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. (12.3)
- 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 (ACS)
- Recent MI, recent stroke, or established peripheral arterial disease: 75 mg once daily orally without a loading dose (2.2)

Dosage 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)
- Bleeding: Plavix increases risk of bleeding. (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)
- 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, 7.3, 7.4, 7.5)
- Nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRIs, SNRIs): Increases risk of bleeding. (7.6)
- Repaglinide (CYP2C8 substrates): Increases substrate plasma concentrations. (7.6)

USE IN SPECIFIC POPULATIONS

Nursing mothers: Discontinue drug or nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2018
1 INDICATIONS AND USAGE

1.1 Acute Coronary Syndrome (ACS)

- Plavix is indicated to reduce the rate of myocardial infarction (MI) and stroke 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 is indicated to reduce the rate of myocardial infarction and stroke in patients with acute ST-elevation myocardial infarction (STEMI), who are to be managed medically, medically. Plavix should be administered in conjunction with aspirin.

1.2 Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

In patients with established peripheral arterial disease or with a history of recent myocardial infarction (MI) or recent stroke, Plavix is indicated to reduce the rate of MI and stroke.

2 DOSAGE AND ADMINISTRATION

2.1 Acute Coronary Syndrome

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)].

2.2 Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

75 mg once daily orally without a loading dose [see Clinical Pharmacology (12.3) and Clinical Studies (14.2)].

3 DOSAGE FORMS AND STRENGTHS

- 75 mg tablets: Pink, round, biconvex, film-coated tablets debossed with “75” on one side and “1171” on the other.
- 300 mg tablets: Pink, oblong, film-coated tablets debossed with “300” on one side and “1332” on the other.

4 CONTRAINDICATIONS

4.1 Active Bleeding

Plavix is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

4.2 Hypersensitivity

Plavix is contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to clopidogrel or any component of the product [see Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Diminished Antiplatelet Activity 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].

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. Concomitant use of Plavix with omeprazole or esomeprazole is contraindicated in patients with a history of hypersensitivity or hemato logic reaction to other thienopyridines [see Contraindications (4.2) and Adverse Reactions (6.2)].

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, hematura, and bruise.

The overall incidence of bleeding is described in Table 1.

Table 1: CURE Incidence of Bleeding Complications (% patients)

<table>
<thead>
<tr>
<th>Event</th>
<th>Plavix (+ aspirin) (n=6259)</th>
<th>Placebo (+ aspirin) (n=6303)</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>
<tr>
<td>Intracranial bleeding with significant loss of vision</td>
<td>0.05</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Requiring 2–3 units of blood</td>
<td>1.3</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Minor bleeding*</td>
<td>5.1</td>
<td>2.4</td>
<td></td>
</tr>
</tbody>
</table>

*Life-threatening and other major bleeding.

†Led to interruption of study medication.

COMMIT

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 2: Incidence of Bleeding Events in COMMIT (% patients)

<table>
<thead>
<tr>
<th>Type of Bleeding</th>
<th>Plavix (+ aspirin) (n=22961)</th>
<th>Placebo (+ aspirin) (n=22891)</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 compared to 2.7% in those taking aspirin; bleeding 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 hematorrhea.
Other Adverse Events

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 increases the risk of reduced platelet inhibition and an increase in platelet reactivity [see Warnings and Precautions (5.1)].

Omeprazole or Esomeprazole
Avoid concomitant use of Plavix with omeprazole or esomeprazole. In clinical studies, concomitant use of Plavix and 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. Dexlansoprazole, lansoprazole concomitantly or 12 hours apart. A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with Plavix. Dexlansoprazole, lansoprazole, or omeprazole [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 with NSAIDs increases the risk of gastrointestinal bleeding.

7.4 Warfarin (CYP2C9 Substrates)
Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INH 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 SNRLs
Since selective serotonin reuptake inhibitors (SSRIs) and serotonin nonselective reuptake inhibitors (SNRIs) affect platelet activation, the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding.

7.6 Regapilidene (CYP2C9 Substrates)
The acyl-1-s-tramexene 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 regapilidene exposures by 3.9-fold to 5.1-fold [see Clinical Pharmacology (12.3)]. Avoid concomitant use of regapilidene with Plavix. If concomitant use cannot be avoided, initiate regapilidene 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
Pregnancy Category B
Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day, respectively (65 and 78 times the recommended daily human dose, respectively, on a mg/m² basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Plavix should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers
Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from clopidogrel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Safety and effectiveness in pediatric populations have not been established.

A randomized, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with symptomatic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome were the dose of clopidogrel, the concomitant administration of aspirin and the late initiation of therapy following shunt palliation. It cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population.

8.5 Geriatric Use
Of the total number of subjects in the CAPRIE and CURE controlled clinical studies, approximately 50% of patients treated with Plavix were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with Plavix were 60 years and older, 26% of whom were 70 years and older. The observed risk of bleeding events with Plavix plus aspirin versus placebo plus aspirin by age category is provided in Table 1 and Table 2 for the CURE and COMMIT trials, respectively [see Adverse Reactions (6.1)]. 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 (12.2)].

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 rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting, prostration, difficulty swallowing, and gastrointestinal hemorrhage in animals. Based on biological plausibility, platelet transfusion may restore clotting ability.

11. DESCRIPTION
Plavix (clopidogrel bisulfate) is a thienopyridine class inhibitor of P2Y12 ADP platelet receptors. Chemically it is methyl (+)-(S)-2-[(2-chloropyridin-3-yl)oxy]-6,7-dihydrothieno[2,3-c] pyridazine-4(3H)-acetate sulfonic acid. The empirical form of clopidogrel bisulfate is C13H16ClNO4SH,SO4 and its molecular weight is 419.9.

The structural formula is as follows:

Clpidogrel 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 75 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base or pink, oblong, debossed film-coated tablets containing 315 mg of clopidogrel bisulfate which is the molar equivalent of 300 mg of clopidogrel base.

Each tablet contains hydroxypropyl cellulose, microcrystalline cellulose and polyethylene glycol 8000 as inactive ingredients. The tablets are polished with Carnauba wax.

12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets.

12.2 Pharmacodynamics
Clopidogrel must be metabolized by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. This action is irreversible. Consequently, platelets exposed to clopidogrel’s active metabolite are affected for the remainder of their lifespan (about 7 to 10 days). Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Plavix. Repeated doses of 75 mg Plavix per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg Plavix per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Geriatric Patients
Elderly (≥75 years) and young healthy subjects had similar effects on platelet aggregation.

Reproduced Impaired Platelet Aggregation
After repeated doses of 75 mg Plavix per day, patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) and moderate renal impairment (creatinine clearance from 30 to 60 mL/min) showed low (25%) inhibition of ADP-induced platelet aggregation.

Other Adverse Events

In CAPRIE 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.

4.2 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, panmyelopaenia, thrombotic thrombocytopenic purpura (TTP), acquired hemophagocytic syndrome.

Gastrointestinal disorders: Collitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, gastrointestinal ulcer, diarrhea.

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.

Musculoskeletal, connective tissue and bone disorders: Myalgia, arthralgia, arthritis.

Nervous system disorders: Taste disturbances, headache, paresthesia.

Psychiatric disorders: Confusion, hallucinations.

Respiratory, thoracic and mediastinal disorders: Bronchospasm, interstitial pulmonary nephritis, 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, lichen planus, generalized pruritus.

Vascular disorders: Vasculitis, hypertension.

8. Adverse Reactions
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.

12.3 Pharmacokinetics
Clopidogrel is a prodrug 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 when Plavix 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was reduced by 15%. The active metabolite $AUC_{\text{max}}$ was unchanged in the presence of food, while there was a 57% decrease in active metabolite $C_{\text{max}}$.

Metabolism
Similar results were observed when a Plavix 300 mg loading dose was administered with a high-fat breakfast.

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. In the 75 to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: 4-fold the dose range in 2.0-fold and 2.7-fold the $C_{\text{max}}$ and $AUC$, respectively.

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.

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/day evaluated in dedicated drug interaction studies is presented in Figure 1.

12.5 Pharmacogenomics
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. 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.

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.

<table>
<thead>
<tr>
<th>Table 3: Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metabolizer Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>Poor (n=10)</td>
</tr>
<tr>
<td>300 mg (24 h)</td>
</tr>
<tr>
<td>600 mg (24 h)</td>
</tr>
<tr>
<td>75 mg (Day 5)</td>
</tr>
<tr>
<td>150 mg (Day 5)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

*Intermediate metabolizers have one but not two nonfunctional alleles.
†Ultrapid metabolizers have at least one gain-of-function allele.
‡Inhibition of platelet aggregation with 5 mcM 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 tumorigenicity 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 at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m<sup>2</sup> 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 compatible with new ischemia (without ST-elevation) or elevated cardiac enzymes or troponin I or T 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) 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).

### Table 4: Outcome Events in the CURE Primary Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Plavix (+ aspirin)</th>
<th>Placebo (+ aspirin)</th>
<th>Relative Risk Reduction (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome (Cardiovascular death, MI, stroke)</td>
<td>582 (9.3%)</td>
<td>719 (11.4%)</td>
<td>20% (10.3, 27.9)</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 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 GPIb/IIa 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 or without stenting), (2253 patients [36.0%] in the Plavix group, 2324 patients [36.9%] in the placebo group; relative risk reduction of 4.0%).

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 thrombolics 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 effect of Plavix did not differ significantly in various prespecified subgroups as shown in Figure 6. The effect was also similar in non-prespecified subgroups including those based on infarct location, Killip class or prior MI history. Such subgroup analyses should be interpreted cautiously.
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, round, biconvex, 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 Blister packs 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

Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F) [see USP].

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 (5.3)].

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. DEXIASOPRAZOLE, Lansoprazole and pantoprazole had less pronounced effects on the antiplatelet activity of Plavix than did omeprazole or esomeprazole [see Drug Interactions (7.1)].

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 prescribed 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

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. You and your doctor should decide if you will take Plavix or breastfeed. You should not do both without talking to your doctor
- have had an allergy or reaction to any medicine used to treat your disease.
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
  - seizure
  - low amount of urine, or urine that is pink or has blood in it
  - stomach area (abdominal) pain
  - nausea, vomiting, or diarrhea
  - vision changes

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:**

- Table: 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.

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