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

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1, 12.3)
- Tests are available to identify patients who are CYP2C19 poor metabolizers. (12.5)
- Consider use of another platelet P2Y₁₂ inhibitor in patients identified as CYP2C19 poor metabolizers. (5.1)

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 reduce the rate of myocardial infarction (MI) and stroke. (1.1)
  - For patients with ST-elevation myocardial infarction (STEMI), Plavix has been shown to reduce the rate of MI and stroke. (1.1)
- Recent MI, recent stroke, or established peripheral arterial disease. Plavix has been shown to reduce the rate of MI and stroke. (1.2)

- Acute coronary syndrome (2.1)
  - 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.

DOSE FORMS AND STRENGTHS

Tablets: 75 mg, 300 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding, such as peptic ulcer or intracranial hemorrhage (4.1)
- Hypersensitivity to clopidogrel or any component of the product (4.2)

WARNINGS AND PRECAUTIONS

- CYP2C19 inhibitors: Avoid concomitant use of omeprazole or esomeprazole. (5.1)
- Discontinuation: Premature discontinuation increases risk of cardiovascular events. Discontinue 5 days prior to elective surgery that has a major risk of bleeding. (5.3)
- Thrombotic thrombocytopenic purpura (TTP) has been reported. (5.4)
- Cross-reactivity among thienopyridines has been reported. (5.5)

ADVERSE REACTIONS

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Opioids: Decreased exposure to clopidogrel. Consider use of parenteral antiplatelet agent. (7.2)
- Nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRIs, SNRIs): Increases risk of bleeding. (7.3, 7.4, 7.5)
- Repaglinide (CYP2C8 substrates): Increases substrate plasma concentrations. (7.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2019
6 ADVERSE REACTIONS
The following serious adverse reactions are discussed below and elsewhere in the labeling:
• Bleeding [see Warnings and Precautions (5.2)]
• Thrombotic thrombocytopenic purpura [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions and durations of follow-up, 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.
Plavix has been evaluated for safety in more than 54,000 patients, including over 21,000 patients treated for one year or more. The clinically important adverse reactions observed in trials comparing Plavix plus aspirin to placebo plus aspirin and trials comparing Plavix alone to aspirin alone are discussed below.

Bleeding
CURE
In CURE, Plavix use with aspirin was associated with an increase in major bleeding (primarily gastrointestinal and at puncture sites) compared to placebo with aspirin (see Table 1). The incidence of intracranial hemorrhage (0.1%) and fatal bleeding (0.2%) were the same in both groups. Other bleeding events that were reported more frequently in the clopidogrel group were epistaxis, hematuria, and bruise.

The overall incidence of bleeding is described in Table 1.

<table>
<thead>
<tr>
<th>Event</th>
<th>Plavix (+ aspirin)</th>
<th>Placebo (+ aspirin)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>3.7</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>2.2</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>5 g/dL hemoglobin drop</td>
<td>0.9</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Requiring surgical intervention</td>
<td>0.7</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic strokes</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Requiring inotropes</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Requiring transfusion (≥4 units)</td>
<td>1.2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Other major bleeding</td>
<td>1.6</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Significantly disabling</td>
<td>0.4</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>
| Intracranial bleeding with significant loss of vision | 0.05 | 0.03 | \n
*Life-threatening and other major bleeding.
†Led to interruption of study medication.

COMMl
In COMMIT, similar rates of major bleeding were observed in the Plavix and placebo groups, both of which also received aspirin (see Table 2).

<table>
<thead>
<tr>
<th>Type of Bleeding</th>
<th>Plavix (+ aspirin)</th>
<th>Placebo (+ aspirin)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major’ noncerebral or cerebral bleeding</td>
<td>0.6</td>
<td>0.5</td>
<td>0.59</td>
</tr>
<tr>
<td>Major noncerebral</td>
<td>0.4</td>
<td>0.3</td>
<td>0.48</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.2</td>
<td>0.2</td>
<td>0.90</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.2</td>
<td>0.2</td>
<td>0.91</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.2</td>
<td>0.2</td>
<td>0.81</td>
</tr>
<tr>
<td>Other noncerebral bleeding (nonmajor)</td>
<td>3.6</td>
<td>3.1</td>
<td>0.005</td>
</tr>
<tr>
<td>Any noncerebral bleeding</td>
<td>3.9</td>
<td>3.4</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Major bleeds were cerebral bleeds or noncerebral bleeds thought to have caused death or that required transfusion.

CAPRIE (Plavix vs Aspirin)
In CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2.0% in those taking Plavix plus aspirin, versus 2.7% in those taking aspirin; Plavix requiring hospitalization occurred in 0.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for Plavix compared to 0.5% for aspirin.

Other bleeding events that were reported more frequently in the Plavix group were epistaxis and hematomas.
Other Adverse Events

In CURE and CHARISMA, which compared Plavix plus aspirin to aspirin alone, there was no difference in the rate of adverse events (other than bleeding) between Plavix and placebo. In CAPRIE, which compared Plavix to aspirin, pruritus was more frequently reported in those taking Plavix. No other difference in the rate of adverse events (other than bleeding) was reported.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Plavix. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hemorrhages, including those with fatal outcome, have been reported in patients treated with Plavix.

- **Blood and lymphatic system disorders:** Agranulocytosis, aplastic anemia, pancytopenia, thrombotic thrombocytopenic purpura (TTP), acquired hemophilia A
- **Gastrointestinal disorders:** Collitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, gastric/duodenal ulcer, diaphragmatic hernia
- **General disorders and administration site condition:** Fever
- **Hepatobiliary disorders:** Acute liver failure, hepatitis (noninfectious), abnormal liver function test
- **Immune system disorders:** Hypersensitivity reactions, anaphylactoid reactions, serum sickness, insulin autoimmune syndrome, which can lead to severe hypoglycemia
- **Musculoskeletal, connective tissue and bone disorders:** Myalgia, arthralgia, arthritis
- **Nervous system disorders:** Taste disorder, headache, ageusia
- **Psychiatric disorders:** Confusion, hallucinations
- **Respiratory, thoracic and mediastinal disorders:** Bronchospasm, interstitial pneumonitis, eosinophilic pneumonia
- **Renal and urinary disorders:** Increased creatinine levels
- **Skin and subcutaneous tissue disorders:** Maculopapular, erythematous or exfoliative rash, urticaria, bullous, exfoliative 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, lichen planus, generalized pruritus
- **Vascular disorders:** Vasculitis, hypotension

7 DRUG INTERACTIONS

7.1 CYP2C19 Inhibitors

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of 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)].

Omeprazole or Esomeprazole

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 similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with Plavix. Dextansprazole, lansoprazole, and pantoprazole had less effect on the antiplatelet activity of Plavix than did omeprazole or esomeprazole [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

7.2 Opioids

As with other P2Y12 inhibitors, coadministration of opioid agonists delay and reduce the absorption of clopidogrel, presumably because of slowed gastric emptying, resulting in reduced exposure to its metabolites [see Clinical Pharmacology (12.3)]. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring coadministration of morphine or other opioid agonists.

7.3 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Coadministration of Plavix and NSAIDs increases the risk of gastrointestinal bleeding [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

7.4 Warfarin (CYP2C9 Substrates)

Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of 5-S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of Plavix with warfarin increases the risk of bleeding because of independent effects on hemostasis. However, at high concentrations in vitro, clopidogrel inhibits CYP2C9.

7.5 SSRIs and SNRIs

Since selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) affect platelet activation, the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding.

7.6 Repaglinide (CYP2C9, CYP2C19 Substrates)

The acyl-β-glucuronide metabolite of clopidogrel is a strong inhibitor of CYP2C9. Plavix can increase the systemic exposure to drugs that are primarily cleared by CYP2C9, thereby needing dose adjustment and appropriate monitoring.

Plavix increased repaglinide exposures by 5.9-fold to 5.1-fold [see Clinical Pharmacology (12.3)]. Avoid concomitant use of repaglinide with Plavix. If concomitant use cannot be avoided, initiate repaglinide at 0.5 mg before each meal and do not exceed a total daily dose of 4 mg. Increased frequency of glucose monitoring may be required during concomitant use.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Safety and effectiveness in pediatric populations have not been established.

There are no data on the presence of clopidogrel in human milk or the effects on milk production. No adverse effects on breastfed infants have been observed with maternal clopidogrel use during lactation in a small number of postmarketing cases. Studies in rats have shown that clopidogrel and its metabolites are present in the milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with mother’s clinical need for clopidogrel and any potential adverse effects on the breastfed infant from PLAVIX or from underlying maternal condition.

8.2 Lactation

Other Adverse Events

8.3 Lactation

No dosage adjustment is necessary in elderly patients.

8.6 Renal Impairment

Experience is limited in patients with severe and moderate renal impairment [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

No dosage adjustment is necessary in patients with hepatic impairment [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE

Platelet inhibition by Plavix is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting, prostration, difficult breathing, and gastrointestinal disturbance. Based on biological plausibility, platelet transfusion may restore clotting ability.

11 DESCRIPTION

Plavix (clopidogrel bisulfate) is a thienopyridine class inhibitor of P2Y12 ADP platelet receptor. Chemically, it is methyl (1H-1,2,4-triazol-5-yl)-2-chlorophenyl)-6,7-dihydrothieno[3,2-c]-pyridine-5(4H)-acetate sulfone (1:1). The empirical formula of clopidogrel bisulfate is C14H11ClN3O2SHSO3 and its molecular weight is 419.9.

The structural formula is as follows:

Clodipodreg bisulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°.

Plavix for oral administration is provided as either pink, round, biconvex, debossed, film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar
Drug Interactions

radioactivity was excreted in urine and approximately 46% in feces over the 5 days post
C
that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits
loading dose as it is after four days of 75 mg maintenance dose. 

Absorption
After single and repeated oral doses of 75 mg Plavix per day, clopidogrel is rapidly absorbed. 
Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Effect of other drugs on Plavix

Absorption
Plavix 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects.

Gender
In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women.

Effect of Plavix on other drugs

Methodology
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.

Pharmacodynamic and pharmacokinetic parameters measured in these studies showed that the interaction was highest with omeprazole and least with dexlansoprazole.

Proton pump inhibitors (PPI)
The effect of proton pump inhibitors (PPI) on the systemic exposure to the clopidogrel active metabolite following multiple doses of Plavix 75 mg evaluated in dedicated drug interaction studies is presented in Figure 1.

Figure 1: Exposure to Clopidogrel Active Metabolite Following Multiple Doses of Plavix 75 mg Alone or with Proton Pump Inhibitors (PPIs)

<table>
<thead>
<tr>
<th>Proton pump inhibitor (PPI)</th>
<th>Effect on active metabolite (AUC$_{0-24}$)</th>
<th>90% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 40 mg</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Lansoprazole 30 mg</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Pantoprazole 80 mg</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Esomeprazole 40 mg</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Pharmacodynamic and pharmacokinetic properties were measured in these studies showing that the interaction was highest with omeprazole and least with dexlansoprazole.

Clopidogrel is a produg and is metabolized to a pharmacologically active metabolite and inactive metabolites.

Absorption
After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Effect of food
Plavix can be administered with or without food. In a study in healthy male subjects who Plavix 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was reduced by less than 9%. The active metabolite AUC$_{0-24}$ was unchanged in the presence of food, while there was a 57% decrease in active metabolite C$_{max}$. Similar results were observed when a Plavix 300 mg loading dose was administered with a high-fat breakfast.

Hepatically Impaired Patients
After repeated doses of 75 mg Plavix per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects.

Effect of food
Plavix can be administered with or without food. In a study in healthy male subjects who Plavix 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was reduced by less than 9%. The active metabolite AUC$_{0-24}$ was unchanged in the presence of food, while there was a 57% decrease in active metabolite C$_{max}$. Similar results were observed when a Plavix 300 mg loading dose was administered with a high-fat breakfast.

Hepatically Impaired Patients
After repeated doses of 75 mg Plavix per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects.

Gender
In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women.

Effect of Plavix on other drugs

Methodology
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.

Pharmacodynamic and pharmacokinetic parameters measured in these studies showed that the interaction was highest with omeprazole and least with dexlansoprazole.

Proton pump inhibitors (PPI)
The effect of proton pump inhibitors (PPI) on the systemic exposure to the clopidogrel active metabolite following multiple doses of Plavix 75 mg evaluated in dedicated drug interaction studies is presented in Figure 1.

Figure 1: Exposure to Clopidogrel Active Metabolite Following Multiple Doses of Plavix 75 mg Alone or with Proton Pump Inhibitors (PPIs)

<table>
<thead>
<tr>
<th>Proton pump inhibitor (PPI)</th>
<th>Effect on active metabolite (AUC$_{0-24}$)</th>
<th>90% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 40 mg</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Lansoprazole 30 mg</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Pantoprazole 80 mg</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Esomeprazole 40 mg</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Pharmacodynamic and pharmacokinetic properties were measured in these studies showing that the interaction was highest with omeprazole and least with dexlansoprazole.

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-
clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antplatelet effects, as measured by ex vivo platelet aggregation assays, differ according to CYP2C19 genotype. 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.

Metabolism
Clopidogrel is extensively metabolized by two major 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 the formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from other CYP enzymes, including 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 C$_{max}$ 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. C$_{max}$ 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: 4-fold the dose results in 2.0-fold and 2.7-fold the C$_{max}$ and AUC, respectively.

Elimination
Following an oral dose of $^{14}$C-labeled clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post dosing. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The half-life of the active metabolite is about 30 minutes.

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.

Table 3: Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metabolizer Status

<table>
<thead>
<tr>
<th>Dose (mg/mL)</th>
<th>Poor (n=10)</th>
<th>Intermediate (n=10)</th>
<th>Normal (n=10)</th>
<th>Ultrarapid (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_{max}$ (mg/mL)</td>
<td>300 (24 h)</td>
<td>11 (4)</td>
<td>23 (11)</td>
<td>32 (21)</td>
</tr>
<tr>
<td></td>
<td>600 (24 h)</td>
<td>17 (6)</td>
<td>39 (23)</td>
<td>44 (27)</td>
</tr>
<tr>
<td></td>
<td>75 (Day 5)</td>
<td>4 (1)</td>
<td>12 (5)</td>
<td>13 (7)</td>
</tr>
<tr>
<td></td>
<td>150 (Day 5)</td>
<td>7 (2)</td>
<td>18 (7)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>IPA (%)</td>
<td>300 (24 h)</td>
<td>24 (26)</td>
<td>37 (21)</td>
<td>39 (28)</td>
</tr>
<tr>
<td></td>
<td>600 (24 h)</td>
<td>32 (25)</td>
<td>56 (22)</td>
<td>49 (23)</td>
</tr>
<tr>
<td></td>
<td>75 (Day 5)</td>
<td>37 (23)</td>
<td>60 (18)</td>
<td>58 (19)</td>
</tr>
<tr>
<td></td>
<td>150 (Day 5)</td>
<td>61 (14)</td>
<td>74 (14)</td>
<td>73 (9)</td>
</tr>
<tr>
<td>VASP-PRI (%)</td>
<td>300 (24 h)</td>
<td>91 (12)</td>
<td>78 (12)</td>
<td>68 (16)</td>
</tr>
<tr>
<td></td>
<td>600 (24 h)</td>
<td>85 (14)</td>
<td>56 (26)</td>
<td>48 (20)</td>
</tr>
</tbody>
</table>
Table 3: Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metabolizer Status (continued)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Poor (n=10)</th>
<th>Intermediate (n=10)</th>
<th>Normal (n=10)</th>
<th>Ultrarapid (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg</td>
<td>83 (13)</td>
<td>50 (16)</td>
<td>39 (14)</td>
<td>40 (9)</td>
</tr>
<tr>
<td>(Day 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mg</td>
<td>61 (18)</td>
<td>29 (11)</td>
<td>24 (10)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>(Day 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 5 μM ADP; larger value indicates greater platelet inhibition.
§Vasodilator-stimulated phosphoprotein – platelet reactivity index; smaller value indicates greater platelet inhibition.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of tumorigenesis when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg. Clopidogrel was not genotoxic in four in vitro tests (Ames test, DNA-repair test in Rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one in vivo test (micronucleus test by oral route in mice).

Clopidogrel was found to have no effect on fertility of male and female rats treated prior to pairing and throughout gestation at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m² basis).

14 CLINICAL STUDIES

14.1 Acute Coronary Syndrome

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. 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) 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.

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). The effect of Plavix 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 use of Plavix was observed independently of the dose of aspirin (75–325 mg once daily). The use of oral anticoagulants, nonstudy antplatelet drugs, and chronic NSAIDs was not allowed in CURE.

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

The use of Plavix in CURE was associated with a decrease in the use of thrombolytic therapy (71 patients [1.1%] in the Plavix group, 126 patients [2.0%] in the placebo group; relative risk reduction of 43%), and GPIIb/IIIa inhibitors (369 patients [5.9%] in the Plavix group, 454 patients [7.2%] in the placebo group, relative risk reduction of 18%). The use of Plavix in CURE did not affect the number of patients treated with CABG or PCI (with other standard therapies were used as appropriate.

Table 4: Outcome Events in the CURE Primary Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (n=6259)</th>
<th>Placebo (n=6303)</th>
<th>Relative Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td>20% (10.3, 27.9) p &lt;0.001</td>
</tr>
<tr>
<td>(Cardiovascular death,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI, stroke)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Individual Outcome Events‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>318 (5.1%)</td>
<td>345 (5.5%)</td>
<td>7% (-7.7, 20.6)</td>
</tr>
<tr>
<td>MI</td>
<td>324 (5.2%)</td>
<td>419 (6.6%)</td>
<td>23% (11.0, 33.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>75 (1.2%)</td>
<td>87 (1.4%)</td>
<td>14% (-17.7, 36.6)</td>
</tr>
</tbody>
</table>

*Other standard therapies were used as appropriate.
†The individual components do not represent a breakdown of the primary and coprimary outcomes, but rather the total number of subjects experiencing an event during the course of the study.

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).
or without stenting) (2253 patients [36.0%] in the Plavix group, 2324 patients [36.9%] in the placebo group; relative risk reduction of 4.9%).

**COMMIT**

In patients with STEMI, the safety and efficacy of Plavix were evaluated in the randomized, placebo-controlled, double-blind study, COMMIT. COMMIT included 45,852 patients presenting within 24 hours of the onset of the symptoms of myocardial infarction with supporting ECG abnormalities (i.e., ST-elevation, ST-depression or left bundle-branch block). Patients were randomized to receive Plavix (75 mg once daily) or placebo, in combination with aspirin (162 mg per day), for 28 days or until hospital discharge, whichever came first.

The primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death.

The patient population was 28% women and 58% age ≥60 years (26% age ≥70 years). Fifty-five percent (55%) of patients received thrombolytics and only 3% 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 COMMIT

<table>
<thead>
<tr>
<th>Event</th>
<th>Plavix (+ aspirin) (N=22961)</th>
<th>Placebo (+ aspirin) (N=22891)</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite endpoint: Death, MI, or Stroke†</td>
<td>2121 (9.2%)</td>
<td>2310 (10.1%)</td>
<td>0.91 (0.86, 0.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death</td>
<td>1726 (7.5%)</td>
<td>1845 (8.1%)</td>
<td>0.93 (0.87, 0.99)</td>
<td>0.029</td>
</tr>
<tr>
<td>Nonfatal MI†</td>
<td>270 (1.2%)</td>
<td>330 (1.4%)</td>
<td>0.81 (0.69, 0.95)</td>
<td>0.011</td>
</tr>
<tr>
<td>Nonfatal Stroke†</td>
<td>127 (0.6%)</td>
<td>142 (0.6%)</td>
<td>0.89 (0.70, 1.13)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*9 patients (2 clopidogrel and 7 placebo) suffered both a nonfatal stroke and a nonfatal MI.
†Nonfatal MI and nonfatal stroke exclude patients who died (of any cause).
The CAPRIE trial enrolled a population that had recent MI, recent stroke, or PAD. The statistical significance favoring Plavix over aspirin was marginal (p=0.045). However, because aspirin is itself effective in reducing cardiovascular events in patients with recent myocardial infarction or stroke, the effect of Plavix is substantial.

The curves showing the overall event rate are shown in Figure 7. The event curves separated early and continued to diverge over the 3-year follow-up period. Figure 8: Hazard Ratio and 95% CI by Baseline Subgroups in the CAPRIE Study

The statistical significance favoring Plavix over aspirin was marginal (p=0.045). However, because aspirin is itself effective in reducing cardiovascular events in patients with recent myocardial infarction or stroke, the effect of Plavix is substantial.

The CAPRIE trial was not designed to evaluate the relative benefit of Plavix over aspirin in the prevention of ischemic events in patients with vascular disease or multiple risk factors for atherosclerosis. All subjects were treated with aspirin 75–162 mg daily. The mean duration of treatment was 23 months. The study failed to demonstrate a reduction in the occurrence of the primary endpoint, a composite of CV death, MI, or stroke. A total of 534 (6.9%) patients in the Plavix group versus 573 (7.4%) patients in the placebo group experienced a primary outcome event (p=0.22). Bleeding of all severities was more common in the subjects randomized to Plavix.

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

CHARISMA
The CHARISMA trial was a 15,603 subject, randomized, double-blind, parallel group study comparing Plavix (75 mg daily) to placebo for prevention of ischemic events in patients with vascular disease or multiple risk factors for atherosclerosis. All subjects were treated with aspirin 75–162 mg daily. The mean duration of treatment was 23 months. The study failed to demonstrate a reduction in the occurrence of the primary endpoint, a composite of CV death, MI, or stroke. A total of 534 (6.9%) patients in the Plavix group versus 573 (7.4%) patients in the placebo group experienced a primary outcome event (p=0.22). Bleeding of all severities was more common in the subjects randomized to Plavix.

16 HOW SUPPLIED/STORAGE AND HANDLING
Plavix (clopidogrel bisulfate) 75 mg tablets are available as pink, oblong, film-coated tablets debossed with “75” on one side and “1171” on the other. Tablets are provided as follows:
- NDC 63653-1171-6 Bottles of 30
- NDC 63653-1171-1 Bottles of 90
- NDC 63653-1171-5 Bottles of 500
- NDC 63653-1171-3 Blisters of 100

Plavix (clopidogrel bisulfate) 300 mg tablets are available as pink, oblong, film-coated tablets debossed with “300” on one side and “1332” on the other. Tablets are provided as follows:
- NDC 63653-1332-2 Unit-dose packages of 30
- NDC 63653-1332-1 Bottles of 500
- NDC 63653-1332-6 Bottles of 30

17 PATIENT COUNSELING INFORMATION
Advise patients to read FDA approved patient labeling (Medication Guide).

Discontinuation
Advise patients not to discontinue Plavix without first discussing it with the healthcare 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)].

Medication Guide
Plavix® (PLAV-iks) (clopidogrel bisulfate) tablets
Read this Medication Guide before you start taking Plavix and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Plavix?

1. Plavix may not work as well in people who:
- have certain genetic factors that affect how the body breaks down Plavix. Your doctor may do genetic tests to make sure Plavix is right for you.
- take certain medicines, especially omeprazole (Prilosec®) or esomeprazole (Nexium®). Your doctor may change the medicine you take for stomach acid problems while you take Plavix.

2. Plavix can cause bleeding which can be serious and can sometimes lead to death. Plavix is a blood thinner medicine that lowers the chance of blood clots forming in your body. While you take Plavix:
- you may bruise and bleed more easily
- you are more likely to have nose bleeds
- it will take longer for any bleeding to stop
Call your doctor right away if you have any of these signs or symptoms of bleeding:
- unexpected bleeding or bleeding that lasts a long time
- blood in your urine (pink, red or brown urine)
- red or black stools (looks like tar)
- bruises that happen without a known cause or get larger
- cough up blood or blood clots
- vomit blood or your vomit looks like coffee grounds

Do not stop taking Plavix without talking to the doctor who prescribes it for you. People who stop taking Plavix too soon have a higher risk of having a heart attack or dying. If you must stop Plavix because of bleeding, your risk of a heart attack may be higher.

What is Plavix?
Plavix is a prescription medicine used to treat people who have any of the following:
- chest pain due to heart problems
- poor circulation in their legs (peripheral arterial disease)
- a heart attack
- a stroke
Plavix is used alone or with aspirin to lower your chance of having another serious problem with your heart or blood vessels such as heart attack, stroke, or blood clot that can lead to death.
Platelets are blood cells that help your blood clot normally. Plavix helps to prevent platelets from sticking together and forming a clot that can block an artery. It is not known if Plavix is safe and effective in children.

Who should not take Plavix?
Do not take Plavix if you:
- currently have a condition that causes bleeding, such as a stomach ulcer
- are allergic to clopidogrel or other ingredients in Plavix. See the end of this leaflet for a complete list of ingredients in Plavix.

What should I tell my doctor before taking Plavix?
Before you take Plavix, tell your doctor if you:
- have a history of bowel (gastrointestinal) or stomach ulcers
- have a history of bleeding problems
- plan to have surgery or a dental procedure. See “How should I take Plavix?”
- are pregnant or plan to become pregnant. It is not known if Plavix will harm your unborn baby
- are breastfeeding or plan to breastfeed. It is not known if Plavix passes into your breast milk. A decision should be made with your healthcare provider to avoid or discontinue breastfeeding when continuing Plavix is needed.

Tell all of your doctors and your dentist that you are taking Plavix. They should talk to the doctor who prescribed Plavix for you before you have any surgery or invasive procedure.

Tell your doctor about all the medicines you take, including prescription, non-prescription medicines, vitamins and herbal supplements. Plavix may affect the way other medicines work, and other medicines may affect how Plavix works. See “What is the most important information I should know about Plavix?”

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

Taking Plavix with certain other medicines may increase your risk of bleeding. Especially tell your doctor if you take:
- aspirin, especially if you have had a stroke. Always talk to your doctor about whether you should take aspirin along with Plavix to treat your condition.
- non-steroidal anti-inflammatory drugs (NSAIDs). Ask your doctor or pharmacist for a list of NSAID medicines if you are not sure.
- warfarin (Coumadin®, Jantoven®). Selective serotonin reuptake inhibitors (SSRIs) and serotonin nor-epinephrine reuptake inhibitors (SNRIs). Ask your doctor or pharmacist for a list of SSRI or SNRI medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take Plavix?
- Take Plavix exactly as your doctor tells you.
- Do not change your dose or stop taking Plavix without talking to your doctor first. Stopping Plavix may increase your risk of heart attack or stroke.
- Take Plavix with aspirin as instructed by your doctor.
- If you miss a dose, take Plavix as soon as you remember. If it is almost time for your next dose, skip the missed dose. Take the next dose at your regular time. Do not take 2 doses of Plavix at the same time unless your doctor tells you to.
- If you take too much Plavix, call your doctor or go to the nearest emergency room right away.
- Talk with your doctor about stopping your Plavix before you have surgery. Your doctor may tell you to stop taking Plavix at least 5 days before you have surgery to avoid excessive bleeding during surgery.

What are the possible side effects of Plavix?
Plavix can cause serious side effects including:
- See “What is the most important information I should know about Plavix?”
- A blood clotting problem called Thrombotic Thrombocytopenic Purpura (TTP). TTP can happen with Plavix; sometimes after a short time (less than 2 weeks). TTP is a blood clotting problem where blood clots form in blood vessels; and can happen anywhere in the body. TTP needs to be treated in a hospital right away, because it may cause death. Get medical help right away if you have any of these symptoms and they can not be explained by another medical condition:
  - purplish spots (called purpura) on the skin or in the mouth (mucous membranes) due to bleeding under the skin
  - your skin or the whites of your eyes are yellow (jaundice)
  - you feel tired or weak
  - your skin looks very pale
  - fever
  - fast heart rate or feeling short of breath
  - headache
  - speech changes
  - confusion
  - coma
  - stroke
  - low amount of urine, or urine that is pink or has blood in it
  - stomach area (abdominal) pain
  - nausea, vomiting, or diarrhea
  - vision changes
  - persistent low blood sugar symptoms

Tell your doctor if you have any side effect that bothers you or that does not go away. Tell your doctor if you develop an allergic reaction including skin reactions while taking Plavix. These are not all the possible side effects of Plavix. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Plavix?
- Store Plavix at 59°F to 86°F (15°C to 30°C).

Keep Plavix and all medicines out of the reach of children.

General information about Plavix
Medicines are sometimes used for purposes other than those listed in a Medication Guide. Do not take Plavix for a condition for which it was not prescribed. Do not give Plavix to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Plavix. If you would like more information, talk to your doctor. Ask your doctor or pharmacist for information about Plavix that was written for healthcare professionals.

For more information, go to www.sanofi-aventis.us or www.bms.com or call 1-800-321-1335.

What are the ingredients in Plavix?
Active ingredient: clopidogrel bisulfate
Inactive ingredients:
- Tablet: hydrogenated castor oil, hydroxypropyl cellulose, mannitol, microcrystalline cellulose, polyethylene glycol 6000
- Film coating: ferric oxide, hypromellose 2910, lactose monohydrate, titanium dioxide, triacetin, Carnauba wax

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

Revised: May 2019

Distributed by: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership
Bridgewater, NJ 08807

Plavix® is a registered trademark of sanofi-aventis.
All other trademarks are property of their respective owners.

CLO-FPLR-SL-MAY19 Rx Only