

# Day...

Daily protection for your patients<sup>†</sup> from the ongoing threat of thrombotic events<sup>‡</sup> begins by adding **PLAVIX**

- Proven to reduce the risk of MI, stroke, or CV death<sup>1</sup>
- Clopidogrel bisulfate has a Class I recommendation in the 2002 ACC/AHA UA/NSTEMI guideline update<sup>2</sup>

Initiate PLAVIX plus ASA to help reduce the risk of future thrombotic events (MI, stroke, or CV death; or MI, stroke, CV death, or refractory ischemia) in patients with UA/non-Q-wave MI.<sup>3</sup>

<sup>1</sup> In CURE, benefits were seen up to 1 year.

<sup>2</sup> MI, stroke, or unstable angina.

<sup>3</sup> MI, stroke, or CV death.

<sup>3</sup> Including patients who are to be managed medically and those to be managed with percutaneous coronary intervention (with or without stent) or CABG.

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ONCE-A-DAY

**Plavix**<sup>®</sup>

(clopidogrel bisulfate) 75mg tablets

# PLAVIX®

## clopidogrel bisulfate tablets

**BRIEF SUMMARY**—Please see package insert for full prescribing information.

**INDICATIONS AND USAGE:** PLAVIX (clopidogrel bisulfate) is indicated for the reduction of thrombotic events as follows:

**Recent MI, Recent Stroke, or Established Peripheral Arterial Disease, Recent Stent**

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, PLAVIX has been shown to reduce the rate of a combined end point of new ischemic stroke (fatal or non-fatal), nonfatal MI (fatal or non-fatal), and other vascular death.

**Acute Coronary Syndrome**

For patients with acute coronary syndrome (unstable angina—2-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (PCI) with or without stents or CABG, PLAVIX has been shown to decrease the rate of a combined end point of cardiovascular death, MI, or stroke as well as the rate of a combined end point of cardiovascular death, MI, stroke, or infarction.

**CONTRAINDICATIONS:** The use of PLAVIX is contraindicated in patients with a hypersensitivity to the drug substance or any component of the product, and with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

**WARNINGS:** Thrombotic thrombocytopenic purpura (TTP) has been reported rarely following use of PLAVIX, sometimes after a short exposure (<2 weeks). TTP is a serious condition requiring prompt treatment. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. TTP has not been clearly associated with PLAVIX use in clinical trials, which included over 17,500 clopidogrel-treated patients. However, TTP has been reported at a rate of about four cases per million patients exposed, or about 11 cases per million patient-years. The background rate is thought to be about four cases per million person-years.

**PRECAUTIONS: General:** PLAVIX prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intracranial). If a patient is to undergo elective surgery and an antiplatelet drug is indicated, PLAVIX should be discontinued 5 days prior to surgery. Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment. (See **ADVERSE REACTIONS**). GI bleeding in CAPRIE, PLAVIX was associated with a rate of gastrointestinal bleeding of 2.8%, vs 2.7% as aspirin. In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs 1.1% (PLAVIX + aspirin vs placebo + aspirin, respectively). PLAVIX should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking PLAVIX. Use in Hepatically Impaired Patients: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. PLAVIX should be used with caution in this population. Use in Renally Impaired Patients: Experience is limited in patients with severe renal impairment. PLAVIX should be used with caution in this population.

**Information for Patients:** Patients should be told that it may take them longer than usual to stop bleeding when they take PLAVIX, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking PLAVIX before any surgery is scheduled and before any new drug is taken.

**Drug Interactions:** Study of specific drug interactions yielded the following results: Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concurrent administration of 825 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by PLAVIX. PLAVIX potentiated the effect of aspirin on collagen-induced platelet aggregation. PLAVIX and aspirin have been administered together for up to one year. Aspirin: In a study in healthy volunteers, PLAVIX did not require metabolic modification of the hepatic dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on inhibition of platelet aggregation induced by PLAVIX. Nonsteroidal Anti-inflammatory Drug (NSAID): In healthy volunteers receiving regular, concurrent administration of PLAVIX was associated with increased acute gastrointestinal blood loss. NSAIDs and PLAVIX should be co-administered with caution. Warfarin: Because of the increased risk of bleeding, the concurrent administration of warfarin with PLAVIX should be undertaken with caution. (See **PRECAUTIONS: General**).

**Other Concomitant Therapy:** No clinically significant pharmacodynamic interactions were observed when PLAVIX was administered with **atenolol, verapamil, or both atenolol and verapamil.** The pharmacodynamic activity of PLAVIX was also not significantly influenced by the administration of **placental, clonidine, or acetaminophen.** The pharmacokinetics of **aspirin or theophylline** were not modified by the co-administration of PLAVIX (clopidogrel bisulfate). At high concentrations in vitro, theophylline inhibits P<sub>2</sub>U<sub>1</sub> (ADP). Accordingly, PLAVIX may interfere with the metabolism of **phenytoin, lamotrigine, valproic acid, levetiracetam, fosphenytoin, and many low-molecular-weight anti-inflammatory agents**, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is co-administered with PLAVIX. In addition to the above specific interaction studies, patients entered into clinical trials with PLAVIX received a variety of concomitant medications including **diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antipsychotic agents, hormone replacement therapy, heparin (unfractionated and LMWH), and GII/HA antagonists** without evidence of clinically significant adverse interactions. The use of oral anticoagulants, non-study antiplatelet drug and chronic NSAIDs was not assessed in CURE and there are no data on their concomitant use with clopidogrel.

**Drug/Laboratory Test Interactions:** None known.

**Contraception, Maternal and Infant Exposure:** There was no evidence of fetotoxicity when clopidogrel was administered for 75 weeks to mice and 174 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 found to be teratogenic in mice, rats, or dogs. In mice, DM-SP-100, a gene mutation active in Chinese hamster fibroblasts, and multiple chromosome analysis of human lymphocytes and in one in vitro 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 (32 times the recommended human dose at 75 mg/kg basis).

**Pregnancy:** Pregnancy Category B. Reproductive studies performed in rats and rabbits at doses up to 500 and 380 mg/kg/day (respectively 65 and 49 times the recommended daily human dose on a mg/kg basis), revealed no evidence of impaired fertility or teratogenicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, PLAVIX should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether the 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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

**Pediatric Use:** Safety and effectiveness in the pediatric population have not been established.

**ADVERSE REACTIONS:** PLAVIX has been evaluated for safety in more than 17,500 patients, including over 9,200 patients treated for 1 year or more. The overall tolerability of PLAVIX in CAPRIE was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. The clinically important adverse events observed in CAPRIE and CURE are discussed below.

**Hemorrhagic:** In CAPRIE patients receiving PLAVIX, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 1.1%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for PLAVIX compared with 0.5% for aspirin.

In CURE, PLAVIX use with aspirin was associated with an increase in bleeding compared with placebo plus aspirin (see Table 3). There was an excess in major bleeding in patients receiving PLAVIX plus aspirin compared with placebo plus aspirin, primarily gastrointestinal and at puncture sites. The incidence of intracranial hemorrhage (0.3%), and total bleeding (0.2%), was the same in both groups.

In patients receiving both PLAVIX and aspirin in CURE, the incidence of bleeding is described below.

**CURE Incidence of Bleeding Complications (% patients)**

| Event   | PLAVIX (+ aspirin) <sup>a</sup> (n=6229) | Placebo (+ aspirin) <sup>a</sup> (n=6202) | P value |
|---|--|---|---------|
| <b>Major bleeding<sup>b</sup></b>                     | 3.7 <sup>c</sup>                         | 2.7 <sup>c</sup>                          | 0.001   |
| Life-threatening bleeding                             | 2.2                                      | 1.8                                       | 0.13    |
| Fatal   | 0.2                                      | 0.3                                       |         |
| ≥ 5 g/dL hemoglobin drop                              | 0.9                                      | 0.9                                       |         |
| Requiring surgical intervention                       | 1.0                                      | 0.7                                       |         |
| Requiring transfusion                                 | 3.1                                      | 2.1                                       |         |
| Requiring transfusion (≥4 units)                      | 1.5                                      | 0.5                                       |         |
| <b>Other major bleeding</b>                           | 1.6                                      | 1.8                                       | 0.005   |
| Significantly disabling                               | 0.4                                      | 0.3                                       |         |
| Intracranial bleeding with significant loss of vision | 0.05                                     | 0.03                                      |         |
| Requiring ≥3 units of blood                           | 1.3                                      | 0.9                                       |         |
| <b>Minor bleeding<sup>d</sup></b>                     | 5.1                                      | 2.4                                       | <0.001  |

<sup>a</sup> Other standard therapies were used as appropriate.

<sup>b</sup> Life-threatening and other major bleeding.

<sup>c</sup> Major bleeding event rate for PLAVIX + aspirin was dose-dependent: at aspirin <100 mg 2.6%, 100-200 mg 3.5%, ≥200 mg 4.9%.

<sup>d</sup> Major bleeding event rate for placebo + aspirin was dose-dependent: at aspirin <100 mg 2.9%, 100-200 mg 2.3%, ≥200 mg 4.2%.

<sup>e</sup> Led to discontinuation of study medication.

Nearly two percent (20%) of the patients in the CURE study received heparin/LMWH, and the rate of bleeding in these patients was similar to the overall results.

There was no excess in major bleeds within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate 4.4% PLAVIX + aspirin, 5.2% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 8.6% for PLAVIX + aspirin, and 6.3% for placebo + aspirin.

**Neuropharmacology:** Ticlopidine, a drug chemically similar to PLAVIX, is associated with a 0.3% rate of severe neutropenia (less than 450 neutrophils/μL). In CAPRIE, severe neutropenia was observed in six patients, four on PLAVIX and two on aspirin. Two of the six patients who received PLAVIX and none of the 2500 patients who received aspirin had neutrophil counts of zero. One of the four PLAVIX patients in CAPRIE was receiving other cytotoxic chemotherapy, and another received and returned to the trial after only temporarily interrupting treatment with PLAVIX (clopidogrel bisulfate). In CURE, the numbers of patients with thrombocytopenia (18 PLAVIX + aspirin vs 24 placebo + aspirin) or neutropenia (3 vs 5) were similar.

Although the risk of myelotoxicity with PLAVIX thus appears to be quite low, this possibility should be considered when a patient receiving PLAVIX demonstrates fever or other sign of infection.

**Gastrointestinal:** Overall, the incidence of gastrointestinal events (eg, abdominal pain, dyspepsia, gastritis and constipation) in patients receiving PLAVIX (clopidogrel bisulfate) was 37.1%, compared with 35.8% in those receiving aspirin in the CAPRIE trial. In the CURE trial,

**References:** 1. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001;345:494-502. 2. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). 2002. Available at: www.americanheart.org or www.acc.org. Accessed June 3, 2003.

the incidence of these gastrointestinal events for patients receiving PLAVIX + aspirin was 11.7% compared with 12.9% for those receiving placebo + aspirin.

In the CAPRIE trial, the incidence of peptic, gastric or duodenal ulcers was 0.7% for PLAVIX and 1.2% for aspirin. In the CURE trial, the incidence of peptic, gastric or duodenal ulcers was 0.4% for PLAVIX + aspirin and 0.3% for placebo + aspirin.

**Cases of diarrhea were reported in the CAPRIE trial in 4.5% of patients in the PLAVIX group (compared with 3.4% in the aspirin group). However, these were rarely severe (PLAVIX 0.2% and aspirin 0.1%). In the CURE trial, the incidence of diarrhea for patients receiving PLAVIX + aspirin was 2.1% (compared with 2.2% for those receiving placebo + aspirin).**

In the CAPRIE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for PLAVIX and 4.0% for aspirin. In the CURE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.9% for PLAVIX + aspirin compared with 0.8% for placebo + aspirin.

**Risk and Other Side Effects:** The incidence of skin and appendage disorders in patients receiving PLAVIX was 15.8% (0.7% serious); the corresponding rate in aspirin patients was 13.1% (0.5% serious). In the CURE trial, the incidence of such or other side disorders in patients receiving PLAVIX + aspirin was 4.0% compared with 3.3% for those receiving placebo + aspirin.

In the CAPRIE trial, the overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for PLAVIX and 0.9% for aspirin. In the CURE trial, the incidence of patients withdrawing because of skin and appendage disorders adverse reactions was 0.7% for PLAVIX + aspirin compared with 0.3% for placebo + aspirin.

Adverse events occurring in ≥0.5% of patients on PLAVIX in the CAPRIE controlled clinical trial are shown below regardless of relationship to PLAVIX. The median duration of therapy was 20 months, with a maximum of 3 years.

**Adverse Events Occurring in ≥0.5% of PLAVIX Patients in CAPRIE**

| Body System/Event  | PLAVIX (n=6229) | % Incidence (% Discontinuation) Aspirin (n=6202) |
|--|-----------------|--|
| <b>Body as a Whole—general disorders</b>                 |                 |  |
| Chest Pain   | 0.3 (0.2)       | 0.3 (0.2)  |
| Accident/infectious injury                               | 1.9 (0.1)       | 1.7 (0.1)  |
| Influenza-like symptoms                                  | 1.5 (<0.1)      | 1.3 (<0.1)                                       |
| Pain   | 6.4 (0.1)       | 6.3 (0.1)  |
| Fatigue  | 2.3 (0.1)       | 3.4 (0.1)  |
| <b>Cardiovascular disorders, general</b>                 |                 |  |
| Edema  | 4.1 (<0.1)      | 4.5 (<0.1)                                       |
| Hypertension   | 4.3 (<0.1)      | 5.1 (<0.1)                                       |
| <b>Central &amp; peripheral nervous system disorders</b> |                 |  |
| Headache   | 7.6 (0.3)       | 7.2 (0.2)  |
| Dizziness  | 6.2 (0.2)       | 6.7 (0.2)  |
| <b>Gastrointestinal system disorders</b>                 |                 |  |
| Abdominal pain   | 5.6 (0.7)       | 7.1 (1.0)  |
| Dyspepsia  | 5.2 (0.6)       | 6.1 (0.7)  |
| Diarrhea   | 4.5 (0.4)       | 3.4 (0.3)  |
| Nausea   | 3.4 (0.5)       | 3.8 (0.4)  |
| <b>Metabolic &amp; nutritional disorders</b>             |                 |  |
| Hypertension   | 4.0 (0)         | 4.4 (0.1)  |
| <b>Musculoskeletal system disorders</b>                  |                 |  |
| Arthralgia   | 6.3 (0.1)       | 6.2 (0.1)  |
| Back Pain  | 5.8 (0.1)       | 5.3 (0.1)  |
| <b>Palmit, Bleeding &amp; clotting disorders</b>         |                 |  |
| Prophylaxis  | 5.3 (0.2)       | 3.7 (0.1)  |
| Cystitis   | 2.9 (0.2)       | 2.5 (0.1)  |
| <b>Psychiatric disorders</b>                             |                 |  |
| Depression   | 2.6 (0.1)       | 3.8 (0.2)  |
| <b>Respiratory system disorders</b>                      |                 |  |
| Upper respiratory tract infection                        | 8.7 (<0.1)      | 8.3 (<0.1)                                       |
| Dyspnea  | 4.5 (0.1)       | 4.7 (0.1)  |
| Pharyngitis  | 4.2 (0.1)       | 4.2 (<0.1)                                       |
| Bronchitis   | 3.7 (0.1)       | 3.7 (0)  |
| Coughing   | 3.1 (<0.1)      | 2.7 (<0.1)                                       |
| <b>Skin &amp; appendage disorders</b>                    |                 |  |
| Rash   | 4.2 (0.0)       | 3.5 (0.2)  |
| Pruritus   | 3.3 (0.3)       | 1.8 (0.1)  |
| <b>Urinary system disorders</b>                          |                 |  |
| Urinary tract infection                                  | 3.1 (0.1)       | 3.5 (0.1)  |

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Adverse events occurring in ≥2.0% of patients on PLAVIX in the CURE controlled clinical trial are shown below regardless of relationship to PLAVIX.

**Adverse Events Occurring in ≥2.0% of PLAVIX Patients in CURE**

| Body System/Event  | PLAVIX (+ aspirin) <sup>a</sup> (n=6258) | % Incidence (% Discontinuation) Placebo (+ aspirin) <sup>a</sup> (n=6202) |
|--|--|---|
| <b>Body as a Whole—general disorders</b>                 |  |   |
| Chest Pain   | 2.7 (<0.1)                               | 2.8 (0.0)   |
| <b>Central &amp; peripheral nervous system disorders</b> |  |   |
| Headache   | 3.1 (0.1)                                | 3.2 (0.1)   |
| Dizziness  | 2.4 (0.1)                                | 2.8 (<0.1)  |
| <b>Gastrointestinal system disorders</b>                 |  |   |
| Abdominal pain   | 2.3 (0.3)                                | 2.8 (0.3)   |
| Dyspepsia  | 2.0 (0.1)                                | 1.9 (<0.1)  |
| Diarrhea   | 2.1 (0.1)                                | 2.2 (0.1)   |

<sup>a</sup>Other standard therapies were used as appropriate.

Other adverse experiences of potential importance occurring in 1% to 2.0% of patients receiving PLAVIX (clopidogrel bisulfate) in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE).

**Autonomic:** Nervous System Disorders: Syncope, Paresthesia. **Body as a Whole—general disorders:** Asthenia, Fever, Hemia, Cardiovascular disorders: Cardiac failure, Central and peripheral nervous system disorders: Cramps/legs, Hypoacusis, Neurogia, Paresthesia, Vertigo, Gastrointestinal system disorders: Constipation, Vomiting, Abnormal rate and rhythm disorders: Bradycardia, Tachycardia, Extrasystolic disorders: Hepatic enzymes increased, Metabolic and nutritional disorders: Gout, hyperuricemia, non-protein nitrogen (NPN) increased, Alcohol-related system disorders: Anorexia, Anorexia, Patient bleeding & clotting disorders: GI hemorrhage, hematuria, platelets decreased, Peptic ulcer disorders: Anorexia, Insomnia, Red blood cell disorders: Anemia, Respiratory system disorders: Pneumonia, Sinusitis, Skin and appendage disorders: Eczema, Skin ulceration, Urinary system disorders: Cystitis, Urinary disorders: Catarrh, Conjunctivitis. Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received PLAVIX in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE). **Body as a whole:** Allergic reaction, necrosis ischemic, Cardiovascular disorders: Ectopic generalized, Gastrointestinal system disorders: Gastric ulcer perforated, gastric hemorrhagic, upper GI ulcer hemorrhagic, Liver and Biliary system disorders: Biliary cirrhosis, hepatitis infectious, liver fatty, Platelet bleeding and clotting disorders: hemorrhoids, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, scolar hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia, Red blood cell disorders: Anemia aplastic, anemia hypochromic, Reproductive disorders: testicular hemorrhage, Respiratory system disorders: Hemorrhagic, Skin and appendage disorders: Bullous impetigo, rash erythematous, rash maculopapular, urticaria, Urinary system disorders: Abnormal renal function, acute renal failure, Abnormal cell and subcutaneous/systemic disorders: Agranulocytosis, granulocytopenia, leukopenia, leukopenia, neutrophils decreased.

**Postmarketing Experience:** The following events have been reported spontaneously from worldwide postmarketing experience. **Body as a whole:** hypersensitivity reactions: angioedema, anaphylactic reactions, Central and Peripheral Nervous System disorders: hallucinations, taste disorders, Liver and Biliary system disorders: abnormal liver function test, hepatitis (non-infectious), Patient, Bleeding and Clotting disorders: cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage), agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP) — see **WARNINGS**, conjunctivitis, ocular and retinal bleeding, Respiratory system disorders: bronchospasm, Skin and Appendage disorders: angelioma, erythema multiforme, Urinary system disorders: glomerulonephritis, abnormal creatinine level, Colleague disorders: vasculitis, Gastrointestinal disorders: colitis (including ulcerative or lymphocytic colitis).

**DRUGS:** One case of dilated cardiomyopathy with PLAVIX was reported in the large, CAPRIE controlled clinical study. A 34-year-old woman took a single 1,000-mg dose of PLAVIX (equivalent to 14 standard 75-mg tablets). There were no associated adverse events. Her special therapy was instituted, and she recovered without sequelae. No adverse events were reported after single and administration of 800 mg (equivalent to 8 standard 75-mg tablets) of PLAVIX in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75 mg of PLAVIX per day. 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 (in baboons), prostration, ataxic breathing and gastrointestinal hemorrhage in all species.

**Reactions to Other Specific Treatments:** Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of PLAVIX if such reversal is required.

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References: 1. Data on file (Study 0179), Ross Products Division, Abbott Laboratories, July 2002 (Based on 8-oz Glucerna® Shake). 2. Fox BM, Lowe W, Cockram DB, et al. Effect of a liquid nutritional supplement containing a novel carbohydrate system on glucose tolerance in subjects with type 2 diabetes. *Ann Nutr Metab* 2001;45(suppl 1):277. 3. Data on file, Ross Products Division, Abbott Laboratories, July 2002.

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The Cardiology Division in the Department of Medicine at the University of Minnesota is seeking applications for training positions in both its clinical and its research fellowship training programs. These NIH funded positions with opportunities are available in (1) molecular and integrative cardiovascular biology, (2) clinical and epidemiologic studies with the option of obtaining a Master of Science degree in Clinical Research, (3) stem cell biology for cardiac and vascular repair, and (4) cardiovascular applications of nuclear magnetic resonance. A broad variety of experimental techniques and model systems are available to investigate these areas. Information can be obtained from our website ([www.dom.umn.edu](http://www.dom.umn.edu)) or by contacting Dr. Robert J. Bache by email ([bache001@umn.edu](mailto:bache001@umn.edu)) or fax: 612-626-4411. The University of Minnesota is an Affirmative Action / Equal Opportunity Employer.

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Department of Human Genetics at Virginia Commonwealth University is currently recruiting for a Research Associate position. The research focus is in the following areas: aging, functional senescence and neurodegeneration in *Drosophila*. The successful candidate should have a PhD or equivalent doctoral degree and at least 2 years of post-doctoral research experience in a relevant field. Interested applicants should send their CV with three letters of reference to Joyce Lloyd, PhD, Chair, Search Committee, Department of Human Genetics, PO Box 980033, Richmond, VA 23298-0033 by March 31, 2004.

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## Brief Summary

### NORVASC® (amlodipine besylate) Tablets

#### For Oral Use

**CONTRAINDICATIONS:** NORVASC is contraindicated in patients with known sensitivity to amlodipine.  
**WARNINGS:** Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting or during chronic therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

**PRECAUTIONS:** General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration of NORVASC. Nonetheless, caution should be exercised when administering NORVASC as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

**Use in Patients with Congestive Heart Failure:** In general, calcium channel blockers should be used with caution in patients with heart failure. NORVASC (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). NORVASC has been compared to placebo in four 8-12 week studies of patients with NYHA Class III or IV heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

**Beta-Blocker Withdrawal:** NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

**Patients with Hepatic Failure:** Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life ( $t_{1/2}$ ) is 36 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment.

**Drug Interactions:** *In vitro* data in human p-azima indicate that NORVASC has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indometacin).

**Special Studies: Effect of other agents on NORVASC:** Cimetidine: co-administration of NORVASC with cimetidine did not alter the pharmacokinetics of NORVASC. GRAPEFRUIT JUICE: co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 26 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. IMAILOX (antacid): co-administration of the antacid IMAILOX with a single dose of NORVASC had no significant effect on the pharmacokinetics of NORVASC. SILDENAFIL: a single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of NORVASC. When NORVASC and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

**Special Studies: Effect of NORVASC on other agents:** ATORVASTATIN: co-administration of multiple 10 mg doses of NORVASC with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin. DIGOXIN: co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. ETHANOL (alcohol): single and multiple 10 mg doses of NORVASC had no significant effect on the pharmacokinetics of ethanol. WARFARIN: co-administration of NORVASC with warfarin did not change the warfarin prothrombin response time.

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, oral sodium salicylates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antiacids, and oral hypoglycemic drugs.

**Drug/Laboratory Test Interactions:** None known.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice) the maximum recommended clinical dose of 10 mg on a mg/m<sup>2</sup> basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels. There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg/kg/day (8 times\* the maximum recommended human dose of 10 mg on a mg/m<sup>2</sup> basis).

**Pregnancy Category C:** No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats or rabbits were treated orally with up to 10 mg/kg amlodipine (respectively 8 times\* and 23 times\* the maximum recommended human dose of 10 mg on a mg/m<sup>2</sup> basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats administered 10 mg/kg amlodipine for 14 days before mating and throughout mating and gestation. An odipine has been shown to pro-ovulate both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

**Pediatric Use:** Safety and effectiveness of NORVASC in children have not been established.

**Geriatric Use:** Clinical studies of NORVASC did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required (see **DOSAGE AND ADMINISTRATION**).

**ADVERSE REACTIONS:** NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) at doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose-related manner are as follows: edema (1.8% at 2.5 mg, 3.8% at 5.0 mg, and 10.8% at 10.0 mg, compared with 0.6% placebo); dizziness (1.1% at 2.5 mg, 3.4% at 5.0 mg, and 3.4% at 10.0 mg, compared with 1.5% placebo); flushing (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 2.0% at 10.0 mg, compared with 0.0% placebo); and palpitation (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 4.5% at 10.0 mg, compared with 0.6% placebo).

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in a placebo-controlled clinical trial include the following: headache (7.3%, compared with 7.8% placebo); fatigue (4.5% compared with 2.8% placebo); nausea (2.9%, compared with 1.9% placebo); abdominal pain (1.6%, compared with 0.3% placebo); and somnolence (1.4%, compared with 0.6% placebo).

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with an odipine treatment as follows: edema (5.6% in men, 14.6% in women, compared with a placebo incidence in men of 1.4% and 5.1% in women); flushing (1.5% in men, 4.5% in women, compared with a placebo incidence of 0.3% in men and 0.9% in women); palpitations (1.4% in men, 3.3% in women, compared with a placebo incidence of 0.9% in men and 0.9% in women); and somnolence (1.3% in men, 1.8% in women, compared with a placebo incidence of 0.6% in men and 0.3% in women).

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis; **central and peripheral nervous system:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo; **gastrointestinal:** anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia; **general:** allergic reaction, asthenia, back pain, hot flashes, malaise, pain, rigors, weight gain, weight decrease; **musculoskeletal system:** arthralgia, arthritis, muscle cramps, myalgia; **psychiatric:** social dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **respiratory system:** dyspnea, epistaxis; **skin and appendages:** angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular; **special senses:** abnormal vision, conjunctivitis, diplopia, eye pain, lacrimation; **urinary system:** micturition frequency, micturition disorder, nocturia; **autonomic nervous system:** dry mouth, sweating increased; **metabolic and nutritional:** hyperglycemia, thirst, hypocalcemia; leukopenia, purpura, thrombocytopenia.

The following events occurred in <0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness twitching, ataxia, hypertension, migraine, cold and clammy skin, apathy, agitation, anorexia, gastritis, increased appetite, loose stool, coughing, thin lips, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: glycosuria. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

**OVERDOSAGE:** Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused death. A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained nonemetic; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm, blood was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

Intensive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

\* Based on patient weight of 50 kg

\*\* These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

More detailed professional information available on request.

Rev. 0 December 2001

**References:** 1. Bakris GL, Williams M, Dworkin L, et al, for the National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis.* 2001;38:648-661. 2. Data on file, Pfizer Inc., New York, NY. 3. Scott Levin Formulary Drug Audit, Fall 2002. 4. IMS International Prescription Data (total prescriptions based on 35 countries moving annual total), March 2003; IMS National Prescription Audit (total prescriptions), 2002; IMS Health Services MIDAS Data (journalistive patient-days total), 1990-March 2003.

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(amlodipine besylate)

**THE MOST PRESCRIBED  
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IN THE WORLD™**



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NORVASC is indicated for hypertension and angina.

ACEs  
ARBs  
Diuretics  
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**While they duke it out among themselves to see who's better...  
Isn't it nice to know Norvasc works well with others?**



**With no known drug interactions, excellent tolerability, and proven efficacy, NORVASC works well in virtually any kind of patient at any time.**

It's common knowledge that drugs that lower BP lower the risk of stroke and myocardial infarction. It's also common knowledge that it takes multiple medications to get patients' BP down to where it needs to be.<sup>1</sup> That's why there's NORVASC.

NORVASC, indicated for the treatment of hypertension and angina, has no known drug interactions and can be used safely with other BP-lowering agents. NORVASC can also be used safely in all patient types, including patients with diabetes and kidney disease. And NORVASC delivers 24-hour BP-lowering efficacy regardless of patient type and provides additional BP reductions when used in combination with other BP-lowering agents.<sup>2</sup>

The most common side effects versus placebo were edema (8.3% vs 2.4%), headache (7.3% vs 7.8%), fatigue (4.5% vs 2.8%), and dizziness (3.2% vs 3.4%).

And when you consider that NORVASC is covered by 97% of plans, it's hard not to consider it for all of your patients with hypertension.<sup>3</sup>

*Please see brief summary of prescribing information for NORVASC on the adjacent page.*

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**CONTENTS—FEBRUARY 2004/VOL. 96, NO. 2**

**PRESIDENT'S COLUMN**

- 156  
**Healthcare Solutions for Black Americans**  
Randall Maxey, MD, PhD

**EDITORIAL**

- 160  
**The Phoenix Has Risen But Has Failed to Thrive: Hope on the Horizon for King-Drew Medical Center**  
José L. Calderón, MD and Robert Beltrán, MBA, MD

**ORIGINAL COMMUNICATIONS**

- 169  
**Age 14 Starts a Child's Increased Risk of Major Knife or Gun Injury in Washington, DC**  
Howard A. Freed, MD; David P. Milzman, MD; Richard W. Holt, MD; and Anthony Wang
- 176  
**Knowledge, Behaviors, and Attitudes About Hearing Loss and Hearing Protection Among Racial/Ethnically Diverse Young Adults**  
Carl Crandell, PhD; Terry L. Mills, PhD; and Ricardo Gauthier, AuD
- 187  
**Maternal Support in the Delivery Room and Birthweight Among African-American Women**  
Antoine Alexandra Lespinasse, MD; Richard J. David, MD; James W. Collins, MD, MPH; Arden S. Handler, DrPH; and Stephen N. Wall, MD
- 196  
**Doxorubicin Cardiotoxicity in African Americans**  
Syed Hasan, MD, FABHP; Kimberly Dinh, PharmD; Fred Lombardo, PharmD, MS; and John Kark, MD

- 200  
**Prevalence and Correlates of Initiation of Smoking Behavior Among Preteen Black and White Children**  
Nasar U. Ahmed, PhD; Noushin S. Ahmed; Kofi A. Semanya, PhD; Jared D. Elzey, BA; Celia Larson, PhD; C. Ray Bennett DDS; and Joseph E. Hinds MD, PhD

- 209  
**Harris-Benedict Equations Do Not Adequately Predict Energy Requirements in Elderly Hospitalized African Americans**  
Charlene Compher, PhD; Robert Cato, MD; Joan Bader, MS; and Bruce Kinosian, MD

- 215  
**Racial Disparities in Sexual Risk Behaviors and Drug Use Among Older Gay/Bisexual and Heterosexual Men Living with HIV/AIDS**  
Karolynn Siegel, PhD; Eric W. Schrimshaw, MA; and Daniel Karus, MS

- 224  
**Hemoglobinopathy and Pattern of Musculoskeletal Infection in Children**  
Lateef O.A. Thanni, FWACS; Olusoga B. Ogunfowora, FWACP; and Durotoye M. Olanrewaju, FWACP

- 229  
**Trends in the Incidence, Clinical Presentation, and Management of Traumatic Rupture of the Corpus Cavernosum**  
Paul D. Ekwere, FRCS and Mohammed Al Rashid, FRCSI

- 234  
**Sonographic Assessment of Postvoid Residual Urine Volumes in Patients With Benign Prostatic Hyperplasia**  
Adewumi O. Amole, FWACS; Sulyman A. Kuranga, FWACS; and Benjamin A. Oyejola, PhD

240

**Secondary School Athletes:  
A Study of Mouthguards**  
Chukwudi Ochi Onyeyaso, BDS (Ib), FWACS

246

**John Henry Active Coping, Education, and  
Blood Pressure Among Urban Blacks**  
Anita F. Fernander, PhD; Ron E.F. Durán, PhD;  
Patrice G. Saab, PhD; and Neil Schneiderman, PhD

### CASE REPORT

256

**Twenty-Eight-Year-Old Female With Primary  
Amenorrhea and Chronic Renal Failure:  
A Case of Frasier Syndrome?**  
Raphael Onyemekeihia and Efosa Oviasu

### LETTER TO THE EDITOR

262

**Hepatitis C Virus in Sickle Cell Disease**  
Mark H. Jackson, MD

### HEALTH TIDBITS

147

**Influenza Update 2003**

**Reduce Risks of Fatal Errors**

**Relationship Between Poverty and the Mental  
Health of Children**

**After ED Treatment for Acute Asthma, Giving  
Disadvantaged Inner-City Adults Systemic  
Corticosteroids May Prevent Relapses**

**Racial Differences Exist in Survival Following  
Cardiac Arrest**

**Increase in the Prescription of Antidepressants  
for Elderly Primary-Care Patients**

**Pediarix**

**Influenza Vaccine**

**BSE or Mad Cow Disease Found in an  
American Cow**

**Gold Humanism Honor Society Provides  
Recognition for Humanistic Doctors**

**Virus Created From Scratch in Two Weeks**

**NCI Holds Meeting to Examine Barriers to  
NIH Funding for Minority Researchers**

**DC Site of the Germ Attack to Open Soon  
System for Detecting Bio Agents Enacted**

**Playground Cancer Risk for Children**

**Does Lung Cancer Screening Have a Future?**

**Heart Patients Short-Changed on Basic Medicines**

**African Americans More Accepting of  
Larger Body Images**

**Experts Calling for More Drug Treatment  
Programs—Not Prisons—for Addicts**

**Vital Statistics and the African-American  
Community, Part 1—Deaths**

**Vital Statistics and the African-American  
Community, Part 2—Births**

**Shocker: It's the Whole Tomato, Not a Pill**

### BOOK REVIEWS

263

*The Directory of  
Hospital Personnel*

**Grey House Publishing**

Reviewed by Georges C. Benjamin, MD

*Blessed Health: The African-American Woman's  
Guide to Physical and Spiritual Well-Being*

**Melody T. McCloud, MD, and Angela Ebron**

Reviewed by J. Gary Linn, PhD and  
Susan Seager, RN, PhD

264

*Depression Sourcebook*

Reviewed by Roger O.A. Makanjuola, MB BS,  
PhD, MRCPsych, FMCPsych, FWACP (Psych)

*Unequal Treatment—Confronting Racial and  
Ethnic Disparities in Healthcare*

**Brian Smedley, Adrienne Stith, Alan Nelson, eds.**

Reviewed by Olusola Osundeko, MD, MRCPsych,  
FACE

### DEPARTMENTS

137

**JNMA/NMA Directory**

140, 166, 174, 186, 198, 199, 208, 214, 228, 245,  
255, 262

**Career Opportunities**

158

**Library Subscriptions**

267

**Membership Application**

268

**Calendar**

## LIPITOR® (Atorvastatin Calcium) Tablets

### Brief Summary of Prescribing Information

**CONTRAINDICATIONS:** Active liver disease or unexplained persistent elevations of serum transaminases. Hypersensitivity to any component of this medication. **Pregnancy and Lactation** — Atorvastatin is a cholesteric process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILD-BEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS.** If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

**WARNINGS: Liver Dysfunction** — HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations 3-5 times the upper limit of normal (ULN) occurring on 2 or more occasions in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials.** The incidence of these abnormalities was 0.2%, 0.6%, 0.8%, and 2.3% for 10, 20, 40, and 80 mg, respectively. One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 38 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS). **Skeletal Muscle** — Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or elevated creatine phosphokinase (CPK). Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporin, fibrin acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibrin acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

**PRECAUTIONS: General** — Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in full prescribing information). **Information for Patients** — Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Drug Interactions** — The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of cyclosporin, fibrin acid derivatives, niacin, niacin inositol acid, erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle). **Antacid** When atorvastatin and Maalox® TC suspension were administered, plasma concentrations of atorvastatin decreased approximately 30%. However, LDL-C reduction was not altered. **Antipyretic** Because atorvastatin does not affect the pharmacokinetics of aspirin, interactions with other drugs metabolized via the same cytochrome isoenzymes are not expected. **Coloalop** Plasma concentrations of atorvastatin decreased approximately 25% when coloalop and atorvastatin were administered. However, LDL-C reduction was greater when atorvastatin and coloalop were administered than when either drug was given alone. **Cimetidine** Atorvastatin plasma concentrations and LDL-C reduction were not altered by administration of cimetidine. **Digoxin** When multiple doses of atorvastatin and digoxin were administered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately. **Erythromycin** In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle). **Oral Contraceptives** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin. **Niacin** Atorvastatin had no clinically significant effect on preference time when administered to patients receiving chronic warfarin treatment. **Endocrine Function** — HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as leteclosovir, spirocyclopropanes, and cimetidine. **CNS Toxicity** — Brain hemorrhage was seen in a female dog treated for 3 months at 10 mg/kg/day. Brain hemorrhage and optic nerve vasculature were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 200 mg/kg/day. The 100 mg/kg dose resulted in a systemic exposure approximately 10 times the human plasma concentration (AUC<sub>0-24</sub> based on the maximum human dose of 80 mg/day). A single toxic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 180 mg/kg/day. These doses were 6 to 11 times (based on 8 to 16 times) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Ballerian degeneration of retinal ganglion cell fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility** — In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 180 mg/kg/day, 7 rare tumors were found in muscle in high-dose females; in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC<sub>0-24</sub> value of approximately 18 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given 100, 300, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 8 times the mean human plasma drug exposure after an 80 mg oral dose. In rats, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (115 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymus of 2 of 30 rats treated with 100 mg/kg/day of atorvastatin for 3 months (18 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 180 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, sperm head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 100 mg/kg for two years. **Pregnancy** — **Pregnancy Category X: See CONTRAINDICATIONS.** Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 180 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 28 times (rabbit) the human exposure based on surface area (mg/m<sup>2</sup>). In a study in rats given 30, 100, or 225 mg/kg/day from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonatal, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 180 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (incisor performance at 180 mg/kg/day and acoustic startle at 225 mg/kg/day; pinna detachment and eye opening at 225 mg/kg/day). These doses correspond to 8 times (100

mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bone deformity (tracheo-oesophageal fistula, and anal atresia [VACTER associated]) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. **LIPITOR** should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking **LIPITOR**, it should be discontinued and the patient advised again as to the potential hazards to the fetus. **Nursing Mothers** — Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking **LIPITOR** should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use** — Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 6 months duration in adolescent boys and postmenarcheal girls. Patients treated with **LIPITOR** had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experience observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In the limited controlled study, there was no discernible effect on growth or sexual maturation in boys or on menstrual cycle length in girls. See CLINICAL PHARMACOLOGY, Clinical Studies section in full prescribing information. **ADVERSE REACTIONS: Pediatric Patients and DOSAGE AND ADMINISTRATION, Pediatric Patients 10-17 years of age with Heterozygous Familial Hypercholesterolemia in full prescribing information.** Adolescent females should be counseled on appropriate contraceptive methods while on **LIPITOR** therapy (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). **LIPITOR has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.** Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with heterozygous FH including 8 pediatric patients. See CLINICAL PHARMACOLOGY, Clinical Studies in Heterozygous Familial Hypercholesterolemia in full prescribing information. **Geriatric Use** — The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (>65 years of age) was evaluated in the ACCESS study. In this 94-week open-label trial, 1368 patients initiated therapy with atorvastatin 10 mg. Of these, 825 were elderly (>65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was -38.2% in the elderly patients versus -34.6% in the non-elderly group. The rates of discontinuation due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

**ADVERSE REACTIONS:** **LIPITOR** is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain. **Clinical Adverse Experiences** — Adverse experiences reported in >2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in the following table.

| Adverse Event                 | Adverse Events in Placebo-Controlled Studies (% of Patients) |                                  |                                 |                                 |                                 |
|-------------------------------|--|----------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                               | Placebo<br>N = 276   | Atorvastatin<br>10 mg<br>N = 863 | Atorvastatin<br>20 mg<br>N = 26 | Atorvastatin<br>40 mg<br>N = 79 | Atorvastatin<br>80 mg<br>N = 34 |
| <b>BODY SYSTEM</b>            |  |                                  |                                 |                                 |                                 |
| Adverse Event                 |  |                                  |                                 |                                 |                                 |
| <b>ADVERSE REACTIONS</b>      |  |                                  |                                 |                                 |                                 |
| <b>BODY AS A WHOLE</b>        |  |                                  |                                 |                                 |                                 |
| Infection                     | 10.8   | 10.3                             | 2.8                             | 10.1                            | 7.4                             |
| Headache                      | 7.8  | 5.4                              | 16.7                            | 2.5                             | 6.4                             |
| Accidental injury             | 3.7  | 4.2                              | 0.8                             | 1.3                             | 3.2                             |
| Ru Syndrome                   | 1.8  | 2.2                              | 0.8                             | 2.5                             | 3.2                             |
| Abdominal Pain                | 0.7  | 2.8                              | 0.8                             | 3.8                             | 2.1                             |
| Back Pain                     | 3.8  | 2.8                              | 0.8                             | 3.8                             | 1.1                             |
| Allergic Reaction             | 2.8  | 0.8                              | 2.8                             | 1.3                             | 0.8                             |
| Asthma                        | 1.8  | 2.2                              | 0.8                             | 2.8                             | 0.8                             |
| <b>DIGESTIVE SYSTEM</b>       |  |                                  |                                 |                                 |                                 |
| Constipation                  | 1.8  | 2.1                              | 0.8                             | 2.5                             | 1.1                             |
| Diarrhea                      | 1.5  | 2.7                              | 0.8                             | 3.8                             | 5.3                             |
| Dyspepsia                     | 4.1  | 2.3                              | 2.8                             | 1.3                             | 2.1                             |
| Flatulence                    | 3.3  | 2.1                              | 2.8                             | 1.3                             | 1.1                             |
| <b>RESPIRATORY SYSTEM</b>     |  |                                  |                                 |                                 |                                 |
| Sinusitis                     | 2.8  | 2.8                              | 0.8                             | 2.5                             | 6.4                             |
| Pharyngitis                   | 1.5  | 2.5                              | 0.8                             | 1.3                             | 2.1                             |
| <b>SKIN AND APPENDAGES</b>    |  |                                  |                                 |                                 |                                 |
| Rash                          | 0.7  | 3.8                              | 2.8                             | 3.8                             | 1.1                             |
| <b>MUSCULOSKELETAL SYSTEM</b> |  |                                  |                                 |                                 |                                 |
| Arthralgia                    | 1.5  | 2.8                              | 0.8                             | 5.1                             | 0.8                             |
| Myalgia                       | 1.1  | 2.2                              | 5.8                             | 1.3                             | 0.8                             |

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in italics occurred in <2% of patients and the events in plain type occurred in <2% of patients.

**Body as a Whole:** Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. **Digestive System:** Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cholelith, duodenal ulcer, dyspepsia, dysphagia, enteritis, melena, gum hemorrhage, stomach acid, tenesmus, alcoholic stomatitis, hepatitis, epistaxis, gastroenteric, cholelithic jaundice. **Respiratory System:** Acrocystitis, rhinitis, pneumonia, dyspnea, asthma, apnoeic, epistaxis. **Nervous System:** Incontinence, dizziness, paraesthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hyposthesia, hypotonia. **Musculoskeletal System:** Arthritis, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. **Skin and Appendages:** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, vitiligo, eczema, seborrhea, skin ulcer. **Urogenital System:** Ovary dysfunction, urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. **Special Senses:** Amblyopia, blepharitis, dry eyes, refractive disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. **Cardiovascular System:** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension. **Metabolic and Nutritional:** Diabetes. **Ophthalmic:** Periphlebotomy, hyperglycemia, creatine phosphokinase increased, goiter, weight gain, hyperglycemia. **Hemic and Lymphatic System:** Echinocystosis, anemia, lymphadenopathy, thrombocytopenia, ptochitis.

**Postmarketing Reports** — Adverse events associated with **LIPITOR** therapy reported since market introduction, that are not listed above, of causality assessment, include the following: anaphylaxis, angioedema, edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis. **Pediatric Patients (ages 10-17 years)** In a 26-week controlled study in boys and postmenarcheal girls (n=343), the safety and tolerability profile of **LIPITOR** 10 to 20 mg daily was generally similar to that of placebo (see CLINICAL PHARMACOLOGY, Clinical Studies section in full prescribing information and PRECAUTIONS, Pediatric Use).

**OVERDOSAGE:** There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

Please see full prescribing information for additional information about **LIPITOR**.

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Manufactured by:  
Pfizer Ireland Pharmaceuticals  
Dublin, Ireland

**Distributed by:**  
**Pfizer Parke-Davis**  
Divs of Pfizer Inc., NY, NY 10017

Rev. 2, November 2002



Successful at **10** 



Accomplished at **20** 



Fulfilled at **40** 



Satisfied at **80** 

## Power to help patients meet their lipid goals

When used with diet and exercise to reduce LDL-C and TG and increase HDL-C



**LIPITOR**  
atorvastatin calcium  
tablets

**POWER YOU CAN TRUST™**

### Important information:

LIPITOR® (atorvastatin calcium) is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.

LIPITOR is contraindicated in patients with hypersensitivity to any component of this medication; in patients with active liver disease or unexplained persistent elevations of serum transaminases; in women during pregnancy and in nursing mothers.

With any statin, tell patients to promptly report muscle pain, tenderness, or weakness. Discontinue drug if myopathy is suspected, if creatine phosphokinase (CPK) levels rise markedly, or if the patient has risk factors for rhabdomyolysis.

It is recommended that liver function tests be performed prior to and 12 weeks following both the initiation of therapy and any elevation of dose, and periodically thereafter.

In clinical trials, the most common adverse events were constipation, flatulence, dyspepsia, and abdominal pain.

The effect of LIPITOR on cardiovascular morbidity and mortality has not been determined.

*Please see brief summary of prescribing information on adjacent page.*

*Tablets not shown to scale.*