg/kg~~ mg/m^2 body surface area basis) the maximum oral human dose of 10 mg and an average adult body weight of 70 kg. These effects were absent at a maternal dosage 17 x the human dose based on mg/m^2.

In the **CLINICAL PHARMACOLOGY** section, subsection 12.2 **Pharmacodynamics**:

FROM:

Cardiac Electrophysiology

In a randomized, positive and placebo controlled, parallel group study, healthy subjects received either Letairis 10 mg daily followed by a single dose of 40 mg, placebo followed by a single dose of moxifloxacin 400 mg, or placebo alone. Letairis 10 mg daily had no significant effect on the QTc interval. The 40 mg dose of Letairis increased mean QTc at tmax by 5 ms with an upper 95% confidence limit of 9 ms. For patients receiving Letairis 5–10 mg daily and not taking metabolic inhibitors, no significant QT prolongation is expected.

TO:

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received either Letairis 10 mg daily followed by a single dose of 40 mg, placebo followed by a single dose of moxifloxacin 400 mg, or placebo alone. Letairis 10 mg daily had no significant effect on the QTc interval. The 40 mg dose of Letairis increased mean QTc at t_{max} by 5 ms with an upper 95% confidence limit of 9 ms. For patients receiving Letairis 5–10 mg daily and not taking metabolic inhibitors, no significant QT prolongation is expected.

N-terminal pro-B-type natriuretic peptide (NT-proBNP)

In AMBITION *[see Clinical Studies (14.2)]*, the decrease in NT-proBNP in patients on Letairis plus tadalafil was observed early (Week 4) and was sustained, with a reduction of 63% on Letairis plus tadalafil, 50% on Letairis alone, and 41% on tadalafil alone at Week 24.

In the **CLINICAL STUDIES** section, subsection 14.2 was inserted as follows, and subsection 14.2 and 14.3 were renumbered:

New Subsection 14.2:

14.2 Combination Treatment of PAH

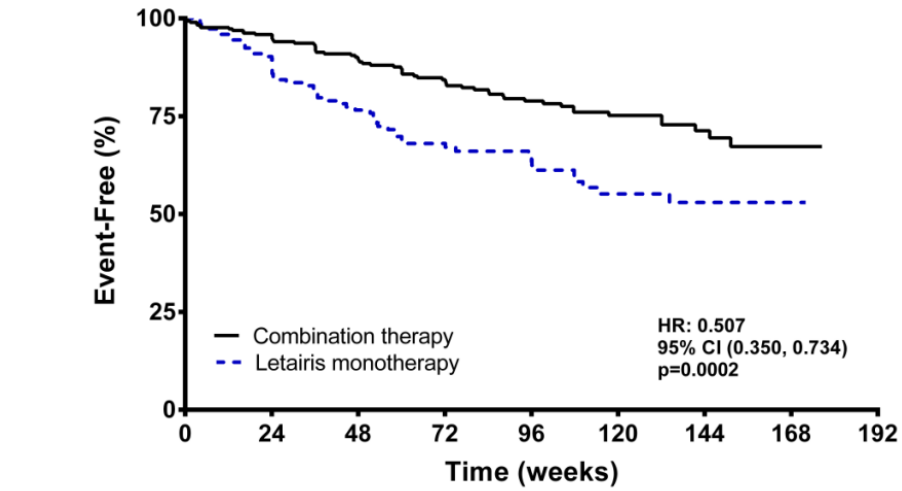
In a randomized, double-blind, active-controlled trial (AMBITION), 605 patients with WHO Functional Class II or III PAH were randomized 2:1:1 to once daily Letairis plus tadalafil or to Letairis or tadalafil alone. Treatment was initiated with Letairis 5 mg and tadalafil 20 mg. If tolerated, tadalafil was increased to 40 mg at 4 weeks and Letairis was increased to 10 mg at 8 weeks.

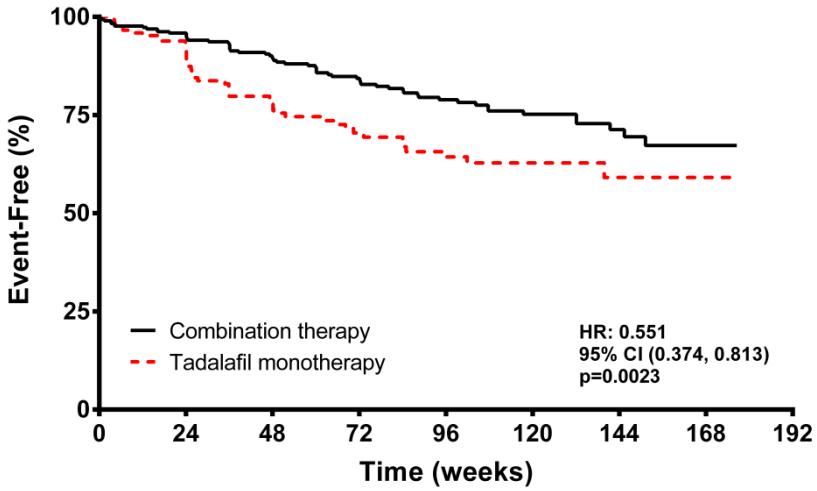
The primary endpoint was time to first occurrence of (a) death, (b) hospitalization for worsening PAH, (c) >15% decrease from baseline in 6MWD combined with WHO Functional Class III or IV symptoms sustained over 14 days (short term clinical worsening), or (d) reduction in 6MWD sustained over 14 days combined with WHO Functional Class III or IV symptoms sustained over 6 months (inadequate long term clinical response).

Patients had idiopathic PAH (55%), heritable PAH (3%), or PAH associated with connective tissue diseases, congenital heart disease, stable HIV infection, or drugs or toxins (APAH, 43%). Median time from diagnosis to first study drug administration was 25 days. Approximately 32% and 68% of patients were in WHO Functional Class II and III, respectively. The mean patient age was 55.7 years (34% were ≥65 years old). Most patients were white (90%) and female (76%); 45% were North American.

Principal results are shown in Figures 6 and 7.

Figure 6 Time to Primary Endpoint Event (AMBITION)

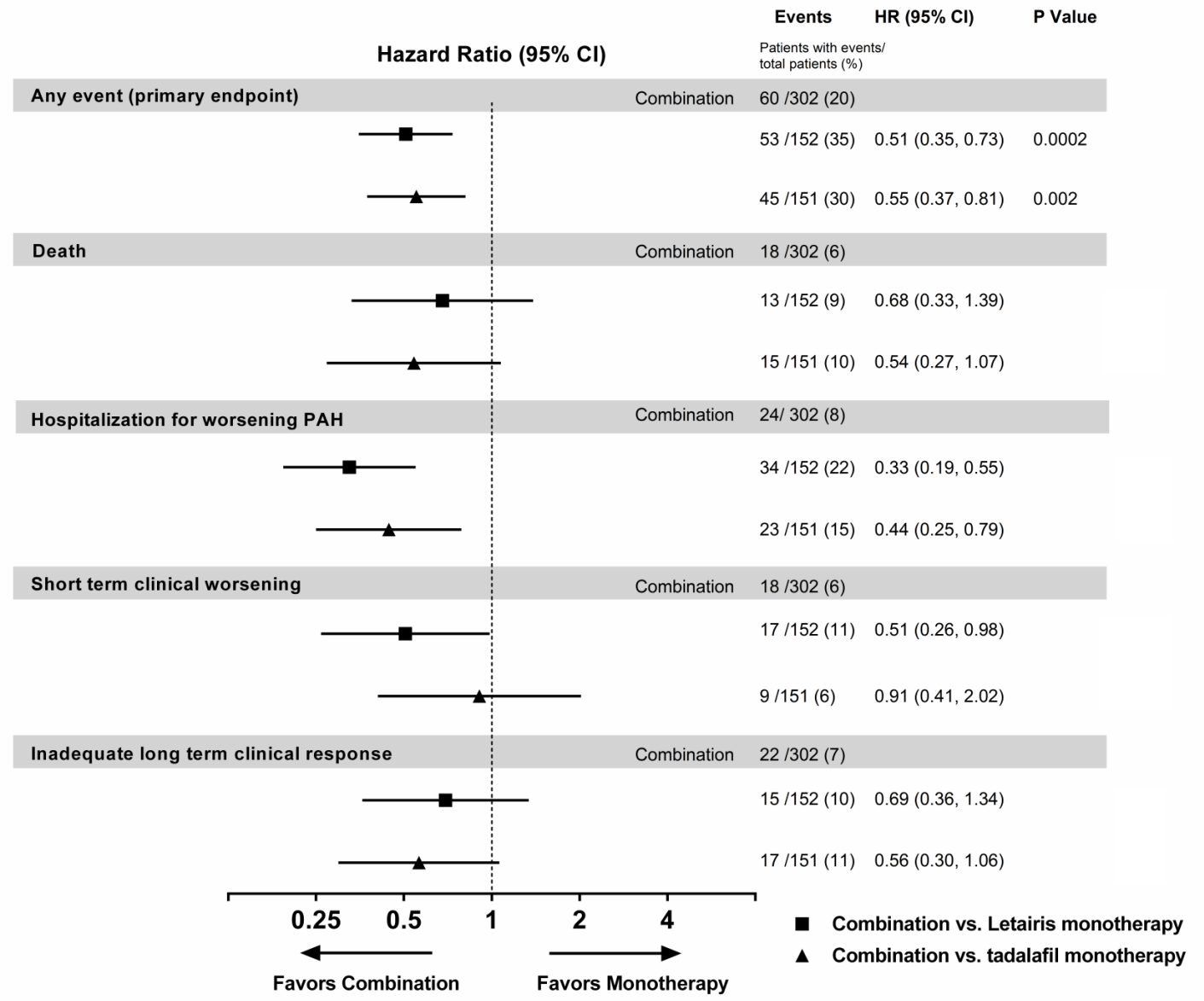




Number at risk:

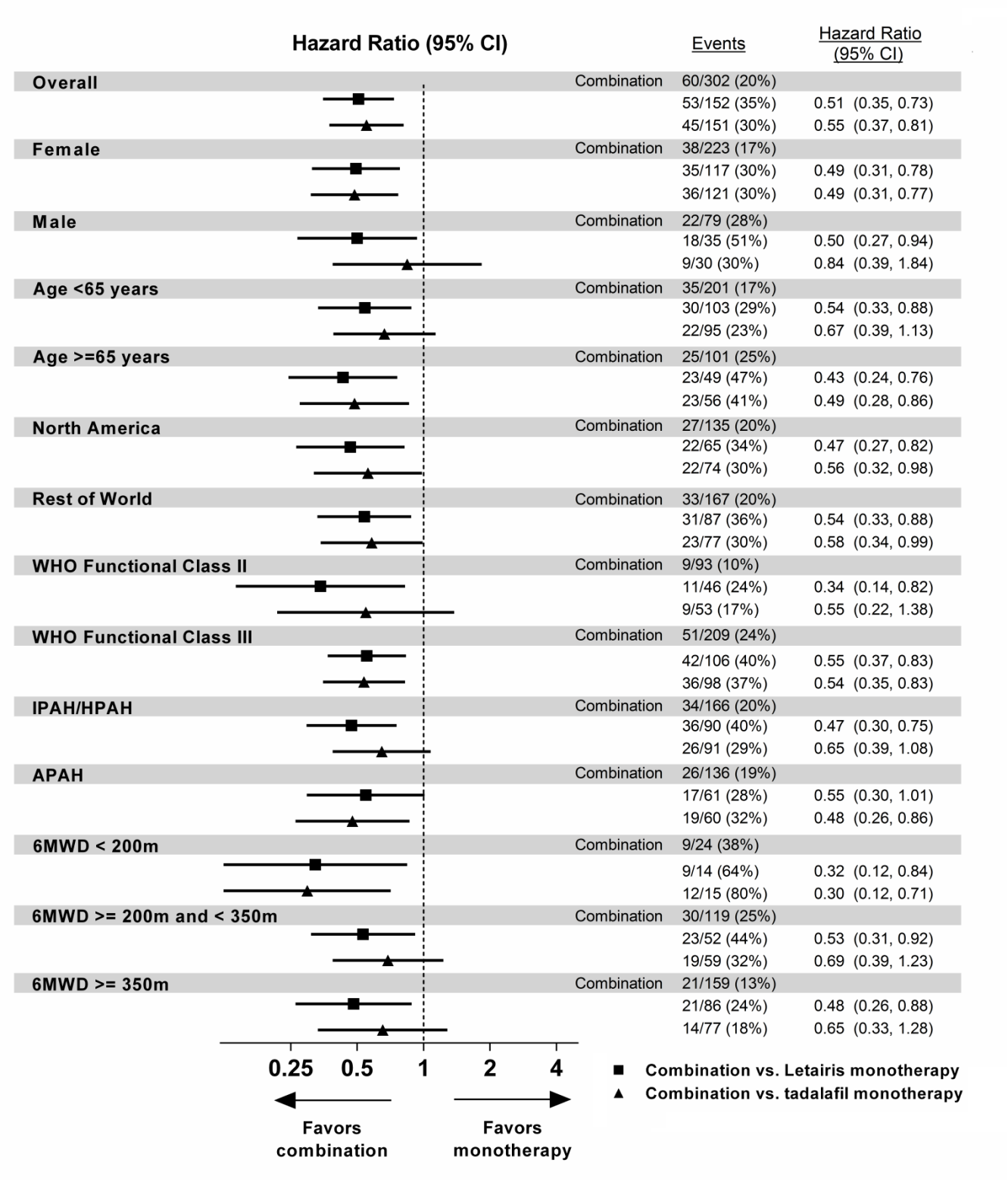
Combination:	302	270	217	170	126	85	45	9
Tadalafil monotherapy:	151	128	92	65	48	33	15	3

Figure 7 Primary Endpoint Events and First Occurrences of Each Component at Any Time (AMBITION)



The treatment effect of Letairis plus tadalafil compared with individual monotherapy on time to first primary endpoint event was consistent across subgroups. (Figure 8).

Figure 8 Primary Endpoint by Subgroups (AMBITION)



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over interpreted.

Exercise Ability

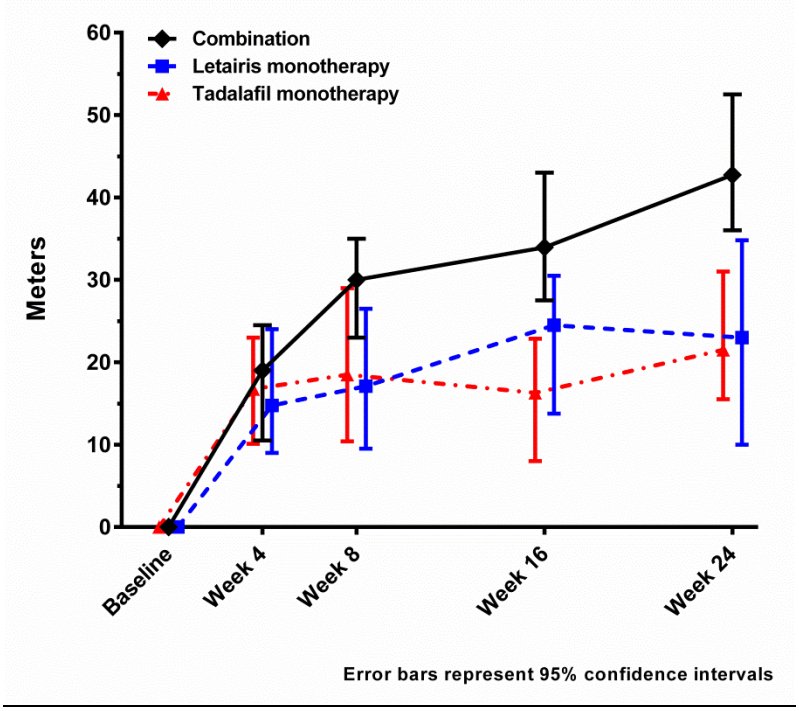
Results of the 6MWD at 24 weeks for the AMBITION study are shown in Table 5 and Figure 9.

Table 5 6-Minute Walk Distance at Week 24 (meters)[a] (AMBITION)

	Letairis + Tadalafil (N=302)	**Letairis Monotherapy (N=152)**	**Tadalafil Monotherapy (N=151)**
Baseline (median)	356	366	352
Change from baseline (median)	43	23	22
Median difference from Letairis + Tadalafil (95% CI)		24 (11, 37)	20 (8, 32)
P-Value		0.0004	0.0016

a Missing values at Week 24 were imputed using Worst Rank scores for patients with an adjudicated clinical failure event of death or hospitalization, and Last Observed Carried Forward otherwise.

Figure 9 Median Change in 6-Minute Walk Distance (meters) in AMBITION



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.

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.

NON-FULFILLMENT OF POSTMARKETING COMMITMENT

We refer to the following post-marketing commitment:

1268-1. Gilead agrees to conduct a study examining the effects of LETAIRIS on 6-minute walk distance at peak and trough plasma concentrations, and further agrees to reach agreement on an appropriate study design with the Division.

Protocol Submission:	by 10/1/2007
Study Start:	by 06/2008
Final Report Submission:	by 12/2009

After reviewing your submission, we concluded that the data submitted as part of this supplement were not sufficient to meet the terms of this posmarketing commitment for the following reasons:

The effect of ambrisentan on 6MWD at peak and trough plasma concentration was evaluated in the combination arm by subtracting the effect of tadalafil. No evaluations in the ambrisentan monotherapy arm were performed.

After adjusting for the effect of tadalafil, 6MWD for the combination group was greater at trough (17.4 m) when compared to peak (7 m). As a numerically greater distance at trough when compared to peak is against the expectation, the study results are effectively inconclusive.

In addition, there are issues with the design of this assessment -

- It appears to be assumed that the subtraction of the tadalafil effect from the combination treatment effect represents ambrisentan effect alone. This assumption is not verified.
- Baseline measurements of 6MWD were not time-matched to account for variations in 6MWD based on timing of the day.

Therefore, this postmarketing commitment is not fulfilled and remains an open commitment.

The original milestone due dates were not met, therefore this commitment is considered delayed. This status will be posted on the FDA Postmarketing Requirements and Commitments website, http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Letairis was originally approved on May 29, 2009, and the most recent modification was approved on October 29, 2014. 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 modification to the REMS consists of changes to incorporate the revised indication into the REMS appended material, *Prescriber Guide for the Letairis REMS Program*.

Your proposed modified REMS, submitted on December 5, 2014, amended on September 23, 24, and 28, 2015, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on August 24, 2010.

There are no changes to the REMS assessment plan described in our August 17, 2013, 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 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 22081 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 22081 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22081/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 22081/S-000

PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 22081/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 22081/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 22081

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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, call Wayne Amchin, RAC, Regulatory Project Manager, at (301) 796-0421.

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(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/

NORMAN L STOCKBRIDGE
10/02/2015