DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020839/S-062
NDA 020839/S-064

SUPPLEMENT APPROVAL

Sanofi-Aventis U.S., LLC
Attention: Cristina Di Ramio, PharmD.
Senior Manager, North America & Global Regulatory Affairs
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Bridgewater, NJ 08807

Dear Ms. Di Ramio:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received August 14, 2015 (S-062) and March 15, 2016 (S-064), and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Plavix (clopidogrel bisulfate) 75 mg and 300 mg Tablets.

These supplemental new drug applications provide for revised labeling as follows (additions are shown as underlined text, deletions are shown as ~~strikethrough~~ text):

1. In **HIGHLIGHTS**, the following changes were made:

WARNING: DIMINISHED ANTIPLATELET EFFECT~~IVENESS~~ IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE~~POOR METABOLIZERS~~

See full prescribing information for complete boxed warning.

- **Effectiveness of Plavix depends on ~~activation~~conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1, 12.3)**
- ~~**Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)**~~
- **Tests are available to identify ~~a~~ patient's who are CYP2C19 ~~genotype and can be used as an aid in determining therapeutic strategy~~ poor metabolizers. (12.5)**
- **Consider use of ~~alternative treatment or treatment strategies~~another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers. (~~2.3,~~ 5.1)**

----------**RECENT MAJOR CHANGES**----------

Boxed Warning	09/2016
Indications and Usage (*1.1*, *1.2*)	09/2016
Dosage and Administration (*2*)	09/2016
Warnings and Precautions (*5*)	09/2016

----------**INDICATIONS AND USAGE**----------

Plavix is a P2Y12 platelet inhibitor indicated for:

- Acute coronary syndrome
  - For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], Plavix has been shown to ~~decrease~~ reduce the rate of ~~a combined endpoint of cardiovascular death,~~ myocardial infarction (MI)~~, or~~ and stroke. ~~as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.~~ (1.1)
  - For patients with ST-elevation myocardial infarction (STEMI), Plavix has been shown to reduce the rate of ~~death from any cause and the rate of a combined endpoint of death, re-infarction, MI or~~and stroke. ~~The benefit for patients who undergo primary PCI is unknown.~~ (1.1)
- Recent MI, recent stroke, or established peripheral arterial disease. Plavix has been shown to reduce the ~~combined endpoint~~ rate of MI and~~new ischemic~~ stroke, ~~new MI, and other vascular death.~~ (1.2)

----------**DOSAGE AND ADMINISTRATION**----------

- Acute coronary syndrome (2.1)
  - ~~UA/NSTEMI:~~Initiate Plavix with a single 300 mg oral loading dose ~~followed by~~and then continue at 75 mg once daily, ~~in combination with aspirin (75-325 mg once daily)~~
  - ~~STEMI: ~~Initiating Plavix without a loading dose will delay establishment of an antiplatelet effect by several days~~75 mg once daily, in combination with aspirin (75-325 mg once daily), with or without a loading dose~~
- Recent MI, recent stroke, or established peripheral arterial disease: 75 mg once daily orally without a loading dose (2.2)

----------**WARNINGS AND PRECAUTIONS**----------

- CYP2C19 inhibitors: Avoid concomitant use of omeprazole or esomeprazole. (5.1)
- Bleeding: Plavix increases risk of bleeding. ~~Discontinue 5 days prior to elective surgery.~~ (5.2)
- Discontinuation: Premature discontinuation increases risk of cardiovascular events. Discontinue 5 days prior to elective surgery that has a major risk of bleeding. (5.3)
- ~~Recent transient ischemic attack or stroke: Combination use of Plavix and aspirin is not more effective than Plavix alone, but increases major bleeding. (5.4)~~
- Thrombotic thrombocytopenic purpura (TTP) has been reported. (5.4~~5~~)
- Cross-reactivity among thienopyridines has been reported. (5.5~~6~~)

----------**DRUG INTERACTIONS**----------

- Nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRIs, SNRIs): Increases risk of bleeding. (7.2,7.3,7.4)
- Repaglinide (CYP2C8 substrates): Increases substrate plasma concentrations. (7.5)

2. The **FULL PRESCRIBING INFORMATION: CONTENTS** was updated.

3. The Boxed Warning was updated to read:

WARNING: DIMINISHED ANTIPLATELET EFFECT~~IVENESS~~ IN ~~POOR METABOLIZERS~~PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of Plavix ~~is dependent on~~results from its antiplatelet activity~~activation~~ which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*. Plavix at recommended doses forms less of ~~that~~ the active metabolite and so has a ~~smaller~~reduced effect on platelet ~~function~~activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). ~~Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function.~~ Tests are available to identify patients who are CYP2C19 ~~genotype~~poor metabolizers~~; these tests can be used as an aid in determining therapeutic strategy~~ *~~[see Clinical Pharmacology (12.5)]~~*. Consider use of ~~alternative treatment or treatment strategies~~another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers *~~[see Dosage and Administration (2.3)]~~*.

4. Under **INDICATIONS AND USAGE**, the following changes were made:

1.1 Acute Coronary Syndrome (ACS)

- Plavix is indicated to reduce the rate of myocardial infarction and stroke MI) ~~For~~in patients with non ST segment elevation ACS [unstable angina (UA)/non ST elevation myocardial infarction (NSTEMI)], including patients who are to be managed medically and those who are to be managed with coronary revascularization. Plavix should be administered in conjunction with aspirin.~~, Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.~~
- Plavix is indicated to reduce the rate of myocardial infarction and stroke ~~For~~in patients with acute ST elevation myocardial infarction (STEMI) who are to be managed medically. Plavix should be administered in conjunction with aspirin.~~, Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re infarction, or stroke. The benefit for patients who undergo primary percutaneous coronary intervention is unknown.~~

~~The optimal duration of Plavix therapy in ACS is unknown.~~

1.2 Recent MI, Recent Stroke, or Established Peripheral Arterial Disease
In patients with established peripheral arterial disease ~~For patients~~or with a history of recent myocardial infarction (MI), or recent stroke~~, or established peripheral arterial disease,~~ Plavix ~~has been shown~~ is indicated to reduce the rate of MI and stroke ~~a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death~~.

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

2.1 Acute Coronary Syndrome
~~Plavix can be administered with or without food *[see Clinical Pharmacology (12.3)]*.~~
In patients who need an antiplatelet effect within hours, initiate Plavix with a single 300-mg oral loading dose and then continue at 75 mg once daily. Initiating Plavix without a loading dose will delay establishment of an antiplatelet effect by several days *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1)]*.

- ~~For patients with non ST-elevation ACS (UA/NSTEMI), initiate Plavix with a single 300 mg oral loading dose and then continue at 75 mg once daily. Initiate aspirin (75 325 mg once daily) and continue in combination with Plavix *[see Clinical Studies (14.1)]*.~~

- ~~For patients with STEMI, the recommended dose of Plavix is 75 mg once daily orally, administered in combination with aspirin (75 325 mg once daily), with or without thrombolytics. Plavix may be initiated with or without a loading dose *[see Clinical Studies (14.1)]*.~~

2.2 Recent MI, Recent Stroke, or Established Peripheral Arterial Disease
~~The recommended daily dose of Plavix is~~ 75 mg once daily orally without a loading dose, ~~with or without food~~ *[see Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

~~**2.3 CYP2C19 Poor Metabolizers**~~
~~CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response *[see Clinical Pharmacology (12.5)]*, an appropriate dose regimen for this patient population has not been established.~~

~~**2.4 Use with Proton Pump Inhibitors (PPI)**~~
~~Avoid using omeprazole or esomeprazole with Plavix. Omeprazole and esomeprazole significantly reduce the antiplatelet activity of Plavix. When concomitant administration of a PPI is required, consider using another acid reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite *[see Warnings and Precautions (5.1), Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.~~

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

5.1 Diminished Antiplatelet Activity ~~Due to~~ in Patients with Impaired CYP2C19 Function
Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can

be impaired by genetic variations in CYP2C19 *[see Boxed Warning]*. ~~and by concomitant medications that interfere with CYP2C19.~~

~~*Proton Pump Inhibitors*~~
The metabolism of clopidogrel can also be impaired by drugs that inhibit CYP2C19, such as omeprazole or esomeprazole. Avoid concomitant use of Plavix with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of Plavix *[see Drug Interactions (7.1) ~~and Dosage and Administration (2.4)~~]*.

5.2 General Risk of Bleeding
Thienopyridines, including Plavix, increase the risk of bleeding. ~~If a patient is to undergo surgery and an antiplatelet effect is not desired, discontinue Plavix five days prior to surgery. In patients who stopped therapy more than five days prior to CABG the rates of major bleeding were similar (event rate 4.4% Plavix + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of CABG, the major bleeding rate was 9.6% for Plavix + aspirin, and 6.3% for placebo + aspirin.~~

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7 10 days). ~~, so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure.~~ Because the half-life of clopidogrel's active metabolite is short, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.

5.3 Discontinuation of Plavix
Discontinuation of Plavix may increase the risk of cardiovascular events. ~~Avoid lapses in therapy, and I~~if Plavix must be temporarily discontinued (e.g., to treat bleeding or for surgery with a major risk of bleeding), restart it as soon as possible. When possible, interrupt therapy with Plavix for five days prior to such surgery. Resume Plavix as soon as hemostasis is achieved. ~~Premature discontinuation of Plavix may increase the risk of cardiovascular events.~~

~~**5.4 Patients with Recent Transient Ischemic Attack (TIA) or Stroke**~~
~~In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and Plavix has not been shown to be more effective than Plavix alone, but the combination has been shown to increase major bleeding.~~

5.4~~5~~ Thrombotic Thrombocytopenic Purpura (TTP)
TTP, sometimes fatal, has been reported following use of Plavix, sometimes after a short exposure (<2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever *[see Adverse Reactions (6.2)]*.

5.5~~6~~ Cross-Reactivity among Thienopyridines
Hypersensitivity including rash, angioedema or hematologic reaction have been reported in patients receiving Plavix, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines *[see Contraindications (4.2) and Adverse Reactions (6.2)]*.

7. Under **ADVERSE REACTIONS/Clinical Studies Experience**, the following text was deleted under Table 1:

~~* Other standard therapies were used as appropriate.~~
† Life threatening and other major bleeding.
~~‡ Major bleeding event rate for Plavix + aspirin was dose dependent on aspirin: 100 mg = 2.6%; 100-200 mg = 3.5%; 200 mg = 4.9%~~
~~Major bleeding event rates for Plavix + aspirin by age were: <65 years = 2.5%, 65 to <75 years = 4.1%, 75 years = 5.9%~~
~~§ Major bleeding event rate for placebo + aspirin was dose dependent on aspirin: 100 mg = 2.0%; 100-200 mg = 2.3%; 200 mg = 4.0%~~
~~Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, 65 to <75 years = 3.1%, 75 years = 3.6%~~
¶ Led to interruption of study medication.

~~Ninety two percent (92%) of the patients in the CURE study received heparin or low molecular weight heparin (LMWH), and the rate of bleeding in these patients was similar to the overall results.~~

8. Under **ADVERSE REACTIONS/Clinical Studies Experience**, the following text was deleted under Table 2:

* Major bleeds were cerebral bleeds or non - cerebral bleeds thought to have caused death or that required transfusion.
~~** The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for Plavix + aspirin by age were: <60 years = 0.3%, 60 to <70 years = 0.7%, 70 years = 0.8%. Event rates for placebo + aspirin by age were: <60 years = 0.4%, 60 to <70 years = 0.6%, 70 years = 0.7%.~~

9. Under **ADVERSE REACTIONS/Postmarketing Experience,** the following text was added/deleted:

<u>Hemorrhages, including those with fatal outcome, have been reported in patients treated with Plavix.</u>

- Blood and lymphatic system disorders: Agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP), acquired hemophilia A
- ~~Eye disorders: Eye (conjunctival, ocular, retinal) bleeding~~
- <u>Gastrointestinal disorders:</u> Colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, gastric/duodenal ulcer, diarrhea
- General disorders and administration site condition: Fever~~, hemorrhage of operative wound~~
- Hepato biliary disorders: Acute liver failure, hepatitis (non infectious), abnormal liver function test
- Immune system disorders: Hypersensitivity reactions, anaphylactoid reactions, serum sickness

- Musculoskeletal, connective tissue and bone disorders: ~~Musculoskeletal bleeding,~~ ~~m~~Myalgia, arthralgia, arthritis
- Nervous system disorders: Taste disorders, ~~fatal intracranial bleeding,~~ headache
- Psychiatric disorders: Confusion, hallucinations
- Respiratory, thoracic and mediastinal disorders: Bronchospasm, interstitial pneumonitis, ~~respiratory tract bleeding,~~ eosinophilic pneumonia
- Renal and urinary disorders: Increased creatinine levels
- Skin and subcutaneous tissue disorders: Maculopapular, erythematous or exfoliative rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, ~~skin bleeding,~~ lichen planus, generalized pruritus
- Vascular disorders: Vasculitis, hypotension

10. Under **DRUG INTERACTIONS**, the following text was added/deleted:

7.1 CYP2C19 Inhibitors

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of ~~certain~~ drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition *[see Warnings and Precautions (5.1)~~ and Dosage and Administration (2.4)~~]*.

Omeprazole or esomeprazole~~*Proton Pump Inhibitors (PPI)*~~

Avoid concomitant use of Plavix with omeprazole or esomeprazole. In clinical studies, omeprazole was shown to reduce significantly the antiplatelet activity of Plavix when given concomitantly or 12 hours apart. ~~A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established.~~ A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with Plavix. ~~Consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite.~~ Dexlansoprazole, lansoprazole and pantoprazole had less effect on the antiplatelet activity of Plavix than did omeprazole or esomeprazole *[see ~~Dosage and Administration (2.4),~~ Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

7.5 Repaglinide (CYP2C8 Substrates)

The acyl-β-glucuronide metabolite of clopidogrel is a strong inhibitor of CYP2C8. Plavix can increase the systemic exposure to drugs that are primarily cleared by CYP2C8, thereby needing dose-adjustment and/or appropriate monitoring.

Concomitant administration of Plavix with repaglinide significantly increases systemic exposures to repaglinide *[see Clinical Pharmacology (12.3)]*. When concomitant use is required in a patient maintained on clopidogrel, initiate repaglinide at 0.5 mg with each meal and titrate based on blood glucose levels. Do not exceed a total daily dose of 4 mg. If concomitant use of clopidogrel is required in a patient stabilized on higher doses of repaglinide, down titrate the dose of repaglinide based on blood glucose levels to not exceed a total daily dose of 4 mg.

11. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added/deleted:

Metabolism
Clopidogrel is extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes. Cytochromes first oxidize clopidogrel to a 2 oxo clopidogrel intermediate metabolite. Subsequent metabolism of the 2 oxo clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including T~~his metabolic pathway is mediated by CYP2C19, CYP3A, CYP2B6 and~~ CYP1A2, CYP2B6 and CYP3A. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.

The Cmax of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose. Cmax occurs approximately 30 to 60 minutes after dosing. In the 75 to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: ~~increasing~~ 4 fold the dose ~~by a factor of four~~ results in 2.0 and 2.7 fold ~~increases in~~the Cmax and AUC, respectively.

Drug Interactions
Effect of other drugs on Plavix
Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of certain inhibitors of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.

Effect of Plavix on other drugs
In vitro studies have shown that the glucuronide metabolite of clopidogrel is a strong inhibitor of CYP2C8. Concomitant administration of repaglinide with Plavix increased the systemic exposure to repaglinide ($AUC_{0-\infty}$) by 5.1-fold following the loading dose (300 mg) and by 3.9-fold on day 3 of the maintenance dose (75 mg) of Plavix *[see Drug Interactions (7.5)]*.

12. Under **CLINICAL PHARMACOLOGY/Pharmacogenomics**, the following text was added/deleted:

CYP2C19 is involved in the formation of both the active metabolite and the 2 oxo clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by ex vivo platelet aggregation assays, differ according to CYP2C19 genotype. ~~Genetic variants of other CYP450 enzymes may also affect the formation of clopidogrel's active metabolite.~~Patients who are homozygous for nonfunctional alleles of the CYP2C19 gene are termed "CYP2C19 poor metabolizers". Approximately 2% of White and 4% of Black patients are poor metabolizers; the prevalence of poor metabolism is higher in Asian patients (e.g., 14% of Chinese). Tests are available to identify patients who are CYP2C19 poor metabolizers.

~~The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and *3 alleles are nonfunctional. CYP2C19*2 and *3 account for the majority of reduced function alleles in white (85%) and Asian (99%) poor metabolizers. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metabolizer status will possess two loss of function alleles as defined above. Published frequencies for poor CYP2C19 metabolizer genotypes are approximately 2% for whites, 4% for blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.~~

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups. ~~When poor metabolizers received the 600 mg/150 mg regimen, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen (see Table 3). An appropriate dose regimen for this patient population has not been established in clinical outcome trials.~~

-	~~Dose~~	~~Ultrarapid (n=10)~~	~~Extensive (n=10)~~	~~Intermediate (n=10)~~	~~Poor (n=10)~~
~~Cmax (ng/mL)~~	~~300 mg (24 h)~~	~~24 (10)~~	~~32 (21)~~	~~23 (11)~~	~~11 (4)~~
-	~~600 mg (24 h)~~	~~36 (13)~~	~~44 (27)~~	~~39 (23)~~	~~17 (6)~~
-	~~75 mg (Day 5)~~	~~12 (6)~~	~~13 (7)~~	~~12 (5)~~	~~4 (1)~~
-	~~150 mg (Day 5)~~	~~16 (9)~~	~~19 (5)~~	~~18 (7)~~	~~7 (2)~~
-					
~~IPA (%)*~~	~~300 mg (24 h)~~	~~40 (21)~~	~~39 (28)~~	~~37 (21)~~	~~24 (26)~~
-	~~600 mg (24 h)~~	~~51 (28)~~	~~49 (23)~~	~~56 (22)~~	~~32 (25)~~
-	~~75 mg (Day 5)~~	~~56 (13)~~	~~58 (19)~~	~~60 (18)~~	~~37 (23)~~
-	~~150 mg (Day 5)~~	~~68 (18)~~	~~73 (9)~~	~~74 (14)~~	~~61 (14)~~
~~VASP-PRI (%) †~~	~~300 mg (24 h)~~	~~73 (12)~~	~~68 (16)~~	~~78 (12)~~	~~91 (12)~~
	~~600 mg (24 h)~~	~~51 (20)~~	~~48 (20)~~	~~56 (26)~~	~~85 (14)~~
	~~75 mg (Day 5)~~	~~40 (9)~~	~~39 (14)~~	~~50 (16)~~	~~83 (13)~~
	~~150 mg (Day 5)~~	~~20 (10)~~	~~24 (10)~~	~~29 (11)~~	~~61 (18)~~

~~Values are mean (SD)~~
~~* Inhibition of platelet aggregation with 5mcM ADP; larger value indicates greater platelet inhibition~~
~~† Vasodilator-stimulated phosphoprotein – platelet reactivity index; smaller value indicates greater platelet inhibition~~

	Dose	Poor (n=10)	Intermediate* (n=10)	Normal (n=10)	Ultrarapid† (n=10)
Cmax (ng/mL)	300 mg (24 h)	11 (4)	23 (11)	32 (21)	24 (10)
-	600 mg (24 h)	17 (6)	39 (23)	44 (27)	36 (13)
-	75 mg (Day 5)	4 (1)	12 (5)	13 (7)	12 (6)
-	150 mg (Day	7 (2)	18 (7)	19 (5)	16 (9)

	5)				
IPA (%)††	300 mg (24 h)	24 (26)	37 (21)	39 (28)	40 (21)
	600 mg (24 h)	32 (25)	56 (22)	49 (23)	51 (28)
	75 mg (Day 5)	37 (23)	60 (18)	58 (19)	56 (13)
	150 mg (Day 5)	61 (14)	74 (14)	73 (9)	68 (18)
VASP-PRI (%)†††	300 mg (24 h)	91 (12)	78 (12)	68 (16)	73 (12)
	600 mg (24 h)	85 (14)	56 (26)	48 (20)	51 (20)
	75 mg (Day 5)	83 (13)	50 (16)	39 (14)	40 (9)
	150 mg (Day 5)	61 (18)	29 (11)	24 (10)	20 (10)

Values are mean (SD)
* Intermediate metabolizers have one but not two nonfunctional alleles
† Ultrarapid metabolizers have at least one gain-of-function allele
†† Inhibition of platelet aggregation with 5mcM ADP; larger value indicates greater platelet inhibition
††† Vasodilator-stimulated phosphoprotein – platelet reactivity index; smaller value indicates greater platelet inhibition

~~Some published studies suggest that intermediate metabolizers have decreased active metabolite exposure and diminished antiplatelet effects.~~

~~The relationship between CYP2C19 genotype and Plavix treatment outcome was evaluated in retrospective analyses of Plavix-treated subjects in CHARISMA (n=2428) and TRITON-TIMI 38 (n=1477), and in several published cohort studies. In TRITON-TIMI 38 and the majority of the cohort studies, the combined group of patients with either intermediate or poor metabolizer status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers. In CHARISMA and one cohort study, the increased event rate was observed only in poor metabolizers.~~

13. Under **CLINICAL STUDIES**, the following text was added/deleted:

14.1 Acute Coronary Syndrome

CURE

The CURE study included 12,562 patients with ACS without ST elevation (UA or NSTEMI) and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischemia. Patients were required to have either ECG changes compatible with new ischemia (without ST elevation) or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. ~~The patient population was largely Caucasian (82%) and included 38% women, and 52% patients ≥65 years of age.~~

Patients were randomized to receive Plavix (300 mg loading dose followed by 75 mg once daily) or placebo, and were treated for up to one year. Patients also received aspirin (75 325 mg once daily) and other standard therapies such as heparin. The use of GPIIb/IIIa inhibitors was not permitted for three days prior to randomization.

The patient population was largely White (82%) and included 38% women, and 52% age ≥ 65 years of age. Only about 20% of patients underwent revascularization during the initial hospitalization and few underwent emergent or urgent revascularization.

The number of patients experiencing the primary outcome (CV death, MI, or stroke) was 582 (9.3%) in the Plavix treated group and 719 (11.4%) in the placebo treated group, a 20% relative risk reduction (95% CI of 10% 28%; $p < 0.001$) for the Plavix treated group (see Table 4).

Most of the benefit of Plavix occurred in the first two months, but the difference from placebo was maintained throughout the course of the trial (up to 12 months) (see Figure 2).

~~In CURE, the use~~The effect of Plavix ~~was associated with a lower incidence of CV death, MI or stroke in patient populations with different characteristics~~ did not differ significantly in various subgroups, as shown in Figure 3. The benefits associated with Plavix were independent of the use of other acute and long term cardiovascular therapies, including heparin/LMWH, intravenous glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, lipid lowering drugs, beta blockers, and ACE inhibitors. The efficacy of Plavix was observed independently of the dose of aspirin (75 325 mg once daily). The use of oral anticoagulants, non-study antiplatelet drugs, and chronic NSAIDs was not allowed in CURE.

14. Under **CLINICAL STUDIES/ Acute Coronary Syndrome**, the following Figure was revised:

Figure 3: Hazard Ratio for Patient Baseline Characteristics and On-Study Concomitant Medications/Interventions for the CURE Study

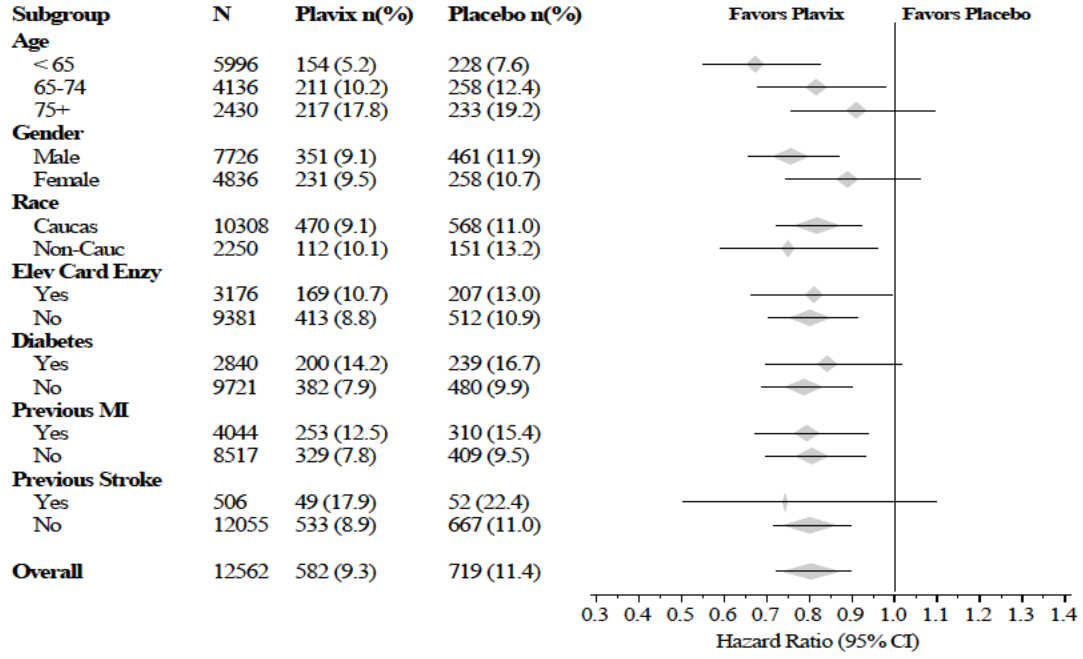
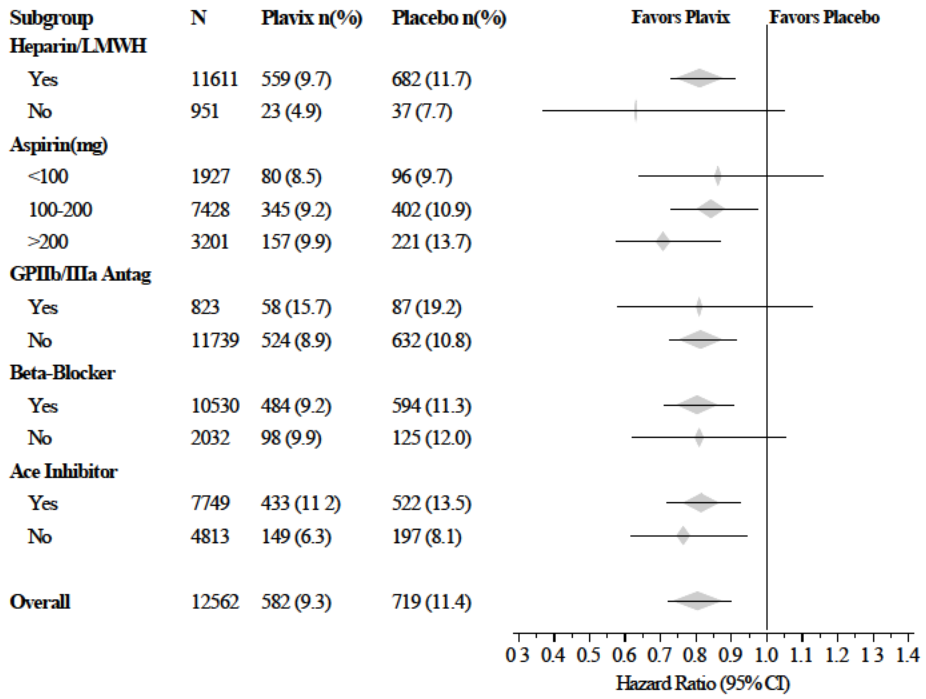


Figure 3: Hazard Ratio for Patient Baseline Characteristics and On-Study Concomitant Medications/Interventions for the CURE Study (continued)



15. Under **CLINICAL STUDIES/ Acute Coronary Syndrome**, the following text was added/deleted:

The patient population~~included~~ was 28% women, and 58% age ≥ 60 years (26% age ≥ 70 years). Fifty-five percent (55%) of patients ~~who~~received thrombolytics, ~~69% who received ACE inhibitors~~ and only 3% ~~who~~ underwent PCI.

As shown in Table 5 and Figure 4 and Figure 5 below, Plavix significantly reduced the relative risk of death from any cause by 7% (p=0.029), and the relative risk of the combination of re-infarction, stroke or death by 9% (p=0.002).

Table 5: Outcome Events in ~~the~~COMMIT ~~Analysis~~

Event	Plavix (+ aspirin) (N=22961)	Placebo (+ aspirin) (N=22891)	Odds ratio (95% CI)	p-value
Composite endpoint: Death, MI, or Stroke*	2121 (9.2%)	2310 (10.1%)	0.91 (0.86, 0.97)	0.002
Death	1726 (7.5%)	1845 (8.1%)	0.93 (0.87,	0.029

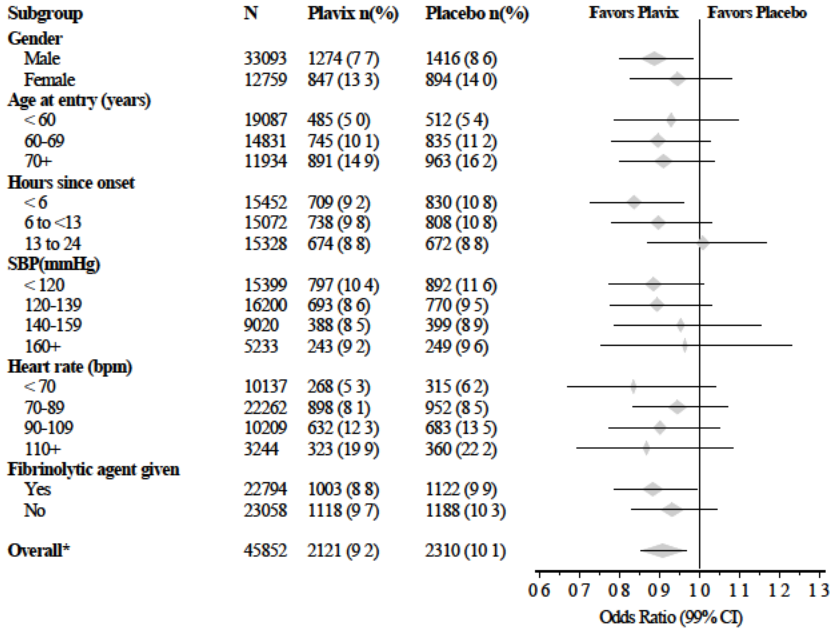
			0.99)	
Non-fatal MI**	270 (1.2%)	330 (1.4%)	0.81 (0.69, 0.95)	0.011
Non-fatal Stroke**	127 (0.6%)	142 (0.6%)	0.89 (0.70, 1.13)	0.33

* ~~The difference between the composite endpoint and the sum of death+non-fatal MI+non-fatal stroke indicates that~~ 9 patients (2 clopidogrel and 7 placebo) suffered both a non-fatal stroke and a non-fatal MI.

** Non-fatal MI and non-fatal stroke exclude patients who died (of any cause).

Figure 6 was revised to read:

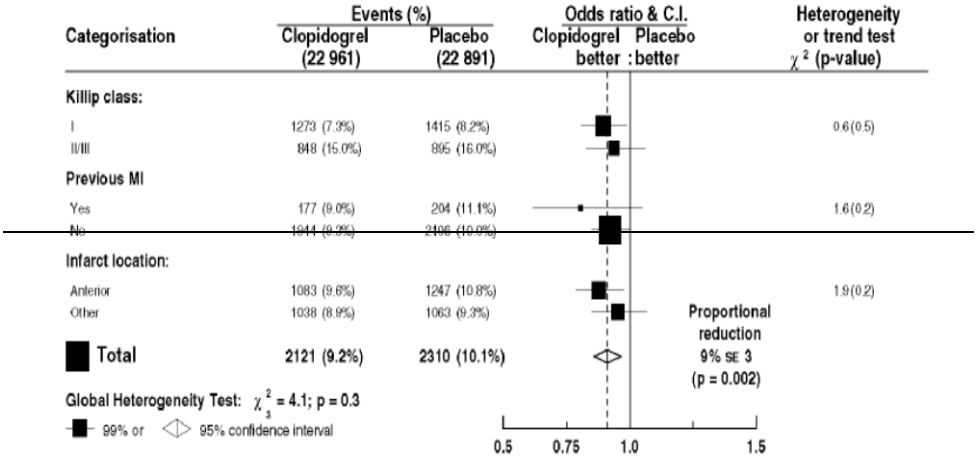
Figure 6: Effects of Adding Plavix to Aspirin on the Combined Primary Endpoint across Baseline and Concomitant Medication Subgroups for the COMMIT Study



*** CI is 95% for Overall row only**

Figure 7 was deleted:

~~**Figure 7: Effects of Adding Plavix to Aspirin in the Non-Prespecified Subgroups in the COMMIT Study**~~

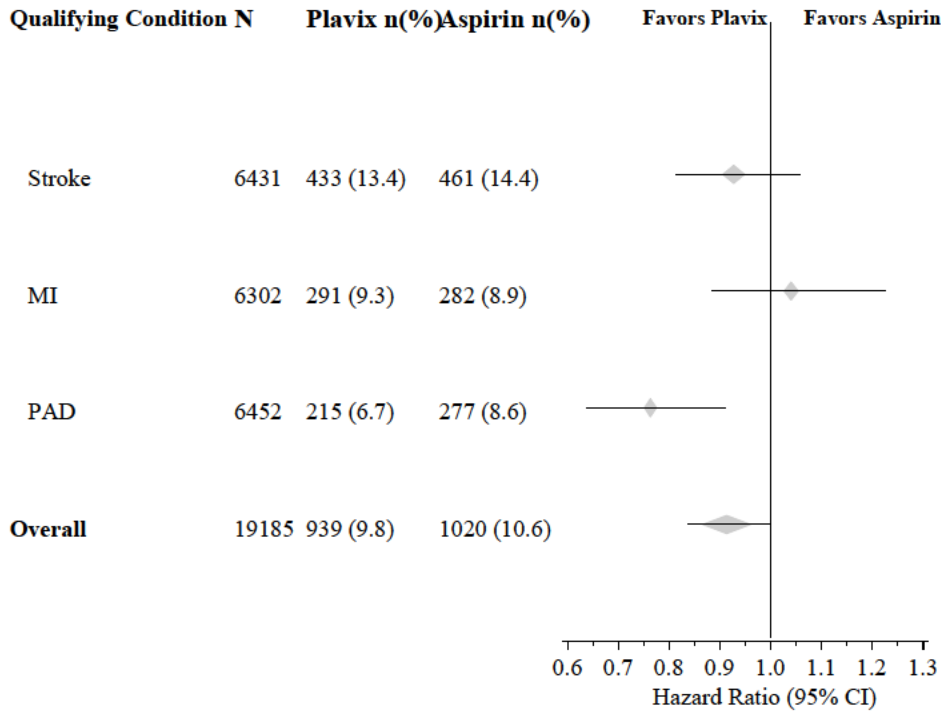


16. Under **CLINICAL STUDIES/Recent Myocardial Infarction, Recent Stroke, or Established Peripheral Arterial Disease**, the following was added/deleted from the first and the sixth paragraphs:

> *CAPRIE*
> The CAPRIE trial was a 19,185 patient, 304 center, international, randomized, double blind, parallel group study comparing Plavix (75 mg daily) to aspirin (325 mg daily). To be eligible to enroll, ~~The~~ patients ~~randomized~~ had to have: 1) recent history~~ies~~ of myocardial infarction (within 35 days); 2) recent histories of ischemic stroke (within 6 months) with at least a week of residual neurological signs; and/or 3) established peripheral arterial disease (PAD). Patients received randomized treatment for an average of 1.6 years (maximum of 3 years).
>
> The CAPRIE trial ~~included~~ enrolled a population that ~~was randomized on the basis of 3 entry criteria~~ had recent MI, recent stroke, or PAD. The efficacy of Plavix relative to aspirin was heterogeneous across these ~~randomized~~ subgroups (p=0.043) (see Figure 8). Nonetheless~~It is not clear whether~~ this difference may be ~~is realor~~ a chance occurrence because~~. Although~~ the CAPRIE trial was not designed to evaluate the relative benefit of Plavix over aspirin in the individual patient subgroups~~,~~. ~~t~~The benefit ~~appeared~~was most apparent ~~to be strongest~~ in patients who were enrolled because of peripheral ~~vascular~~ arterial disease ~~(especially those who also had a history of myocardial infarction) and weaker~~ and less apparent in stroke patients. In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, Plavix was not numerically superior to aspirin.

Figure 8 was revised to read:

Figure 8: Hazard Ratio and 95% CI by Baseline Subgroups in the CAPRIE Study



17. Under **CLINICAL STUDIES,** the following section heading was revised to read:

14.3 ~~Lack of Established~~ No Demonstrated Benefit of Plavix plus Aspirin in Patients with Multiple Risk Factors or Established Vascular Disease

18. Under **PATIENT COUNSELING INFORMATION**, the following text was added/deleted:

Advise patients to read FDA approved patient labeling See (Medication Guide).

Discontinuation
Advise patients not to discontinue Plavix without first discussing it with the health care provider who prescribed it[see Warnings and Precautions (5.3)].

Bleeding:
Advise patients that they:

- will bruise and bleed more easily
- will take longer than usual to stop bleeding
- must report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine [see Warnings and Precautions (5.2)].

Thrombotic Thrombocytopenic Purpura
Instruct patients to get prompt medical attention if they experience symptoms of TTP that cannot otherwise be explained *[see Warnings and Precautions (5.4)]*.
Invasive Procedures

Advise patients to inform physicians and dentists that they are taking Plavix before any surgery or dental procedure *[see Warnings and Precautions (5.2, 5.3)]*.

Proton Pump Inhibitors
Advise patients not to take omeprazole or esomeprazole while taking Plavix. Dexlansoprazole, lansoprazole and pantoprazole had less pronounced effects on the antiplatelet activity of Plavix than did omeprazole or esomeprazole *[see Drug Interactions (7.1)]*.

~~**17.1 Benefits and Risks**~~
~~• Summarize the effectiveness features and potential side effects of Plavix.~~
~~• Tell patients to take Plavix exactly as prescribed.~~
~~• Remind patients not to discontinue Plavix without first discussing it with the physician who prescribed Plavix.~~
~~**17.2 Bleeding**~~
~~Inform patients that they:~~
~~• will bruise and bleed more easily.~~
~~• will take longer than usual to stop bleeding.~~
~~• should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.~~
~~**17.3 Other Signs and Symptoms Requiring Medical Attention**~~
~~• Inform patients that TTP is a rare but serious condition that has been reported with Plavix and other drugs in this class of drugs.~~
~~• Instruct patients to get prompt medical attention if they experience any of the following symptoms that cannot otherwise be explained: fever, weakness, extreme skin paleness, purple skin patches, yellowing of the skin or eyes, or neurological changes.~~
~~**17.4 Invasive Procedures**~~
~~Instruct patients to:~~
~~• inform physicians and dentists that they are taking Plavix before any invasive procedure is scheduled.~~
~~• tell the doctor performing the invasive procedure to talk to the prescribing health care professional before stopping Plavix.~~
~~**17.5 Concomitant Medications**~~
~~Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take *[see Warnings and Precautions (5) and Drug Interactions (7)]*.~~

19. There are numerous editorial changes made, too numerous to mention (e.g. re-numbering of sections, re-numbering of figures and tables).

The following changes were made to the Medication Guide:

1. Under What should I tell my doctor before taking Plavix?, the following text was added:

   Plavix may increase blood levels of other medicines such as repaglinide (Prandin®).

2. Under **How should I take Plavix?**, the fourth bullet was deleted:
   ~~• You can take Plavix with or without food.~~

3. The revision date on the Package Insert and the Medication Guide were updated.

There are no other changes from the last approved package insert.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended, and they are 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, text for the patient 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 include 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).

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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or 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).

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}

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

ENCLOSURE(S):
Content of Labeling

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
09/16/2016
MO review to follow.