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BRILINTA™

(ticagrelor)

Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BRILINTA safely and effectively. See full prescribing information for BRILINTA.

BRILINTA™ (ticagrelor) tablets, for oral use

Initial U.S. Approval: 2011

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).**

INDICATIONS AND USAGE

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis. (1)

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily. (1, 5.2, 14)

DOSAGE AND ADMINISTRATION

- Initiate treatment with 180 mg (two 90 mg tablets) oral loading dose. (2)
- Continue treatment with 90 mg twice daily. (2)
- After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. (2)

DOSAGE FORMS AND STRENGTHS

- 90 mg tablets (3)

CONTRAINDICATIONS

- History of intracranial hemorrhage (4.1)
- Active pathological bleeding (4.2)
- Severe hepatic impairment (4.3)

WARNINGS AND PRECAUTIONS

- Like other antiplatelet agents, BRILINTA increases the risk of bleeding. (5.1)
- In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. (5.2, 14)
- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor. (5.3)
- Dyspnea: Dyspnea was reported more frequently with BRILINTA than with clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes. (5.4)
- Discontinuation of BRILINTA: Premature discontinuation increases the risk of myocardial infarction, stent thrombosis, and death. (5.5)

ADVERSE REACTIONS

Most common adverse reactions are bleeding 12% and dyspnea 14%. (5.1, 5.4, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Avoid use with strong CYP3A inhibitors or CYP3A inducers. (7.1, 7.2)
- Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse effects. (7.3)
- Monitor digoxin levels with initiation of or any change in BRILINTA. (7.4)

See 17 For PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: BLEEDING RISK

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- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).**
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- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

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1 INDICATIONS AND USAGE

Acute Coronary Syndromes

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis [see *Clinical Studies* (14)].

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily [see *Warnings and Precautions* (5.2) and *Clinical Studies* (14)].

2 DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily.

After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg.

ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA.

BRILINTA can be administered with or without food.

A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

3 DOSAGE FORMS AND STRENGTHS

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on one side.

4 CONTRAINDICATIONS

4.1 History of Intracranial Hemorrhage

BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population [see *Clinical Studies* (14)].

4.2 Active Bleeding

BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage [see *Warnings and Precautions* (5.1) and *Adverse Reactions* (6.1)].

4.3 Severe Hepatic Impairment

BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins [see *Clinical Pharmacology* (12.3)].

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased [see *Adverse Reactions* (6.1)].

In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDS]).

When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding.

If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [see *Warnings and Precautions* (5.5) and *Adverse Reactions* (6.1)].

5.2 Concomitant Aspirin Maintenance Dose

In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg [see *Dosage and Administration* (2) and *Clinical Studies* (14)].

5.3 Moderate Hepatic Impairment

BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

5.4 Dyspnea

Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption.

In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

5.5 Discontinuation of BRILINTA

Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

5.6 Strong Inhibitors of Cytochrome CYP3A

Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole [see *Drug Interactions* (7.1) and *Clinical Pharmacology* (12.3)].

5.7 Cytochrome CYP3A Potent Inducers

Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital [see *Drug Interactions* (7.2) and *Clinical Pharmacology* (12.3)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following adverse reactions are also discussed elsewhere in the labeling:

- Dyspnea [see *Warnings and Precautions* (5.4)]

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

BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

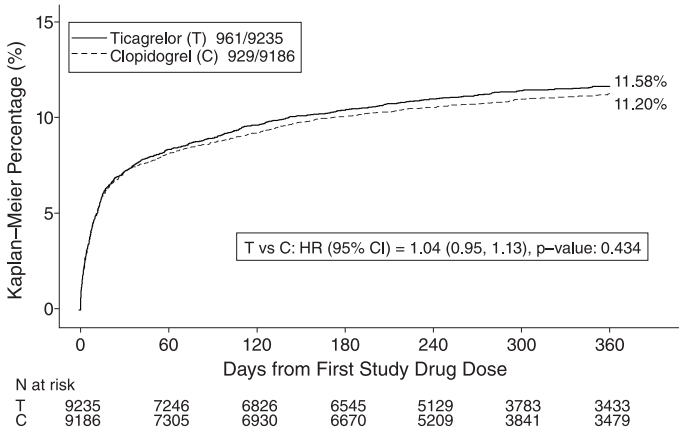
Bleeding

PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1 Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

Table 1 Non-CABG related bleeds (KM%)

	BRILINTA N=9235	Clopidogrel N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel.

In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 CABG bleeds (KM%)

	Patients with CABG	
	BRILINTA N=770	Clopidogrel N=814
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in *in vitro* tests and BRILINTA is a reversibly binding $P2Y_{12}$ inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel.

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation

In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common Adverse Events

A variety of non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more. These are shown in Table 3. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

Table 3 Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group

	BRILINTA N=9235	Clopidogrel N=9186
Dyspnea[a]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[a] Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

Bradycardia

In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively.

In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia

In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel.

Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities

Serum Uric Acid:

Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group).

Serum Creatinine:

In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

7 DRUG INTERACTIONS

Effects of other drugs

Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

7.1 CYP3A inhibitors

Avoid use of strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin) [see *Warnings and Precautions* (5.6) and *Clinical Pharmacology* (12.3)].

7.2 CYP3A inducers

Avoid use with potent inducers of CYP3A (e.g., rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital) [see *Warnings and Precautions* (5.7) and *Clinical Pharmacology* (12.3)].

7.3 Aspirin

Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA [see *Warnings and Precautions* (5.2) and *Clinical Studies* (14)].

Effect of BRILINTA on other drugs

Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

7.4 Simvastatin, lovastatin

BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg [see *Clinical Pharmacology* (12.3)].

7.5 Digoxin

Digoxin: Because of inhibition of the P-glycoprotein transporter, monitor digoxin levels with initiation of or any change in BRILINTA therapy [see *Clinical Pharmacology* (12.3)].

7.6 Other Concomitant Therapy

BRILINTA can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m^2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m^2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m^2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred.

In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m^2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m^2 basis).

8.3 Nursing Mothers

It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of BRILINTA in pediatric patients have not been established.

8.5 Geriatric Use

In PLATO, 43% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups.

No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

BRILINTA has not been studied in the patients with moderate or severe hepatic impairment. Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Hence, BRILINTA is contraindicated for use in patients with severe hepatic impairment and its use should be considered carefully in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment [see *Contraindications* (4), *Warnings and Precautions* (5.3) and *Clinical Pharmacology* (12.3)].

8.7 Renal Impairment

No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied [see *Clinical Pharmacology* (12.3)].

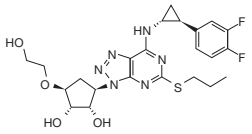
10 OVERDOSAGE

There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.

Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

11 DESCRIPTION

BRILINTA contains ticagrelor, a cyclopentyltriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor. Chemically it is (1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol. The empirical formula of ticagrelor is $C_{23}H_{28}F_2N_6O_4S$ and its molecular weight is 522.57. The chemical structure of ticagrelor is:



Ticagrelor is a crystalline powder with an aqueous solubility of approximately 10 µg/mL at room temperature.

BRILINTA tablets for oral administration contain 90 mg of ticagrelor and the following ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

12.2 Pharmacodynamics

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6 week study examining both acute and chronic platelet inhibition effects in response to 20 µM ADP as the platelet aggregation agonist.

The onset of IPA was evaluated on Day 1 of the study following loading doses of 180 mg ticagrelor or 600 mg clopidogrel. As shown in Figure 2, IPA was higher in the ticagrelor group at all time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours.

The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 µM ADP.

As shown in Figure 3, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in figure 3 shows that after 24 hours, IPA in the ticagrelor group (58%) was similar to IPA in clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to IPA in the placebo group. It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel.

Transitioning from clopidogrel to BRILINTA resulted in an absolute IPA increase of 26.4% and from BRILINTA to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to BRILINTA without interruption of antiplatelet effect [see *Dosage and Administration* (2)].

12.3 Pharmacokinetics

Ticagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy volunteers.

Absorption

Absorption of ticagrelor occurs with a median t_{max} of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median t_{max} of 2.5 h (range 1.5-5.0).

The mean absolute bioavailability of ticagrelor is about 36%, (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21% increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC. BRILINTA can be taken with or without food.

Figure 2 Mean inhibition of platelet aggregation (±SE) following single oral doses of placebo, 180 mg ticagrelor, or 600 mg clopidogrel

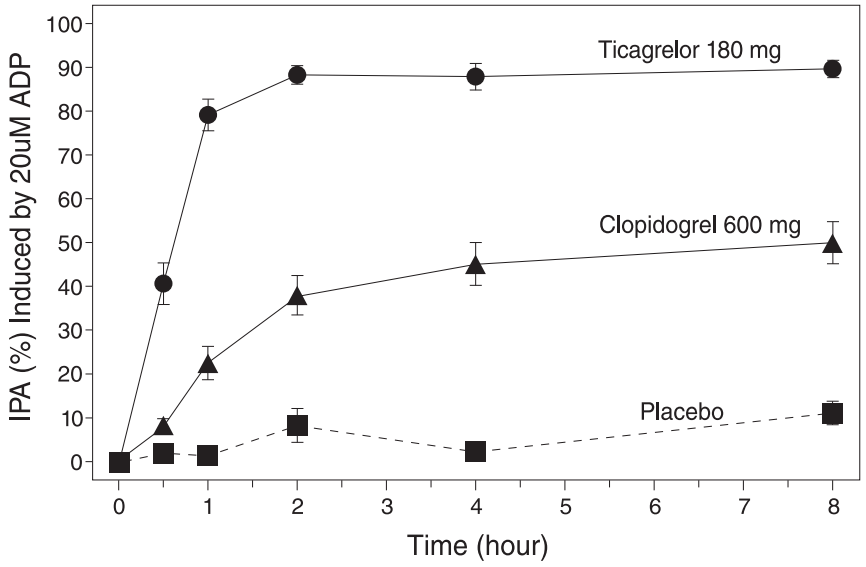
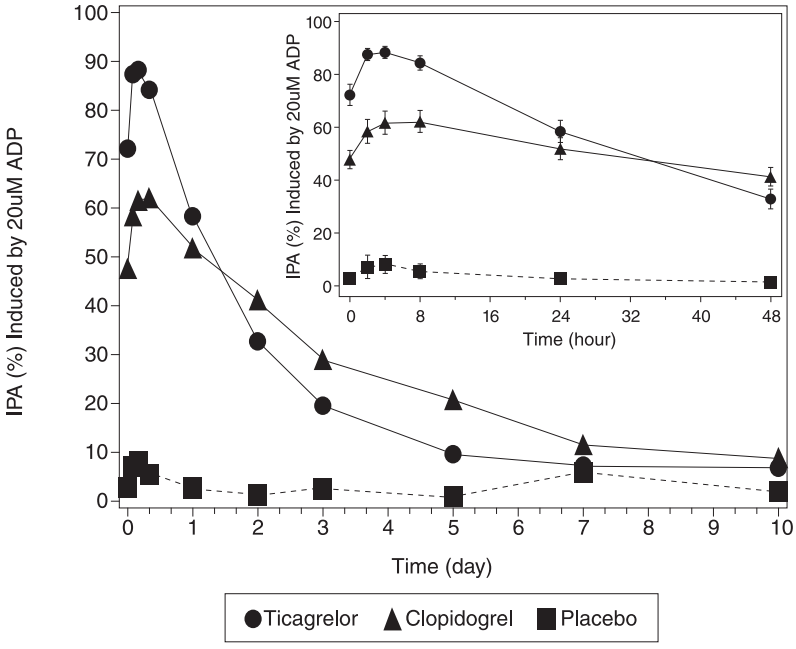


Figure 3 Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily



Distribution

The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (>99%).

Metabolism

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30-40% of the exposure of ticagrelor.

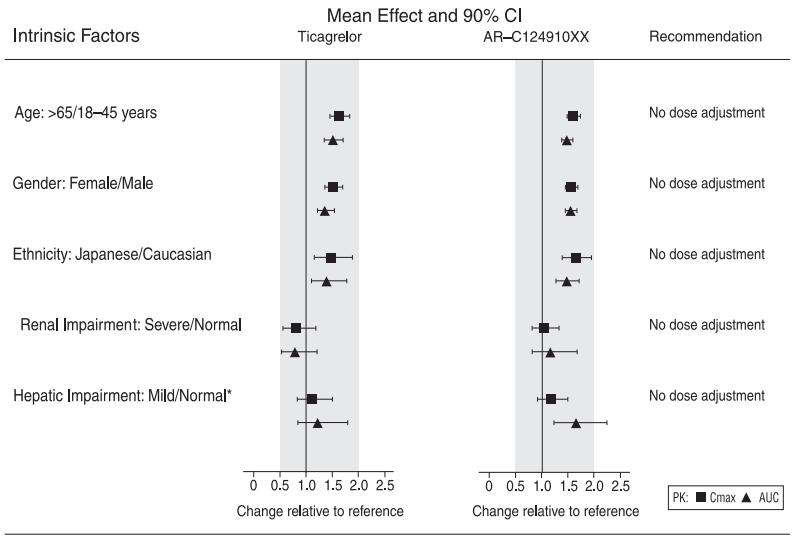
Excretion

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean $t_{1/2}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Special Populations

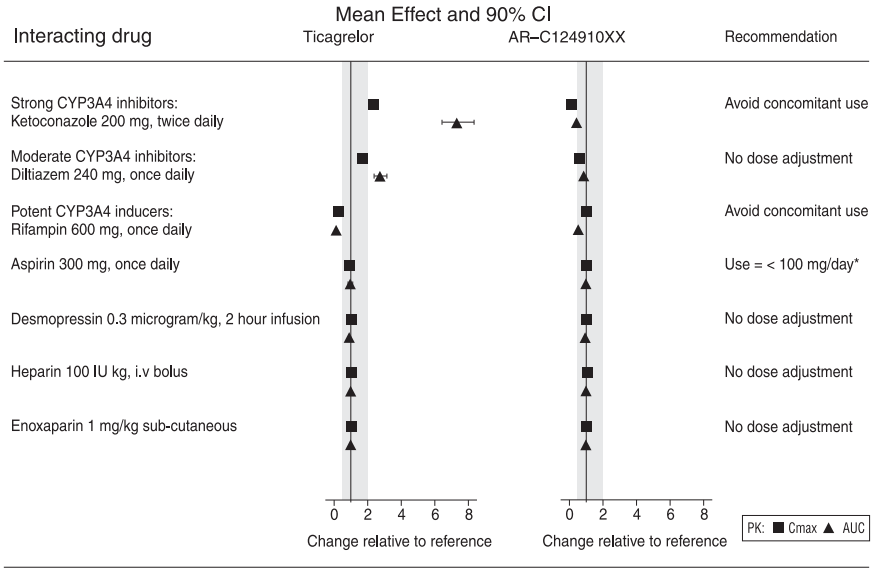
The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 4. Effects are modest and do not require dose adjustment.

Figure 4 Impact of intrinsic factors on the pharmacokinetics of ticagrelor



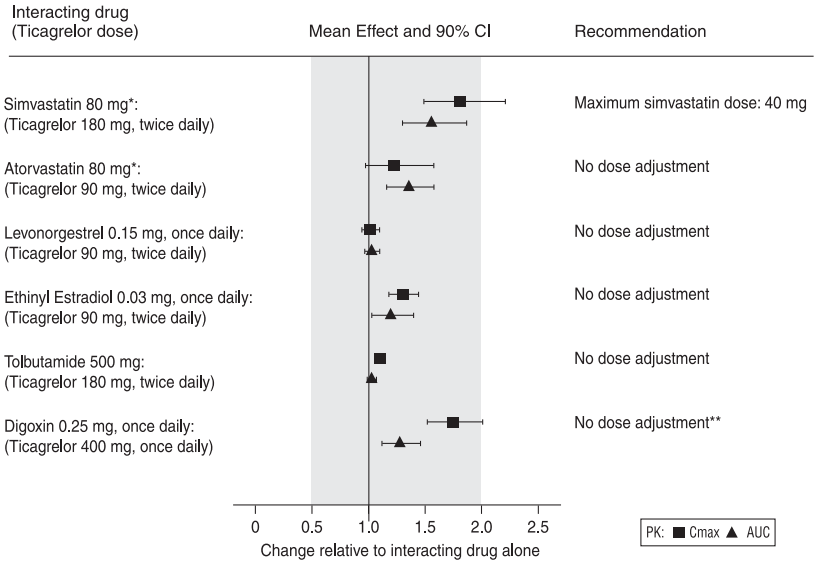
*BRILINTA has not been studied in patients with moderate or severe hepatic impairment.

Figure 5 Effect of co-administered drugs on the pharmacokinetics of ticagrelor



*See *Dosage and Administration (2)*.

Figure 6 Impact of BRILINTA on the pharmacokinetics of co-administered drugs



*Similar increases in AUC and C_{max} were observed for all metabolites
**Monitor digoxin levels with initiation of or change in BRILINTA therapy

Pediatric
Ticagrelor has not been evaluated in a pediatric population [see *Use in Specific Populations* (8.4)].

Body Weight
No dose adjustment is necessary for ticagrelor based on weight.

Smoking
Habitual smoking increased population mean clearance of ticagrelor by approximately 22% when compared to non-smokers. No dose adjustment is necessary for ticagrelor based on smoking status.

Effects of Other Drugs on BRILINTA
CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. The effects of other drugs on the pharmacokinetics of ticagrelor are presented in Figure 5 as change relative to ticagrelor given alone (test/reference). Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors have lesser effects (e.g., diltiazem). CYP3A inducers (e.g., rifampin) substantially reduce ticagrelor blood levels.

Effects of BRILINTA on Other Drugs
In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the P-gp transporter. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. For specific *in vivo* effects on the pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgesterol, tolbutamide, and digoxin, see Figure 6.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29-fold the maximally recommended dose of 90 mg twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

Mutagenesis
Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility
Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

14 CLINICAL STUDIES
The clinical evidence for the effectiveness of BRILINTA is derived from PLATO, a randomized double-blind study comparing BRILINTA (N=9333) to clopidogrel (N=9291), both given in combination with aspirin and other standard therapy, in patients with acute coronary syndromes (ACS). Patients were treated for at least 6 months and for up to 12 months. Study endpoints were obtained until the study was complete, even if drug was discontinued.

Patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms were randomized to receive BRILINTA or clopidogrel. Patients who had already been treated with clopidogrel could be enrolled and randomized to either study treatment. Patients could be included whether there was intent to manage the ACS medically or invasively, but patient randomization was not stratified by this intent. Subjects in the clopidogrel arm were

treated with an initial loading dose of clopidogrel 300 mg, if previous clopidogrel therapy had not been given prior to randomization. Patients undergoing PCI could receive an additional 300 mg of clopidogrel at investigator discretion. All subjects randomized to BRILINTA received a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily. Concomitant aspirin was recommended at a loading dose of 160-500 mg. A daily maintenance dose of aspirin 75-100 mg was recommended, but higher maintenance doses of aspirin were allowed according to local judgment.

Because of ticagrelor's metabolism by CYP3A enzymes, the protocol recommended limiting the maximum dosage of simvastatin and lovastatin to 40 mg in both study arms. Because of an increased bleeding risk, the study excluded patients with previous intracranial hemorrhage, a gastrointestinal bleed within the past 6 months, or other factors that predispose to bleeding.

PLATO patients were predominantly male (72%) and Caucasian (92%). About 43% of patients were >65 years and 15% were >75 years.

The study's primary endpoint was the composite of first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or non-fatal stroke. The components were assessed as secondary endpoints.

Median exposure to study drug was 277 days. About half of the patients received pre-study clopidogrel and about 99% of the patients received aspirin at some time during PLATO. About 35% of patients were receiving a statin at baseline and 93% received a statin sometime during PLATO.

Table 4 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint. Separate secondary endpoint analyses are shown for the overall occurrence of CV death, MI, and stroke and overall mortality.

The difference between treatments on the composite resulted from effects on CV death and MI; each was statistically significant when considered as a secondary endpoint and there was no beneficial effect on strokes. For all-cause mortality the benefit was also statistically significant (p = 0.0003) with a hazard ratio of 0.78.

Among 11289 patients with PCI receiving any stent during PLATO, there was a lower risk of stent thrombosis (1.3% for adjudicated "definite") than with clopidogrel (1.9%) (HR 0.67, 95% CI 0.50-0.91; p=0.0091). The results were similar for drug-eluting and bare metal stents.

The Kaplan-Meier curve (Figure 7) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke in the overall study.

The curves separate by 30 days (RRR 12%) and continue to diverge throughout the 12 month treatment period (RRR 16%).

A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Many of these are shown in Figure 8. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. Most of the analyses show effects consistent with the overall results, but there are two marked exceptions: a finding of heterogeneity by region and a strong influence of the maintenance dose of aspirin. These are considered further below.

Most of the characteristics shown are baseline characteristics, but some reflect post-randomization determinations (e.g., final diagnosis, aspirin maintenance dose, use of PCI). Patients were not stratified by initial diagnosis, but the effect in the unstable angina subset (determined after randomization) appeared smaller than the effect in the NSTEMI and STEMI subsets. The results in the subsets based on final diagnosis (STEMI, NSTEMI and unstable angina) are also presented in Figure 8.

Regional Differences

Results in the rest of the world compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison

Table 4 Patients with Outcome Events, in PLATO (KM%)

	BRILINTA N=9333	Clopidogrel N=9291	Hazard Ratio (95% CI)	p-value
Composite of CV death, MI, or stroke	9.8	11.7	0.84 (0.77, 0.92)	0.0003
CV death	2.9	4.0	0.74	
Non-fatal MI	5.8	6.9	0.84	
Non-fatal stroke	1.4	1.1	1.24	
Secondary endpoints[a]				
CV death	4.0	5.1	0.79 (0.69, 0.91)	0.0013
MI[b]	5.8	6.9	0.84 (0.75, 0.95)	0.0045
Stroke[b]	1.5	1.3	1.17 (0.91, 1.52)	0.22
All-cause mortality	4.5	5.9	0.78 (0.69, 0.89)	0.0003

a First occurrence of specified event at any time b Includes patients that could have had other non-fatal events or died

Figure 7 Time to First Occurrence of CV Death, MI, or Stroke in PLATO

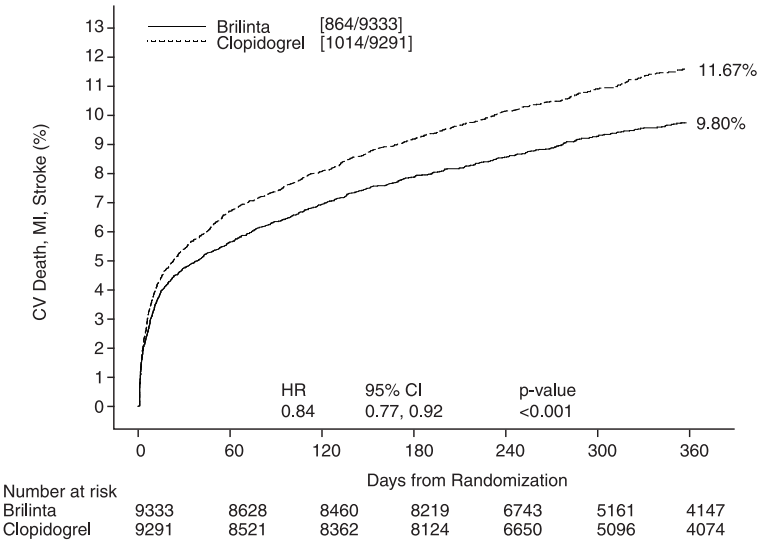


Figure 8 Subgroup analyses of PLATO

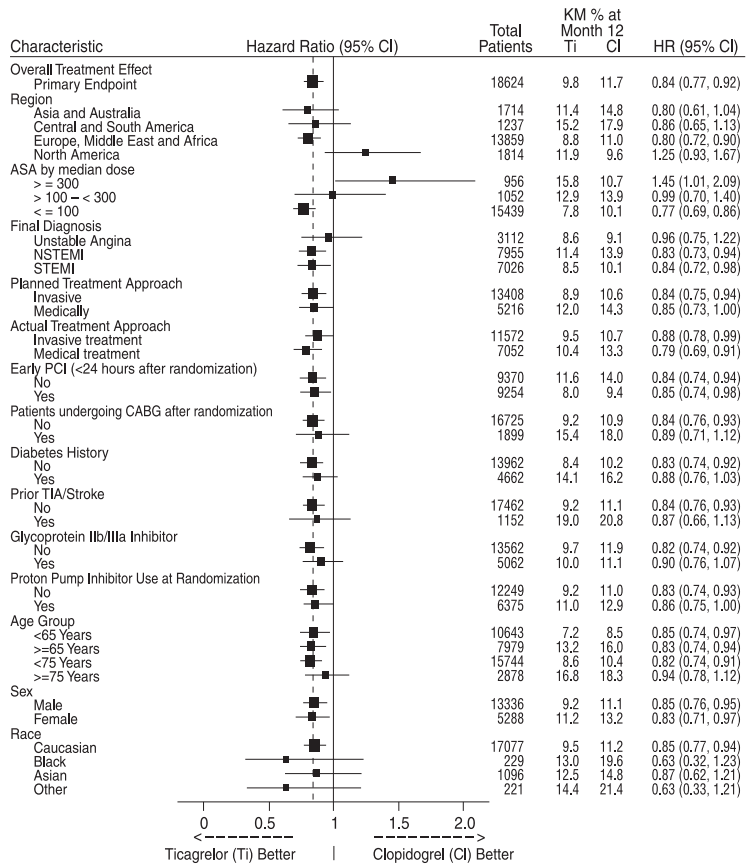
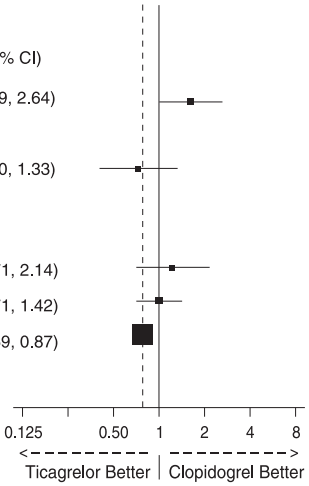


Table 5 PLATO: CV Death, MI, Stroke by maintenance aspirin dose in the US and outside the US

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor Events	Clopidogrel N	Clopidogrel Events	HR (95% CI)
US	>=300	324	40	352	27	1.62 (0.99, 2.64)
	>100 -<300	22	2	16	2	-
	<=100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	>=300	140	28	140	23	1.23 (0.71, 2.14)
	>100 -<300	503	62	511	63	1.00 (0.71, 1.42)
	<=100	7449	546	7443	699	0.78 (0.69, 0.87)



is statistically significant (p=0.009), and the same trend is present for both CV death and non-fatal MI. The individual results and nominal p-values, like all subset analyses, need cautious interpretation, and they could represent chance findings. The consistency of the differences in both the CV mortality and non-fatal MI components, however, supports the possibility that the finding is reliable.

A wide variety of baseline and procedural differences between the US and non-US (including intended invasive vs. planned medical management, use of GPIIb/IIIa inhibitors, use of drug eluting vs. bare-metal stents) were examined to see if they could account for regional differences, but with one exception, aspirin maintenance dose, these differences did not appear to lead to differences in outcome.

Aspirin Dose

The PLATO protocol left the choice of aspirin maintenance dose up to the investigator and use patterns were very different in the US and elsewhere, with about 8% of non-US investigators using aspirin doses above 100 mg, and about 2% using doses above 300 mg, in contrast with US practice, where 57% of patients received doses above 100 mg and 54% received doses above 300 mg. Overall results favored BRILINTA when used with low maintenance doses (≤100 mg) of aspirin, and results analyzed by aspirin dose were similar in the US and elsewhere. Figure 8 shows overall results by median aspirin dose. Table 5 shows results by region and dose.

Like any unplanned subset analysis, especially one where the characteristic is not a true baseline characteristic (but may be determined by usual investigator practice), the above analyses must be treated with caution. It is notable, however, that aspirin dose predicts outcome in both regions with a similar pattern, and that the pattern is similar for the two major components of the primary endpoint, CV death and non-fatal MI.

Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirin maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA.

Pharmacogenetics

In a genetic substudy of PLATO (n=10,285), the effects of BRILINTA compared to clopidogrel on thrombotic events and bleeding were not significantly affected by CYP2C19 genotype.

16 HOW SUPPLIED/STORAGE AND HANDLING

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on one side.

Bottles of 60 – NDC 0186-0777-60
Bottles of 180 – NDC 0186-0777-18
100 count Hospital Unit Dose – NDC 0186-0777-39

Storage and Handling

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

Keep BRILINTA in the container it comes in.

Keep BRILINTA tablets dry.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Benefits and Risks

- Tell patients to take BRILINTA exactly as prescribed.
- Inform patients not to discontinue BRILINTA without discussing it with the prescribing physician.
- Tell patients daily doses of aspirin should not exceed 100 mg and to avoid taking any other medications that contain aspirin.
- Tell patients to read the Medication Guide.

17.2 Bleeding

Inform patients that they:

- Will bleed and bruise more easily
- Will take longer than usual to stop bleeding
- Should report any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that BRILINTA can cause shortness of breath. Tell them to contact their doctor if they experience unexpected shortness of breath, especially if severe.

17.4 Invasive Procedures

Instruct patients to:

- Inform physicians and dentists that they are taking BRILINTA before any surgery or dental procedure.
- Tell the doctor performing any surgery or dental procedure to talk to the prescribing physician before stopping BRILINTA.

17.5 Concomitant Medications

Tell patients to list all prescription medications, over-the-counter medications or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (e.g. warfarin, heparin).

Issued: July 20, 2011

Manufactured by:
AstraZeneca, AB S-151 85 Södertälje Sweden
Marketed by: AstraZeneca LP, Wilmington, DE 19850

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MEDICATION GUIDE

BRILINTA™ (brih-LIN-tah)

(ticagrelor)

Tablets

Read this Medication Guide before you start taking BRILINTA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

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

BRILINTA is used to lower your chance of having a heart attack or dying from a heart attack or stroke **but BRILINTA (and similar drugs) can cause bleeding that can be serious and sometimes lead to death.** In cases of serious bleeding, such as internal bleeding, the bleeding may result in the need for blood transfusions or surgery. While you take BRILINTA:

- you may bruise and bleed more easily
- you are more likely to have nose bleeds
- it will take longer than usual for any bleeding to stop

Call your doctor right away, if you have any of these signs or symptoms of bleeding while taking BRILINTA:

- bleeding that is severe or that you cannot control
- pink, red or brown urine
- vomiting blood or your vomit looks like "coffee grounds"
- red or black stools (looks like tar)
- coughing up blood or blood clots

Do not stop taking BRILINTA without talking to the doctor who prescribes it for you. People who are treated with a stent, and stop taking BRILINTA too soon, have a higher risk of getting a blood clot in the stent, having a heart attack, or dying. If you stop BRILINTA because of bleeding, or for other reasons, your risk of a heart attack or stroke may increase.

When instructed by your doctor, you should stop taking BRILINTA 5 days before you have elective surgery. This will help to decrease your risk of bleeding with your surgery or procedure. Your doctor should tell you when to start taking BRILINTA again, as soon as possible after surgery.

Taking BRILINTA with aspirin

BRILINTA is taken with aspirin. Talk to your doctor about the dose of aspirin that you should take with BRILINTA. You should not take a dose of aspirin higher than 100 mg daily because it can affect how well BRILINTA works. Do not take doses of aspirin higher than what your doctor tells you to take. Tell your doctor if you take other medicines that contain aspirin, and do not take new over-the-counter medicines with aspirin in them.

What is BRILINTA?

BRILINTA is a prescription medicine used to treat people who:

- have had a recent heart attack or severe chest pain that happened because their heart was not getting enough oxygen.
- have had a heart attack or chest pain and are being treated with medicines or with a procedure to open blocked arteries in the heart.

BRILINTA is used with aspirin to lower your chance of having another serious problem with your heart or blood vessels, such as heart attack, stroke, or blood clots in your stent. These can be fatal.

Platelets are blood cells that help with normal blood clotting. BRILINTA helps prevent platelets from sticking together and forming a clot that can block an artery.

It is not known if BRILINTA is safe and works in children.

Who should not take BRILINTA?

Do not take BRILINTA if you:

- are bleeding now
- have a history of bleeding in the brain
- have bleeding from your stomach or intestine now (an ulcer)
- have severe liver problems

When instructed by your doctor, you should stop taking BRILINTA 5 days before you have elective surgery. This will help to decrease your risk of bleeding with your surgery or procedure. Your doctor should tell you when to start taking BRILINTA again, as soon as possible after surgery.

What should I tell my doctor before taking BRILINTA?

Before you take BRILINTA, tell your doctor if you:

- have had bleeding problems in the past
- have had any recent serious injury or surgery
- plan to have surgery or a dental procedure
- have a history of stomach ulcers or colon polyps
- have lung problems, such as COPD or asthma
- have liver problems
- have a history of stroke
- are pregnant, or are plan to become pregnant. It is not known if BRILINTA will harm your unborn baby. You and your doctor should decide if you will take BRILINTA.
- are breastfeeding. It is not known if BRILINTA passes into your breast-milk. You and your doctor should decide if you will take BRILINTA or breastfeed. You should not do both without talking with your doctor.

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

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. **BRILINTA may affect the way other** medicines work, and other medicines may affect how BRILINTA works.

Especially tell your doctor if you take:

- an HIV-AIDS medicine
- medicine for heart conditions or high blood pressure
- medicine for high blood cholesterol levels
- an anti-fungal medicine by mouth
- an anti-seizure medicine
- a blood thinner medicine
- rifampin (Rifater, Rifamate, Rimactane, Rifadin)

Ask your doctor or pharmacist if you are not sure if your medicine is listed above.

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

How should I take BRILINTA?

- Take BRILINTA exactly as prescribed by your doctor.
- Your doctor will tell you how many BRILINTA tablets to take and when to take them.
- Take BRILINTA with a low dose (not more than 100 mg daily) of aspirin. You may take BRILINTA with or without food.
- Take your doses of BRILINTA around the same time every day.
- If you forget to take your scheduled dose of BRILINTA, take your next dose at its scheduled time. Do not take two doses at the same time unless your doctor tells you to.
- If you take too much BRILINTA or overdose, call your doctor or poison control center right away, or go to the nearest emergency room.

What are the possible side effects of BRILINTA?

BRILINTA can cause serious side effects, including:

- **See "What is the most important information I should know about BRILINTA?"**
- **Shortness of breath.** Call your doctor if you have new or unexpected shortness of breath when you are at rest, at night, or when you are doing any activity. Your doctor can decide what treatment is needed.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of BRILINTA. 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 BRILINTA?

- Store BRILINTA at room temperature between 59°F to 86°F (15°C to 30°C).

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

General information about BRILINTA

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

This Medication Guide summarizes the most important information about BRILINTA. If you would like more information about BRILINTA, talk with your doctor. You can ask your pharmacist or doctor for information about BRILINTA that is written for health professionals.

For more information call 1-800-236-9933 or go to www.Brilinta.com.

What are the ingredients in BRILINTA?

Active ingredient: ticagrelor

Inactive ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

Issued: 07/2011

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

Manufactured by: AstraZeneca, AB S-151 85 Södertälje Sweden
Marketed by: AstraZeneca LP, Wilmington, DE 19850

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CRESTOR®
rosuvastatin calcium

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CRESTOR safely and effectively. See full prescribing information for CRESTOR.

CRESTOR (rosuvastatin calcium) tablets

Initial U.S. Approval: 2003

INDICATIONS AND USAGE

CRESTOR is an HMG Co-A reductase inhibitor indicated for:

- patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C (1.1)
- patients with hypertriglyceridemia as an adjunct to diet (1.2)
- patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) as an adjunct to diet (1.3)
- patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB (1.4)
- slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet (1.5)
- pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated total-C, LDL-C and ApoB after failing an adequate trial of diet therapy (1.1)
- risk reduction of MI, stroke, and arterial revascularization procedures in patients without clinically evident CHD, but with multiple risk factors (1.6)

Limitations of use (1.7):

- CRESTOR has not been studied in Fredrickson Type I and V dyslipidemias.

DOSAGE AND ADMINISTRATION

- CRESTOR can be taken with or without food, at any time of day. (2.1)
- Dose range: 5-40 mg once daily. Use 40 mg dose only for patients not reaching LDL-C goal with 20 mg. (2.1)
- **HoFH**: Starting dose 20 mg. (2.3)
- In pediatric patients 10 to 17 years of age with HeFH, the usual dose range is 5-20 mg/day; doses greater than 20 mg have not been studied in this patient population. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg, 20 mg, and 40 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to product components (4)
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4)
- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)

WARNINGS AND PRECAUTIONS

- **Skeletal muscle effects (e.g., myopathy and rhabdomyolysis):** Risks increase with use of 40 mg dose, advanced age (≥65), hypothyroidism, renal impairment, and combination use with cyclosporine, lopinavir/ritonavir, atazanavir/ritonavir, or certain other lipid-lowering drugs. Advise patients to promptly report unexplained muscle pain, tenderness, or weakness and discontinue CRESTOR if signs or symptoms appear (5.1)
- **Liver enzyme abnormalities and monitoring:** Persistent elevations in hepatic transaminases can occur. Monitor liver enzymes before and during treatment (5.2)

ADVERSE REACTIONS

Most frequent adverse reactions (rate ≥2%) are headache, myalgia, abdominal pain, asthenia, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- **Cyclosporine:** Combination increases rosuvastatin exposure. Limit CRESTOR dose to 5 mg once daily. (2.5, 7.1)
- **Gemfibrozil:** Combination should be avoided. If used together, limit CRESTOR dose to 10 mg once daily. (2.6, 5.1, 7.2)
- **Lopinavir/Ritonavir or atazanavir/ritonavir:** Combination increases rosuvastatin exposure. Limit CRESTOR dose to 10 mg once daily. (2.5, 5.1, 7.3)
- **Coumarin anticoagulants:** Combination prolongs INR. Achieve stable INR prior to starting CRESTOR. Monitor INR frequently until stable upon initiation or alteration of CRESTOR therapy. (5.3, 7.4)
- **Concomitant lipid-lowering therapies:** Use with fibrates and niacin products may increase the risk of skeletal muscle effects. (2.6, 5.1, 7.5, 7.6)

USE IN SPECIFIC POPULATIONS

- **Severe renal impairment (not on hemodialysis):** Starting dose is 5 mg, not to exceed 10 mg (2.7, 5.1, 8.6)
- **Asian population:** Consider 5 mg starting dose (2.4, 8.8)

See 17 for PATIENT COUNSELING INFORMATION

Revised: May 2011

*FULL PRESCRIBING INFORMATION: CONTENTS

*Sections or subsections omitted from the full Prescribing Information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hyperlipidemia and Mixed Dyslipidemia

CRESTOR is indicated as adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, nonHDL-C, and triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and nonpharmacological interventions alone has been inadequate.

Pediatric Patients 10 to 17 years of age with Heterozygous Familial Hypercholesterolemia (HeFH)

Adjunct to diet to reduce Total-C, LDL-C and ApoB levels in adolescent boys and girls, who are at least one year postmenarche, 10-17 years of age with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: LDL-C >190 mg/dL or >160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors.

1.2 Hypertriglyceridemia

CRESTOR is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.

1.3 Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

CRESTOR is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).

1.4 Homozygous Familial Hypercholesterolemia

CRESTOR is indicated as adjunctive therapy to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, Total-C, and ApoB in adult patients with homozygous familial hypercholesterolemia.

1.5 Slowing of the Progression of Atherosclerosis

CRESTOR is indicated as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels.

1.6 Primary Prevention of Cardiovascular Disease

In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥50 years old in men and ≥60 years old in women, hsCRP ≥2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, CRESTOR is indicated to:

- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization procedures

1.7 Limitations of Use

CRESTOR has not been studied in Fredrickson Type I and V dyslipidemias.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The dose range for CRESTOR is 5 to 40 mg orally once daily. The usual starting dose is 10-20 mg.

CRESTOR can be administered as a single dose at any time of day, with or without food.

When initiating CRESTOR therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's response and individualized goal of therapy.

After initiation or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly.

The 40 mg dose of CRESTOR should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose [see **Warnings and Precautions** (5.1)].

2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 years of age)

The usual dose range of CRESTOR is 5-20 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy [see **Clinical Pharmacology** (12) and **Indications and Usage** (1.2)]. Adjustments should be made at intervals of 4 weeks or more.

2.3 Homozygous Familial Hypercholesterolemia

The recommended starting dose of CRESTOR is 20 mg once daily. Response to therapy should be estimated from preapheresis LDL-C levels.

2.4 Dosage in Asian Patients

Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients [see **Use in Specific Populations** (8.8) and **Clinical Pharmacology** (12.3)].

2.5 Use with Cyclosporine, Lopinavir/Ritonavir or Atazanavir/Ritonavir

In patients taking cyclosporine, the dose of CRESTOR should be limited to 5 mg once daily [see **Warnings and Precautions** (5.1) and **Drug Interactions** (7.1)]. In patients taking a combination of lopinavir and ritonavir or atazanavir and ritonavir, the dose of CRESTOR should be limited to 10 mg once daily [see **Warnings and Precautions** (5.1) and **Drug Interactions** (7.3)].

2.6 Concomitant Lipid-Lowering Therapy

The risk of skeletal muscle effects may be enhanced when CRESTOR is used in combination with niacin or fenofibrate; a reduction in CRESTOR dosage should be considered in this setting [see **Warnings and Precautions** (5.1) and **Drug Interactions** (7.5, 7.6)].

Combination therapy with gemfibrozil should be avoided because of an increase in CRESTOR exposure with concomitant use; if CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily [see **Warnings and Precautions** (5.1) and **Drug Interactions** (7.2)].

2.7 Dosage in Patients With Severe Renal Impairment

For patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) not on hemodialysis, dosing of CRESTOR should be started at 5 mg once daily and not exceed 10 mg once daily [see **Use in Specific Populations** (8.6) and **Clinical Pharmacology** (12.3)].

3 DOSAGE FORMS AND STRENGTHS

5 mg: Yellow, round, biconvex, coated tablets. Debossed "CRESTOR" and "5" on one side of the tablet.

10 mg: Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "10" on one side of the tablet.

20 mg: Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "20" on one side of the tablet.

40 mg: Pink, oval, biconvex, coated tablets. Debossed "CRESTOR" on one side and "40" on the other side of the tablet.

4 CONTRAINDICATIONS

CRESTOR is contraindicated in the following conditions:

- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including rash, pruritus, urticaria, and angioedema have been reported with CRESTOR [see **Adverse Reactions** (6.1)].
- Patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels [see **Warnings and Precautions** (5.2)].
- Women who are pregnant or may become pregnant. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, CRESTOR may cause fetal harm when administered to pregnant women. Additionally, there is no apparent benefit to therapy during pregnancy, and safety in pregnant women has not been established. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy [see **Use in Specific Populations** (8.1) and **Nonclinical Toxicology** (13.2)].
- Nursing mothers. Because another drug in this class passes into breast milk, and because HMG-CoA reductase inhibitors have the potential to cause serious adverse reactions in nursing infants, women who require CRESTOR treatment should be advised not to nurse their infants [see **Use in Specific Populations** (8.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle Effects

Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including CRESTOR. These risks can occur at any dose level, but are increased at the highest dose (40 mg).

CRESTOR should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age ≥65 years, inadequately treated hypothyroidism, renal impairment).

The risk of myopathy during treatment with CRESTOR may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, lopinavir/ritonavir, or atazanavir/ritonavir [see **Dosage and Administration** (2) and **Drug Interactions** (7)].

CRESTOR therapy should be discontinued if markedly elevated creatinine kinase levels occur or myopathy is diagnosed or suspected. CRESTOR therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

5.2 Liver Enzyme Abnormalities and Monitoring

It is recommended that liver enzyme tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

Increases in serum transaminases [AST (SGOT) or ALT (SGPT)] have been reported with HMG-CoA reductase inhibitors, including CRESTOR. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to CRESTOR therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.

In a pooled analysis of placebo-controlled trials, increases in serum transaminases to >3 times the upper limit of normal occurred in 1.1% of patients taking CRESTOR versus 0.5% of patients treated with placebo.

Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of CRESTOR is recommended.

CRESTOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease [see **Clinical Pharmacology** (12.3)]. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of CRESTOR [see **Contraindications** (4)].

5.3 Concomitant Coumarin Anticoagulants

Caution should be exercised when anticoagulants are given in conjunction with CRESTOR because of its potentiation of the effect of coumarin-type anticoagulants in prolonging the prothrombin time/INR. In patients taking coumarin anticoagulants and CRESTOR concomitantly, INR should be determined before starting CRESTOR and frequently enough during early therapy to ensure that no significant alteration of INR occurs [see **Drug Interactions** (7.4)].

5.4 Proteinuria and Hematuria
In the CRESTOR clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among CRESTOR treated patients. These findings were more frequent in patients taking CRESTOR 40 mg, when compared to lower doses of CRESTOR or comparator HMG-CoA reductase inhibitors, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on CRESTOR therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

5.5 Endocrine Effects
Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CRESTOR [see **Adverse Reactions** (6.1)].

Although clinical studies have shown that CRESTOR alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if CRESTOR is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

6 ADVERSE REACTIONS
The following serious adverse reactions are discussed in greater detail in other sections of the label:
- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis) [see **Warnings and Precautions** (5.1)]
- Liver enzyme abnormalities [see **Warnings and Precautions** (5.2)]

In the CRESTOR controlled clinical trials database (placebo or active-controlled) of 5394 patients with a mean treatment duration of 15 weeks, 1.4% of patients discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were:
- myalgia
- abdominal pain
- nausea

The most commonly reported adverse reactions (incidence ≥2%) in the CRESTOR controlled clinical trial database of 5394 patients were:
- headache
- myalgia
- abdominal pain
- asthenia
- nausea

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

Adverse reactions reported in ≥2% of patients in placebo-controlled clinical studies and at a rate greater than placebo are shown in Table 1. These studies had a treatment duration of up to 12 weeks.

Table 1. Adverse Reactions* Reported by ≥2% of Patients Treated with CRESTOR and >Placebo in Placebo-Controlled Trials (% of Patients)

Adverse Reactions	CRESTOR 5 mg N=291	CRESTOR 10 mg N=283	CRESTOR 20 mg N=64	CRESTOR 40 mg N=106	Total CRESTOR 5 mg – 40 mg N=744	Placebo N=382
Headache	5.5	4.9	3.1	8.5	5.5	5.0
Nausea	3.8	3.5	6.3	0	3.4	3.1
Myalgia	3.1	2.1	6.3	1.9	2.8	1.3
Asthenia	2.4	3.2	4.7	0.9	2.7	2.6
Constipation	2.1	2.1	4.7	2.8	2.4	2.4

* Adverse reactions by COSTART preferred term.

Other adverse reactions reported in clinical studies were abdominal pain, dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema) and pancreatitis. The following laboratory abnormalities have also been reported: dipstick-positive proteinuria and microscopic hematuria [see **Warnings and Precautions** (5.4)]; elevated creatine phosphokinase, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities.

In the METEOR study, involving 981 participants treated with rosuvastatin 40 mg (n=700) or placebo (n=281) with a mean treatment duration of 1.7 years, 5.6% of subjects treated with CRESTOR versus 2.8% of placebo-treated subjects discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: myalgia, hepatic enzyme increased, headache, and nausea [see **Clinical Studies** (14.7)].

Adverse reactions reported in ≥2% of patients and at a rate greater than placebo are shown in Table 2.

Table 2. Adverse Reactions* Reported by ≥2% of Patients Treated with CRESTOR and >Placebo in the METEOR Trial (% of Patients)

Adverse Reactions	CRESTOR 40 mg N=700	Placebo N=281
Myalgia	12.7	12.1
Arthralgia	10.1	7.1
Headache	6.4	5.3
Dizziness	4.0	2.8
Increased CPK	2.6	0.7
Abdominal pain	2.4	1.8
†ALT >3x ULN	2.2	0.7

* Adverse reactions by MedDRA preferred term.
† Frequency recorded as abnormal laboratory value.

In the JUPITER study, 17,802 participants were treated with rosuvastatin 20 mg (n=8901) or placebo (n=8901) for a mean duration of 2 years. A higher percentage of rosuvastatin-treated patients versus placebo-treated patients, 6.6% and 6.2%, respectively, discontinued study medication due to an adverse event, irrespective of treatment causality. Myalgia was the most common adverse reaction that led to treatment discontinuation.

In JUPITER, there was a significantly higher frequency of diabetes mellitus reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in rosuvastatin-treated patients compared to placebo-treated patients. The number of patients with a HbA1c >6.5% at the end of the trial was significantly higher in rosuvastatin-treated versus placebo-treated patients [see **Warnings and Precautions** (5.5) and **Clinical Studies** (14.8)].

Adverse reactions reported in ≥2% of patients and at a rate greater than placebo are shown in Table 3.

Table 3. Adverse Reactions* Reported by ≥2% of Patients Treated with CRESTOR and >Placebo in the JUPITER Trial (% of Patients)

Adverse Reactions	CRESTOR 20 mg N=8901	Placebo N=8901
Myalgia	7.6	6.6
Arthralgia	3.8	3.2
Constipation	3.3	3.0
Nausea	2.4	2.3

* Treatment-emergent adverse reactions by MedDRA preferred term.

6.2 Pediatric patients 10 to 17 years of age
In a 12-week controlled study in boys and postmenarchal girls, the safety and tolerability profile of CRESTOR 5 to 20 mg daily was generally similar to that of placebo [see **Clinical Studies** (14.6) and **Use in Special Populations**, **Pediatric Use** (8.4)].

However, elevations in serum creatine phosphokinase (CK) >10 x ULN were observed more frequently in rosuvastatin compared with placebo-treated children. Four of 130 (3%) children treated with rosuvastatin (2 treated with 10 mg and 2 treated with 20 mg) had increased CK >10 x ULN, compared to 0 of 46 children on placebo.

6.3 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of CRESTOR: arthralgia, hepatic failure, hepatitis, jaundice, memory loss, depression, and sleep disorders (including insomnia and nightmares). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS
7.1 Cyclosporine
Cyclosporine significantly increased rosuvastatin exposure. Therefore, in patients taking cyclosporine, therapy should be limited to CRESTOR 5 mg once daily [see **Dosage and Administration** (2.5), **Warnings and Precautions** (5.1), and **Clinical Pharmacology** (12.3)].

7.2 Gemfibrozil
Gemfibrozil significantly increased rosuvastatin exposure. Therefore, combination therapy with CRESTOR and gemfibrozil should be avoided. If used, do not exceed CRESTOR 10 mg once daily [see **Dosage and Administration** (2.6) and **Clinical Pharmacology** (12.3)].

7.3 Protease Inhibitors
Coadministration of rosuvastatin with certain protease inhibitors given in combination with ritonavir has differing effects on rosuvastatin exposure. The protease inhibitor combinations lopinavir/ritonavir and atazanavir/ritonavir increase rosuvastatin exposure (AUC) up to threefold [see **Table 3 – Clinical Pharmacology** (12.3)]. For these combinations the dose of CRESTOR should be limited to 10 mg. The combinations of tipranavir/ritonavir or fosamprenavir/ritonavir produce little or no change in rosuvastatin exposure. Caution should be exercised when rosuvastatin is coadministered with protease inhibitors given in combination with ritonavir [see **Dosage and Administration** (2.5), **Warnings and Precautions** (5.1) and **Clinical Pharmacology** (12.3)].

7.4 Coumarin Anticoagulants
CRESTOR significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with CRESTOR. In patients taking coumarin anticoagulants and CRESTOR concomitantly, INR should be determined before starting CRESTOR and frequently enough during early therapy to ensure that no significant alteration of INR occurs [see **Warnings and Precautions** (5.3) and **Clinical Pharmacology** (12.3)].

7.5 Niacin
The risk of skeletal muscle effects may be enhanced when CRESTOR is used in combination with niacin; a reduction in CRESTOR dosage should be considered in this setting [see **Warnings and Precautions** (5.1)].

7.6 Fenofibrate
When CRESTOR was coadministered with fenofibrate, no clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. The benefit of further alterations in lipid levels by the combined use of CRESTOR with fibrates should be carefully weighed against the potential risks of this combination [see **Warnings and Precautions** (5.1) and **Clinical Pharmacology** (12.3)].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic effects: Pregnancy Category X.
CRESTOR is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy [see **Contraindications** (4)].

There are no adequate and well-controlled studies of CRESTOR in pregnant women. There have been rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of about 100 prospectively followed pregnancies in women exposed to other HMG-CoA reductase inhibitors, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-fourfold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Rosuvastatin crosses the placenta in rats and rabbits. In rats, CRESTOR was not teratogenic at systemic exposures equivalent to a human therapeutic dose of 40 mg/day. At 10-12 times the human dose of 40 mg/day, there was decreased pup survival, decreased fetal body weight among female pups, and delayed ossification. In rabbits, pup viability decreased and maternal mortality increased at doses equivalent to the human dose of 40 mg/day [see **Nonclinical Toxicology** (13.2)].

CRESTOR may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking CRESTOR, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers

It is not known whether rosuvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. In rats, breast milk concentrations of rosuvastatin are three times higher than plasma levels; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because HMG-CoA reductase inhibitors have a potential to cause serious adverse reactions in nursing infants, women who require CRESTOR treatment should be advised not to nurse their infants [see **Contraindications** (4)].

8.4 Pediatric Use

The safety and effectiveness of CRESTOR in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia were evaluated in a controlled clinical trial of 12 weeks duration followed by 40 weeks of open-label exposure. Patients treated with 5 mg, 10 mg, and 20 mg daily CRESTOR had an adverse experience profile generally similar to that of patients treated with placebo [see **Adverse Reactions** (6.2)]. Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents. There was no detectable effect of CRESTOR on growth, weight, BMI (body mass index), or sexual maturation [see **Clinical Studies** (14.5)] in pediatric patients (10 to 17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on CRESTOR therapy [see **Use in Specific Populations** (8.1)]. CRESTOR has not been studied in controlled clinical trials involving prepubertal patients or patients younger than 10 years of age. Doses of CRESTOR greater than 20 mg have not been studied in the pediatric population.

In children and adolescents with homozygous familial hypercholesterolemia experience is limited to eight patients (aged 8 years and above).

In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10 to 17 years of age with heterozygous FH received single and multiple oral doses of CRESTOR. Both C_{max} and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses.

8.5 Geriatric Use

Of the 10,275 patients in clinical studies with CRESTOR, 3159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients are at higher risk of myopathy and CRESTOR should be prescribed with caution in the elderly [see **Warnings and Precautions** (5.1) and **Clinical Pharmacology** (12.3)].

8.6 Renal Impairment

Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CL_{cr} ≥30 mL/min/1.73 m^2); however, exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment who are not receiving hemodialysis. CRESTOR dosing should be adjusted in patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) not requiring hemodialysis [see **Dosage and Administration** (2.7), **Warnings and Precautions** (5.1) and **Clinical Pharmacology** (12.3)].

8.7 Hepatic Impairment

CRESTOR is contraindicated in patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels. Chronic alcohol liver disease is known to increase rosuvastatin exposure; CRESTOR should be used with caution in these patients [see **Contraindications** (4), **Warnings and Precautions** (5.2), and **Clinical Pharmacology** (12.3)].

8.8 Asian Patients

Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. CRESTOR dosage should be adjusted in Asian patients [see **Dosage and Administration** (2.4) and **Clinical Pharmacology** (12.3)].

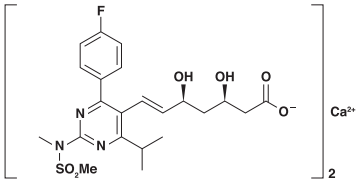
10 OVERDOSAGE

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin.

11 DESCRIPTION

CRESTOR (rosuvastatin calcium) is a synthetic lipid-lowering agent for oral administration.

The chemical name for rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt with the following structural formula:



The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the molecular weight is 1001.14. Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0.

Inactive Ingredients: Each tablet contains: microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, crospovidone NF, magnesium stearate NF, hypromellose NF, triacetin NF, titanium dioxide USP, yellow ferric oxide, and red ferric oxide NF.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CRESTOR is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. *In vivo* studies in animals, and *in vitro* studies in cultured animal and human cells have shown rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

12.3 Pharmacokinetics

- ***Absorption:*** In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both C_{max} and AUC increased in approximate proportion to CRESTOR dose. The absolute bioavailability of rosuvastatin is approximately 20%.

  Administration of CRESTOR with food did not affect the AUC of rosuvastatin.

  The AUC of rosuvastatin does not differ following evening or morning drug administration.
- ***Distribution:*** Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.
- ***Metabolism:*** Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.
- ***Excretion:*** Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours.

  After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.
- ***Race:*** A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group.
- ***Gender:*** There were no differences in plasma concentrations of rosuvastatin between men and women.
- ***Geriatric:*** There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥65 years).
- ***Renal Impairment:*** Mild to moderate renal impairment (CL_{cr} ≥30 mL/min/1.73 m^2) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) not receiving hemodialysis compared with healthy subjects (CL_{cr} >80 mL/min/1.73 m^2).
- ***Hemodialysis:*** Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.
- ***Hepatic Impairment:*** In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased.

  In patients with Child-Pugh A disease, C_{max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function.

Drug-Drug Interactions:

Cytochrome P450 3A4

Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent.

Table 4. Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure

Coadministered drug and dosing regimen	Rosuvastatin		
	Dose (mg)*	Change in AUC**	Change in C_{max}**
Cyclosporine – stable dose required (75 mg – 200 mg BID)	10 mg QD for 10 days	↑ 7-fold†	↑ 11-fold†
Gemfibrozil 600 mg BID for 7 days	80 mg	↑ 1.9-fold†	↑ 2.2-fold†
Lopinavir/ritonavir combination 400 mg/100 mg BID for 10 days	20 mg QD for 7 days	↑ 2-fold†	↑ 5-fold†
Atazanavir/ritonavir combination 300 mg/100 mg QD for 7 days	10 mg	↑ 3-fold†	↑ 7-fold†
Tipranavir/ritonavir combination 500 mg/200mg BID for 11 days	10 mg	↑ 26%	↑ 2-fold
Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 days	10 mg	↑ 8%	↑ 45%
Fenofibrate 67 mg TID for 7 days	10 mg	↑ 7%	↑ 21%
Aluminum & magnesium hydroxide combination antacid			
Administered simultaneously	40 mg	↓ 54%†	↓ 50%†
Administered 2 hours apart	40 mg	↓ 22%	↓ 16%
Erythromycin 500 mg QID for 7 days	80 mg	↓ 20%	↓ 31%
Ketoconazole 200 mg BID for 7 days	80 mg	↑ 2%	↓ 5%
Itraconazole 200 mg QD for 5 days	10 mg	↑ 39%	↑ 36%
	80 mg	↑ 28%	↑ 15%
Fluconazole 200 mg QD for 11 days	80 mg	↑ 14%	↑ 9%

* Single dose unless otherwise noted
** Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.
† Clinically significant [see **Dosage and Administration** (2) and **Warnings and Precautions** (5)]

Table 5. Effect of Rosuvastatin Coadministration on Systemic Exposure To Other Drugs

Rosuvastatin Dosage Regimen	Coadministered Drug		
	Name and Dose	Change in AUC	Change in C_{max}
40 mg QD for 10 days	Warfarin* 25 mg single dose	R-Warfarin ↑ 4% S-Warfarin ↑ 6%	R-Warfarin ↓ 1% S-Warfarin 0%
40 mg QD for 12 days	Digoxin 0.5 mg single dose	↑ 4%	↑ 4%
40 mg QD for 28 days	Oral Contraceptive (ethinyl estradiol 0.035 mg & norgestrel 0.180, 0.215 and 0.250 mg) QD for 21 Days	EE ↑ 26% NG ↑ 34%	EE ↑ 25% NG ↑ 23%

EE = ethinyl estradiol, NG = norgestrel
* Clinically significant pharmacodynamic effects [see **Warnings and Precautions** (5.4)]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses.

In a 107-week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times the human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test.

In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times the human exposure at 40 mg/day based on AUC). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times the human exposure at 40 mg/day based on body surface area. Similar findings have been seen with other drugs in this class.

13.2 Animal Toxicology and/or Pharmacology

Embryo-fetal Development

Rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18.

In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating and continuing through day 7 postcoitus results in decreased fetal body weight (female pups) and delayed ossification at the high dose (systemic exposures 10 times the human exposure at 40 mg/day based on AUC).

In pregnant rats given oral gavage doses of 2, 10, 50 mg/kg/day from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, systemic exposures ≥12 times the human exposure at 40 mg/day based on body surface area.

In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation day 6 to lactation day 18 (weaning), exposures equivalent to the human exposure at 40 mg/day based on body surface area, decreased fetal viability and maternal mortality was observed.

Rosuvastatin was not teratogenic in rats at ≤25 mg/kg/day or in rabbits ≤3 mg/kg/day (systemic exposures equivalent to the human exposure at 40 mg/day based on AUC or body surface area, respectively).

Central Nervous System Toxicity

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at day 24 at 90 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC). Retinal dysplasia and retinal loss were seen in dogs treated for 4 weeks by oral gavage at 90 mg/kg/day (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Doses ≤30 mg/kg/day (systemic exposures ≤60 times the human exposure at 40 mg/day based on AUC) did not reveal retinal findings during treatment for up to one year.

14 CLINICAL STUDIES

14.1 Hyperlipidemia and Mixed Dyslipidemia

CRESTOR reduces Total-C, LDL-C, ApoB, nonHDL-C, and TG, and increases HDL-C, in adult patients with hyperlipidemia and mixed dyslipidemia.

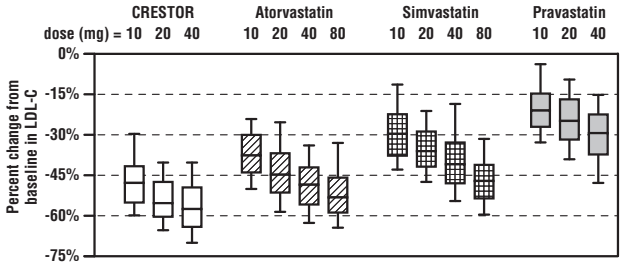
Dose-Ranging Study: In a multicenter, double-blind, placebo-controlled, dose-ranging study in patients with hyperlipidemia CRESTOR given as a single daily dose for 6 weeks significantly reduced Total-C, LDL-C, nonHDL-C, and ApoB, across the dose range (Table 6).

Table 6. Dose-Response in Patients With Hyperlipidemia (Adjusted Mean % Change From Baseline at Week 6)

Dose	N	Total-C	LDL-C	Non-HDL-C	ApoB	TG	HDL-C
Placebo	13	-5	-7	-7	-3	-3	3
CRESTOR 5 mg	17	-33	-45	-44	-38	-35	13
CRESTOR 10 mg	17	-36	-52	-48	-42	-10	14
CRESTOR 20 mg	17	-40	-55	-51	-46	-23	8
CRESTOR 40 mg	18	-46	-63	-60	-54	-28	10

Active-Controlled Study: CRESTOR was compared with the HMG-CoA reductase inhibitors atorvastatin, simvastatin, and pravastatin in a multicenter, open-label, dose-ranging study of 2240 patients with hyperlipidemia or mixed dyslipidemia. After randomization, patients were treated for 6 weeks with a single daily dose of either CRESTOR, atorvastatin, simvastatin, or pravastatin (Figure 1 and Table 7).

Figure 1. Percent LDL-C Change by Dose of CRESTOR, Atorvastatin, Simvastatin, and Pravastatin at Week 6 in Patients with Hyperlipidemia or Mixed Dyslipidemia



Box plots are a representation of the 25th, 50th, and 75th percentile values, with whiskers representing the 10th and 90th percentile values. Mean baseline LDL-C: 189 mg/dL

Table 7. Percent Change in LDL-C From Baseline to Week 6 (LS Mean*) by Treatment Group (sample sizes ranging from 156–167 patients per group)

	Treatment Daily Dose			
Treatment	10 mg	20 mg	40 mg	80 mg
CRESTOR	-46†	-52‡	-55§	—
Atorvastatin	-37	-43	-48	-51
Simvastatin	-28	-35	-39	-46
Pravastatin	-20	-24	-30	—

* Corresponding standard errors are approximately 1.00
† CRESTOR 10 mg reduced LDL-C significantly more than atorvastatin 10 mg; pravastatin 10 mg, 20 mg, and 40 mg; simvastatin 10 mg, 20 mg, and 40 mg. ($p<0.002$)
‡ CRESTOR 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. ($p<0.002$)
§ CRESTOR 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg, and 80 mg. ($p<0.002$)

14.2 Heterozygous Familial Hypercholesterolemia

Active-Controlled Study: In a study of patients with heterozygous FH (baseline mean LDL of 291), patients were randomized to CRESTOR 20 mg or atorvastatin 20 mg. The dose was increased by 6-week intervals. Significant LDL-C reductions from baseline were seen at each dose in both treatment groups (Table 8).

Table 8. Mean LDL-C Percentage Change from Baseline

		CRESTOR (n=435) LS Mean* (95% CI)	Atorvastatin (n=187) LS Mean* (95% CI)
Week 6	20 mg	-47% (-49%, -46%)	-38% (-40%, -36%)
Week 12	40 mg	-55% (-57%, -54%)	-47% (-49%, -45%)
Week 18	80 mg	NA	-52% (-54%, -50%)

* LS Means are least square means adjusted for baseline LDL-C

14.3 Hypertriglyceridemia

Dose-Response Study: In a double-blind, placebo-controlled dose-response study in patients with baseline TG levels from 273 to 817 mg/dL, CRESTOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels (Table 9).

Table 9. Dose-Response in Patients With Primary Hypertriglyceridemia Over 6 Weeks Dosing Median (Min, Max) Percent Change From Baseline

Dose	Placebo (n=26)	CRESTOR 5 mg (n=25)	CRESTOR 10 mg (n=23)	CRESTOR 20 mg (n=27)	CRESTOR 40 mg (n=25)
Triglycerides	1 (-40, 72)	-21 (-58, 38)	-37 (-65, 5)	-37 (-72, 11)	-43 (-80, -7)
nonHDL-C	2 (-13, 19)	-29 (-43, -8)	-49 (-59, -20)	-43 (-74, 12)	-51 (-62, -6)
VLDL-C	2 (-36, 53)	-25 (-62, 49)	-48 (-72, 14)	-49 (-83, 20)	-56 (-83, 10)
Total-C	1 (-13, 17)	-24 (-40, -4)	-40 (-51, -14)	-34 (-61, -11)	-40 (-51, -4)
LDL-C	5 (-30, 52)	-28 (-71, 2)	-45 (-59, 7)	-31 (-66, 34)	-43 (-61, -3)
HDL-C	-3 (-25, 18)	3 (-38, 33)	8 (-8, 24)	22 (-5, 50)	17 (-14, 63)

14.4 Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

In a randomized, multicenter, double-blind crossover study, 32 patients (27 with ε2/ε2 and 4 with apo E mutation [Arg145Cys] with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia) entered a 6-week dietary lead-in period on the NCEP Therapeutic Lifestyle Change (TLC) diet. Following dietary lead-in, patients were randomized to a sequence of treatments in conjunction with the TLC diet for 6 weeks each: rosuvastatin 10 mg followed by rosuvastatin 20 mg or rosuvastatin 20 mg followed by rosuvastatin 10 mg. CRESTOR reduced nonHDL-C (primary end point) and circulating remnant lipoprotein levels. Results are shown in the table below.

Table 10. Lipid-modifying Effects of Rosuvastatin 10 mg and 20 mg in Primary Dysbetalipoproteinemia (Type III hyperlipoproteinemia) after Six weeks by Median Percent Change (95% CI) from Baseline (N=32)

	Median at Baseline (mg/dL)	Median percent change from baseline (95 % CI) CRESTOR 10 mg	Median percent change from baseline (95% CI) CRESTOR 20 mg
Total-C	342.5	-43.3 (-46.9, -37.5)	-47.6 (-51.6, -42.8)
Triglycerides	503.5	-40.1 (-44.9, -33.6)	-43.0 (-52.5, -33.1)
Non-HDL-C	294.5	-48.2 (-56.7, -45.6)	-56.4 (-61.4, -48.5)
VLDL-C + IDL-C	209.5	-46.8 (-53.7, -39.4)	-56.2 (-67.7, -43.7)
LDL-C	112.5	-54.4 (-59.1, -47.3)	-57.3 (-59.4, -52.1)
HDL-C	35.5	10.2 (1.9, 12.3)	11.2 (8.3, 20.5)
RLP-C	82.0	-56.4 (-67.1, -49.0)	-64.9 (-74.0, -56.6)
Apo-E	16.0	-42.9 (-46.3, -33.3)	-42.5 (-47.1, -35.6)

14.5 Homozygous Familial Hypercholesterolemia

Dose-Titration Study: In an open-label, forced-titration study, homozygous FH patients (n=40, 8-63 years) were evaluated for their response to CRESTOR 20 to 40 mg titrated at a 6-week interval. In the overall population, the mean LDL-C reduction from baseline was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL lowering of greater than 6%. In the 27 patients with at least a 15% reduction in LDL-C, the mean LDL-C reduction was 30% (median 28% reduction). Among 13 patients with an LDL-C reduction of <15%, 3 had no change or an increase in LDL-C. Reductions in LDL-C of 15% or greater were observed in 3 of 5 patients with known receptor negative status.

14.6 Pediatric Patients with Heterozygous Familial Hypercholesterolemia

In a double-blind, randomized, multicenter, placebo-controlled, 12-week study, 176 (97 male and 79 female) children and adolescents with heterozygous familial hypercholesterolemia were randomized to rosuvastatin 5, 10 or 20 mg or placebo daily. Patients ranged in age from 10 to 17 years (median age of 14 years) with approximately 30% of the patients 10 to 13 years and approximately 17%, 18%, 40%, and 25% at Tanner stages II, III, IV, and V, respectively. Females were at least 1 year postmenarche. Mean LDL-C at baseline was 233 mg/dL (range of 129 to 399). The 12-week double-blind phase was followed by a 40-week open-label dose-titration phase, where all patients (n=173) received 5 mg, 10 mg or 20 mg rosuvastatin daily.

Rosuvastatin significantly reduced LDL-C (primary end point), total cholesterol and ApoB levels at each dose compared to placebo. Results are shown in Table 11 below.

Table 11. Lipid-modifying effects of rosuvastatin in pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia (least-squares mean percent change from baseline to week 12)

Dose (mg)	N	LDL-C	HDL-C	Total-C	TG[a]	ApoB
Placebo	46	-1%	+7%	0%	-7%	-2%
5	42	-38%	+4% [b]	-30%	-13% [b]	-32%
10	44	-45	+11% [b]	-34%	-15% [b]	-38%
20	44	-50%	+9% [b]	-39%	-16% [b]	-41%

[a] Median percent change
[b] Difference from placebo not statistically significant

At the end of the 12-week, double-blind treatment period, the percentage of patients achieving the LDL-C goal of less than 110 mg/dL (2.8 mmol/L) was 0% for placebo, 12% for rosuvastatin 5 mg, 41% for rosuvastatin 10 mg and 41% for rosuvastatin 20 mg. For the 40-week, open-label phase, 71% of the patients were titrated to the maximum dose of 20 mg and 41% of the patients achieved the LDL-C goal of 110 mg/dL.

The long-term efficacy of rosuvastatin therapy initiated in childhood to reduce morbidity and mortality in adulthood has not been established.

14.7 Slowing of the Progression of Atherosclerosis

In the *Measuring Effects on Intima Media Thickness: an Evaluation Of Rosuvastatin 40 mg (METEOR)* study, the effect of therapy with CRESTOR on carotid atherosclerosis was assessed by B-mode ultrasonography in patients with elevated LDL-C, at low risk (Framingham risk <10% over ten years) for symptomatic coronary artery disease and with subclinical atherosclerosis as evidenced by carotid intimal-medial thickness (cIMT). In this double-blind, placebo-controlled clinical study 984 patients were randomized (of whom 876 were analyzed) in a 5:2 ratio to CRESTOR 40 mg or placebo once daily. Ultrasonograms of the carotid walls were used to determine the annualized rate of change per patient from baseline to two years in mean maximum cIMT of 12 measured segments. The estimated difference in the rate of change in the maximum cIMT analyzed over all 12 carotid artery sites between patients treated with CRESTOR and placebo-treated patients was -0.0145 mm/year (95% CI –0.0196, –0.0093; p<0.0001).

The annualized rate of change from baseline for the placebo group was +0.0131 mm/year (p<0.0001). The annualized rate of change from baseline for the group treated with CRESTOR was -0.0014 mm/year (p=0.32).

At an individual patient level in the group treated with CRESTOR, 52.1% of patients demonstrated an absence of disease progression (defined as a negative annualized rate of change), compared to 37.7% of patients in the placebo group.

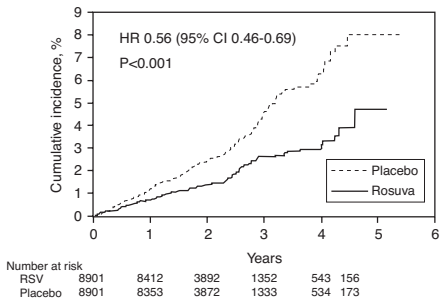
14.8 Primary Prevention of Cardiovascular Disease

In the **J**ustification for the **U**se of Statins in **P**rimary Prevention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin (JUPITER) study, the effect of CRESTOR (rosuvastatin calcium) on the occurrence of major cardiovascular (CV) disease events was assessed in 17,802 men (≥50 years) and women (≥60 years) who had no clinically evident cardiovascular disease, LDL-C levels <130 mg/dL (3.3 mmol/l) and hs-CRP levels ≥2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.6% over 10 years based on the Framingham risk criteria and included a high percentage of patients with additional risk factors such as hypertension (58%), low HDL-C levels (23%), cigarette smoking (16%), or a family history of premature CHD (12%). Study participants had a median baseline LDL-C of 108 mg/dL and hsCRP of 4.3 mg/L. Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years. The JUPITER study was stopped early by the Data Safety Monitoring Board due to meeting predefined stopping rules for efficacy in rosuvastatin-treated subjects.

The primary end point was a composite end point consisting of the time-to-first occurrence of any of the following major CV events: CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina or an arterial revascularization procedure.

Rosuvastatin significantly reduced the risk of major CV events (252 events in the placebo group vs. 142 events in the rosuvastatin group) with a statistically significant (p<0.001) relative risk reduction of 44% and absolute risk reduction of 1.2% (see Figure 2). The risk reduction for the primary end point was consistent across the following predefined subgroups: age, sex, race, smoking status, family history of premature CHD, body mass index, LDL-C, HDL-C, and hsCRP levels.

Figure 2. Time to first occurrence of major cardiovascular events in JUPITER



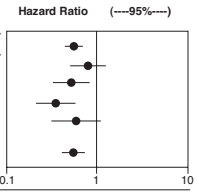
The individual components of the primary end point are presented in Figure 3. Rosuvastatin significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the rosuvastatin and placebo groups for death due to cardiovascular causes or hospitalizations for unstable angina.

Rosuvastatin significantly reduced the risk of myocardial infarction (6 fatal events and 62 nonfatal events in placebo-treated subjects vs. 9 fatal events and 22 nonfatal events in rosuvastatin-treated subjects) and the risk of stroke (6 fatal events and 58 nonfatal events in placebo-treated subjects vs. 3 fatal events and 30 nonfatal events in rosuvastatin-treated subjects).

In a post-hoc subgroup analysis of JUPITER subjects (n=1405; rosuvastatin=725, placebo=680) with a hsCRP ≥2 mg/L and no other traditional risk factors (smoking, BP ≥140/90 or taking antihypertensives, low HDL-C) other than age, after adjustment for high HDL-C, there was no significant treatment benefit with rosuvastatin treatment.

Figure 3. Major CV events by treatment group in JUPITER

End point	Number of events: Rosuva 20 mg (n=8901) n (rate*)	Placebo 20 mg (n=8901) n (rate*)	HR (95% CI)	P value
Primary end point (MCE)	142 (7.6)	252 (13.6)	0.56 (0.46, 0.69)	<0.001
Cardiovascular death**	35 (1.9)	44 (2.4)	0.80 (0.51, 1.24)	0.315
Nonfatal Stroke	30 (1.6)	58 (3.1)	0.52 (0.33, 0.80)	0.003
Nonfatal MI	22 (1.2)	62 (3.3)	0.35 (0.22, 0.58)	<0.001
Hospitalized unstable Angina	16 (0.9)	27 (1.5)	0.59 (0.32, 1.10)	0.093
Arterial revascularization	71 (3.8)	131 (7.1)	0.54 (0.41, 0.72)	<0.001



* event rate/1000-patient years
** Cardiovascular death included fatal MI, fatal stroke, sudden death, and other adjudicated causes of CV death

At one year, rosuvastatin increased HDL-C and reduced LDL-C, hsCRP, total cholesterol and serum triglyceride levels ($p<0.001$ for all versus placebo).

16 HOW SUPPLIED/STORAGE AND HANDLING

CRESTOR® (rosuvastatin calcium) Tablets are supplied as:

- NDC 0310-0755-90: 5 mg. Yellow, round, biconvex, coated tablets. Debossed "CRESTOR" and "5" on one side; bottle of 90 tablets
- NDC 0310-0751-90: 10 mg. Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "10" on one side; bottle of 90 tablets
- NDC 0310-0751-39: 10 mg. Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "10" on one side; unit dose packages of 100
- NDC 0310-0752-90: 20 mg. Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "20" on one side; bottles of 90
- NDC 0310-0752-39: 20 mg. Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "20"on one side; unit dose packages of 100
- NDC 0310-0754-30: 40 mg. Pink, oval, biconvex, coated tablets. Debossed "CRESTOR" on one side and "40" on the other side; bottles of 30

Storage

Store at controlled room temperature, 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

17.1 Skeletal Muscle Effects

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

17.2 Concomitant Use of Antacids

When taking CRESTOR with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after CRESTOR administration.

17.3 Pregnancy

If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy.

17.4 Liver Enzymes

It is recommended that liver enzymes be checked before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

Distributed by:
AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

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CRESTOR® (rosuvastatin calcium) Tablets (Kres-tor)

Read this information carefully before you start taking CRESTOR. Each time you refill your prescription for CRESTOR, read the patient information, as there may be new information. This summary does not include everything there is to know about CRESTOR and does not take the place of talking with your health care professional about your medical condition or treatment.

If you have any questions about CRESTOR, ask your health care professional. Only your health care professional can tell you if CRESTOR is right for you.

What is CRESTOR?

CRESTOR is a prescription medicine that belongs to a group of cholesterol-lowering medicines called statins. Along with diet, CRESTOR lowers "bad" cholesterol (LDL-C), increases "good" cholesterol (HDL-C). If bad cholesterol levels are left untreated, fatty deposits (plaque) can build up in the walls of the blood vessels. This plaque buildup over time, can lead to narrowing of these vessels. This is one of the most common causes of heart disease. By lowering bad cholesterol in your blood, CRESTOR can slow this plaque buildup in the walls of blood vessels. CRESTOR has been proven to reduce the risk of heart attacks and strokes in older adults without known heart disease.

What is Cholesterol?

Cholesterol is a fatty substance, also called a lipid, normally found in your bloodstream. Your body needs a certain amount of cholesterol to function properly. But high cholesterol can lead to health problems. LDL-C is called bad cholesterol because if you have too much in your bloodstream, it can become a danger to your health and can lead to potentially serious conditions. HDL-C is known as good cholesterol because it may help remove excess cholesterol.

Common health factors such as diabetes, high blood pressure, smoking, obesity, family history of early heart disease, and age can make controlling your cholesterol even more important.

What is Atherosclerosis?

Atherosclerosis is the progressive buildup of plaque in the arteries over time. One major cause is high levels of LDL-C. Other health factors, such as family history, diabetes, high blood pressure, or if you smoke, or are overweight, may also play a role in the formation of plaque in arteries. Often this plaque starts building up in arteries in early adulthood and gets worse over time.

How Does CRESTOR Work?

Most of the cholesterol in your blood is made in the liver. CRESTOR works by reducing cholesterol in two ways: CRESTOR blocks an enzyme in the liver causing the liver to make less cholesterol, and CRESTOR increases the uptake and breakdown by the liver of cholesterol already in the blood.

Who Should Not Take CRESTOR?

Do not take CRESTOR if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. CRESTOR may harm your unborn baby. If you become pregnant, stop taking CRESTOR and call your health care professional right away
- are breast-feeding. CRESTOR can pass into your breast milk and may harm your baby
- have liver problems
- have had an allergic reaction to CRESTOR or are allergic to any of its ingredients. The active ingredient is rosuvastatin calcium. The inactive ingredients are: microcrystalline cellulose, lactose monohydrate, tribasic calcium phosphate, crospovidone, magnesium stearate, hypromellose, triacetin, titanium dioxide, yellow ferric oxide, and red ferric oxide

The safety and effectiveness of CRESTOR have not been established in pediatric patients under the age of 10.

What should I tell my health care professional before taking CRESTOR?

Tell your health care professional if you:

- have a history of muscle pain or weakness
- are pregnant or think you may be pregnant, or are planning to become pregnant
- are breast-feeding
- drink more than 2 glasses of alcohol daily
- have liver problems
- have kidney problems
- have thyroid problems
- are Asian or of Asian descent

Tell your health care professional about all medicines you take or plan to take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may interact with CRESTOR, causing side effects. It is particularly important to tell your health care professional if you are taking or plan to take medicines for:

- your immune system
- cholesterol/triglycerides
- blood thinning
- HIV/AIDS
- preventing pregnancy

Know all of the medicines you take and what they look like. It's always a good idea to check that you have the right prescription before you leave the pharmacy and before you take any medicine. Keep a list of your medicines with you to show your health care professional.

If you need to go to the hospital or have surgery, tell all of your health care professionals about all medicines that you are taking.

How Should I Take CRESTOR?

Take CRESTOR exactly as prescribed by your health care professional. Do not change your dose or stop CRESTOR without talking to your health care professional, even if you are feeling well.

Your health care professional may do blood tests to check your cholesterol levels before and during your treatment with CRESTOR. Your dose of CRESTOR may be changed based on these blood tests results.

CRESTOR can be taken at any time of day, with or without food.

Swallow the tablets whole.

Your health care professional may start you on a cholesterol lowering diet before giving you CRESTOR. Stay on this diet when you take CRESTOR.

Wait at least 2 hours after taking CRESTOR to take an antacid that contains a combination of aluminum and magnesium hydroxide.

If you miss a dose of CRESTOR, take it as soon as you remember. However, **do not take 2 doses of CRESTOR within 12 hours of each other.**

If you take too much CRESTOR or overdose, call your health care professional or a Poison Control Center right away or go to the nearest emergency room.

What Should I Avoid While Taking CRESTOR?

Talk to your health care professional before you start any new medicines. This includes prescription and nonprescription medicines, vitamins, and herbal supplements. CRESTOR and certain other medicines can interact, causing serious side effects.

Talk to your health care professional if you are pregnant or plan to become pregnant. Do not use CRESTOR if you are pregnant, trying to become pregnant or suspect that you are pregnant. If you become pregnant while taking CRESTOR, stop taking it and contact your health care professional immediately.

What are the Possible Side Effects of CRESTOR?

CRESTOR can cause side effects in some people.

Serious side effects may include:

Muscle Problems. Call your health care professional right away if you experience unexplained muscle pain, tenderness, or weakness especially with fever. This may be an early sign of a rare muscle problem that could lead to serious kidney problems. The risk of muscle problems is greater in people who are 65 years of age or older, or who already have thyroid or kidney problems. The chance of muscle problems may be increased if you are taking certain other medicines with CRESTOR.

Liver problems. Your health care professional should do blood tests before you start taking CRESTOR and during treatment to check for signs of possible liver problems.

The most common side effects may include:

Headache, muscle aches and pains, abdominal pain, weakness, and nausea.

This is not a complete list of side effects of CRESTOR. Talk to your health care professional for a complete list or if you have side effects that bother you or that do not go away.

How Do I Store CRESTOR?

Store CRESTOR at room temperature, 68 to 77°F (20 to 25°C) and in a dry place.

If your health care professional tells you to stop treatment or if your medicine is out of date, throw the medicine away.

Keep CRESTOR and all medicines in a secure place and out of the reach of children.

What are the Ingredients in CRESTOR?

Active Ingredient: rosuvastatin calcium

Inactive Ingredients: microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, crospovidone NF, magnesium stearate NF, hypromellose NF, triacetin NF, titanium dioxide USP, yellow ferric oxide, and red ferric oxide NF.

General Information About CRESTOR

It is important to take CRESTOR as prescribed and to discuss any health changes you experience while taking CRESTOR with your health care professional. Do not use CRESTOR for a condition for which it was not prescribed. Do not give CRESTOR to other people, even if they have the same medical condition you have. It may harm them.

This leaflet summarizes important information about CRESTOR. If you would like more information about CRESTOR, ask your health care professional. You can also go to the CRESTOR website at www.crestor.com or call 1-800-CRESTOR.

Distributed by:
AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TOPROL-XL® safely and effectively. See full prescribing information for TOPROL-XL.

TOPROL-XL® *(metoprolol succinate)Tablet, Extended-Release for Oral Use*

INITIAL US APPROVAL: 1992

WARNING: ISCHEMIC HEART DISEASE

(See Full Prescribing Information for complete boxed warning)

Following abrupt cessation of therapy with beta-blocking agents, exacerbations of angina pectoris and myocardial infarction have occurred. Warn patients against interruption or discontinuation of therapy without the physician's advice. (5.1)

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

Major Surgery (5.5) 01/2010

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

TOPROL-XL, metoprolol succinate, is a $beta_1$-selective adrenoceptor blocking agent.

TOPROL-XL is indicated for the treatment of:

- Hypertension. (1.1)
- Angina Pectoris. (1.2)
- Heart Failure - for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. (1.3)

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

- Administer once daily. Dosing of TOPROL-XL should be individualized. (2)
- Heart Failure: Recommended starting dose is 12.5 mg or 25 mg doubled every two weeks to the highest dose tolerated or up to 200 mg. (2.3)
- Hypertension: Usual initial dosage is 25 to 100 mg once daily. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. Dosages above 400 mg per day have not been studied. (2.1)
- Angina Pectoris: Usual initial dosage is 100 mg once daily. Gradually increase the dosage at weekly intervals until optimum clinical response has been obtained or there is an unacceptable bradycardia. Dosages above 400 mg per day have not been studied. (2.2)
- Switching from immediate-release metoprolol to TOPROL-XL: use the same total daily dose of TOPROL-XL. (2)

------DOSAGE FORMS AND STRENGTHS------

- TOPROL-XL Extended-Release Tablets (metoprolol succinate): 25 mg, 50 mg, 100 mg and 200 mg. (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to product components. (4)
- Severe bradycardia. (4)
- Heart block greater than first degree. (4)
- Cardiogenic shock. (4)
- Decompensated cardiac failure. (4)
- Sick sinus syndrome without a pacemaker. (4)

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

- Heart Failure: Worsening cardiac failure may occur. (5.2)
- Bronchospastic Disease: Avoid beta blockers. (5.3)
- Pheochromocytoma: If required, first initiate therapy with an alpha blocker. (5.4)
- Major Surgery: Avoid initiation of high-dose extended-release metoprolol in patients undergoing non-cardiac surgery because it has been associated with bradycardia, hypotension, stroke and death. Do not routinely withdraw chronic beta blocker therapy prior to surgery. (5.5, 6.1)
- Diabetes and Hypoglycemia: May mask tachycardia occurring with hypoglycaemia. (5.6)
- Patients with Hepatic Impairment: (5.7)
- Thyrotoxicosis: Abrupt withdrawal in patients with thyrotoxicosis might precipitate a thyroid storm. (5.8)
- Anaphylactic Reactions: Patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction. (5.9)
- Peripheral Vascular Disease: Can aggravate symptoms of arterial insufficiency. (5.10)
- Calcium Channel Blockers: Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly. (5.11).

----------ADVERSE REACTIONS----------

- Most common adverse reactions: tiredness, dizziness, depression, shortness of breath, bradycardia, hypotension, diarrhea, pruritus, rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Catecholamine-depleting drugs may have an additive effect when given with beta-blocking agents. (7.1)
- CYP2D6 Inhibitors are likely to increase metoprolol concentration. (7.2)
- Concomitant use of glycosides, clonidine, and diltiazem and verapamil with beta-blockers can increase the risk of bradycardia. (7.3)
- Beta-blockers including metoprolol, may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. (7.3)

--------USE IN SPECIFIC POPULATIONS-------

- Pregnancy: There are no adequate and well-controlled studies in pregnant women. Use this drug during pregnancy only if clearly needed. (8.1)
- Nursing Mothers: Consider possible infant exposure. (8.3)
- Pediatrics: Safety and effectiveness have not been established in patients < 6 years of age. (8.4)
- Geriatrics: No notable difference in efficacy or safety vs. younger patients. (8.5)
- Hepatic Impairment: Consider initiating TOPROL-XL therapy at low doses and gradually increase dosage to optimize therapy, while monitoring closely for adverse events. (8.6)

--SEE 17 FOR PATIENT COUNSELING INFORMATION--

04/2010

Full Prescribing Information: Contents*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ISCHEMIC HEART DISEASE:
Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered TOPROL-XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 - 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TOPROL-XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Warn patients against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TOPROL-XL therapy abruptly even in patients treated only for hypertension (5.1).

1 INDICATIONS AND USAGE

1.1 Hypertension

TOPROL-XL is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents *[see Dosage and Administration (2)]*.

1.2 Angina Pectoris

TOPROL-XL is indicated in the long-term treatment of angina pectoris, to reduce angina attacks and to improve exercise tolerance.

1.3 Heart Failure

TOPROL-XL is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis. In this population, TOPROL-XL decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure.

2 DOSAGE AND ADMINISTRATION

TOPROL-XL is an extended-release tablet intended for once daily administration. For treatment of hypertension and angina, when switching from immediate-release metoprolol to TOPROL-XL, use the same total daily dose of TOPROL-XL. Individualize the dosage of TOPROL-XL. Titration may be needed in some patients.

TOPROL-XL tablets are scored and can be divided; however, do not crush or chew the whole or half tablet.

2.1 Hypertension

Adults: The usual initial dosage is 25 to 100 mg daily in a single dose. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.

Pediatric Hypertensive Patients ≥ 6 Years of age: A pediatric clinical hypertension study in patients 6 to 16 years of age did not meet its primary endpoint (dose response for reduction in SBP); however some other endpoints demonstrated effectiveness *[see Use in Specific Populations (8.4)]*. If selected for treatment, the recommended starting dose of TOPROL-XL is 1.0 mg/kg once daily, but the maximum initial dose should not exceed 50 mg once daily. Dosage should be adjusted according to blood pressure response. Doses above 2.0 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients *[see Clinical Pharmacology (12.3)]*.

TOPROL-XL is not recommended in pediatric patients < 6 years of age *[see Use in Specific Populations (8.4)]*.

2.2 Angina Pectoris

Individualize the dosage of TOPROL-XL. The usual initial dosage is 100 mg daily, given in a single dose. Gradually increase the dosage at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, reduce the dosage gradually over a period of 1 - 2 weeks *[see Warnings and Precautions (5)]*.

2.3 Heart Failure

Dosage must be individualized and closely monitored during up-titration. Prior to initiation of TOPROL-XL, stabilize the dose of other heart failure drug therapy. The recommended starting dose of TOPROL-XL is 25 mg once daily for two weeks in patients with NYHA Class II heart failure and 12.5 mg once daily in patients with more severe heart failure. Double the dose every two weeks to the highest dosage level tolerated by the patient or up to 200 mg of TOPROL- XL. Initial difficulty with titration should not preclude later attempts to introduce TOPROL-XL. If patients experience symptomatic bradycardia, reduce the dose of TOPROL-XL. If transient worsening of heart failure occurs, consider treating with increased doses of diuretics, lowering the dose of TOPROL-XL or temporarily discontinuing it. The dose of TOPROL-XL should not be increased until symptoms of worsening heart failure have been stabilized.

3 DOSAGE FORMS AND STRENGTHS

25 mg tablets White, oval, biconvex, film-coated scored tablet engraved with "A/β".

50 mg tablets: White, round, biconvex, film-coated scored tablet engraved with "A/mo".

100 mg tablets: White, round, biconvex, film-coated scored tablet engraved with "A/ms".

200 mg tablets: White, oval, biconvex, film-coated scored tablet engraved with "A/my".

4 CONTRAINDICATIONS

TOPROL-XL is contraindicated in severe bradycardia, second or third degree heart block, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), and in patients who are hypersensitive to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Ischemic Heart Disease

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered TOPROL-XL, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 - 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate TOPROL-XL, and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing TOPROL-XL in patients treated only for hypertension.

5.2 Heart Failure

Worsening cardiac failure may occur during up-titration of TOPROL-XL. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of TOPROL-XL *[see Dosage and Administration (2)]*. It may be necessary to lower the dose of TOPROL-XL or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of TOPROL-XL.

5.3 Bronchospastic Disease

PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative $beta_1$ cardio-selectivity, however, TOPROL-XL may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because $beta_1$-selectivity is not absolute, use the lowest possible dose of TOPROL-XL. Bronchodilators, including $beta_2$-agonists, should be readily available or administered concomitantly *[see Dosage and Administration (2)]*.

5.4 Pheochromocytoma

If TOPROL-XL is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

5.5 Major Surgery

Avoid initiation of a high-dose regimen of extended-release metoprolol in patients undergoing non-cardiac surgery, since such use in patients with cardiovascular risk factors has been associated with bradycardia, hypotension, stroke and death.

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

5.6 Diabetes and Hypoglycemia

Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

5.7 Hepatic Impairment

Consider initiating TOPROL-XL therapy at doses lower than those recommended for a given indication; gradually increase dosage to optimize therapy, while monitoring closely for adverse events.

5.8 Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm.

5.9 Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

5.10 Peripheral Vascular Disease

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

5.11 Calcium Channel Blockers

Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in labeling:

- Worsening angina or myocardial infarction. *[see Warnings and Precautions (5)]*
- Worsening heart failure. *[see Warnings and Precautions (5)]*
- Worsening AV block. *[see Contraindications (4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Hypertension and Angina: Most adverse reactions have been mild and transient. The most common (>2%) adverse reactions are tiredness, dizziness, depression, diarrhea, shortness of breath, bradycardia, and rash.

Heart Failure: In the MERIT-HF study comparing TOPROL-XL in daily doses up to 200 mg (mean dose 159 mg once-daily; n=1990) to placebo (n=2001), 10.3% of TOPROL-XL patients discontinued for adverse reactions vs. 12.2% of placebo patients.

The table below lists adverse reactions in the MERIT-HF study that occurred at an incidence of ≥ 1% in the TOPROL-XL group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

Adverse Reactions Occurring in the MERIT-HF Study at an Incidence ≥ 1 % in the TOPROL-XL Group and Greater Than Placebo by More Than 0.5 %

	TOPROL-XL n=1990 % of patients	Placebo n=2001 % of patients
Dizziness/vertigo	1.8	1.0
Bradycardia	1.5	0.4
Accident and/or injury	1.4	0.8

Post-operative Adverse Events: In a randomized, double-blind, placebo-controlled trial of 8351 patients with or at risk for atherosclerotic disease undergoing non-vascular surgery and who were not taking beta–blocker therapy, TOPROL-XL 100 mg was started 2 to 4 hours prior to surgery then continued for 30 days at 200 mg per day. TOPROL-XL use was associated with a higher incidence of bradycardia (6.6% vs. 2.4%; HR 2.74; 95% CI 2.19, 3.43), hypotension (15% vs. 9.7%; HR 1.55; 95% CI 1.37, 1.74), stroke (1.0% vs 0.5%; HR

2.17; 95% CI 1.26, 3.74) and death (3.1% vs 2.3%; HR 1.33; 95% CI 1.03, 1.74) compared to placebo.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of TOPROL-XL or immediate-release metoprolol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular: Cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension.

Respiratory: Wheezing (bronchospasm), dyspnea.

Central Nervous System: Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia.

Gastrointestinal: Nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting.

Hypersensitive Reactions: Pruritus.

Miscellaneous: Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance

Potential Adverse Reactions: In addition, there are adverse reactions not listed above that have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to TOPROL-XL.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, clouded sensorium, and decreased performance on neuropsychometrics.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Laryngospasm, respiratory distress.

6.3 Laboratory Test Findings

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

7 DRUG INTERACTIONS

7.1 Catecholamine Depleting Drugs

Catecholamine depleting drugs (eg, reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Observe patients treated with TOPROL-XL plus a catecholamine depletor for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

7.2 CYP2D6 Inhibitors

Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate-release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol.

7.3 Digitalis, Clonidine, and Calcium Channel Blockers

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta blockers can increase the risk of bradycardia.

If clonidine and a beta blocker, such as metoprolol are coadministered, withdraw the beta-blocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped *[see Warnings and Precautions (5.11)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

8.3 Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Consider possible infant exposure when TOPROL-XL is administered to a nursing woman.

8.4 Pediatric Use

One hundred forty-four hypertensive pediatric patients aged 6 to 16 years were randomized to placebo or to one of three dose levels of TOPROL-XL (0.2, 1.0 or 2.0 mg/kg once daily) and followed for 4 weeks. The study did not meet its primary endpoint (dose response for reduction in SBP). Some pre-specified secondary endpoints demonstrated effectiveness including:

- Dose-response for reduction in DBP,
- 1.0 mg/kg vs. placebo for change in SBP, and
- 2.0 mg/kg vs. placebo for change in SBP and DBP.

The mean placebo corrected reductions in SBP ranged from 3 to 6 mmHg, and DBP from 1 to 5 mmHg. Mean reduction in heart rate ranged from 5 to 7 bpm but considerably greater reductions were seen in some individuals *[see Dosage and Administration (2.1)]*.

No clinically relevant differences in the adverse event profile were observed for pediatric patients aged 6 to 16 years as compared with adult patients.

Safety and effectiveness of TOPROL-XL have not been established in patients < 6 years of age.

8.5 Geriatric Use

Clinical studies of TOPROL-XL in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients.

Of the 1,990 patients with heart failure randomized to TOPROL-XL in the MERIT-HF trial, 50% (990) were 65 years of age and older and 12% (238) were 75 years of age and older. There were no notable differences in efficacy or the rate of adverse reactions between older and younger patients.

In general, use a low initial starting dose in elderly patients given their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

No studies have been performed with TOPROL-XL in patients with hepatic impairment. Because TOPROL-XL is metabolized by the liver, metoprolol blood levels are likely to increase substantially with poor hepatic function. Therefore, initiate therapy at doses lower than those recommended for a given indication; and increase doses gradually in patients with impaired hepatic function.

8.7 Renal Impairment

The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. No reduction in dosage is needed in patients with chronic renal failure *[see Clinical Pharmacology (12.3)]*.

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10 OVERDOSAGE

Signs and Symptoms - Overdosage of TOPROL-XL may lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.

Treatment – Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamic instability. Seek consultation with a regional poison control center and a medical toxicologist as needed. Beta-blocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists. On the basis of the pharmacologic actions of metoprolol, employ the following measures.

There is very limited experience with the use of hemodialysis to remove metoprolol, however metoprolol is not highly protein bound.

Bradycardia: Administer intravenous atropine; repeat to effect. If the response is inadequate, consider intravenous isoproterenol or other positive chronotropic agents. Evaluate the need for transvenous pacemaker insertion.

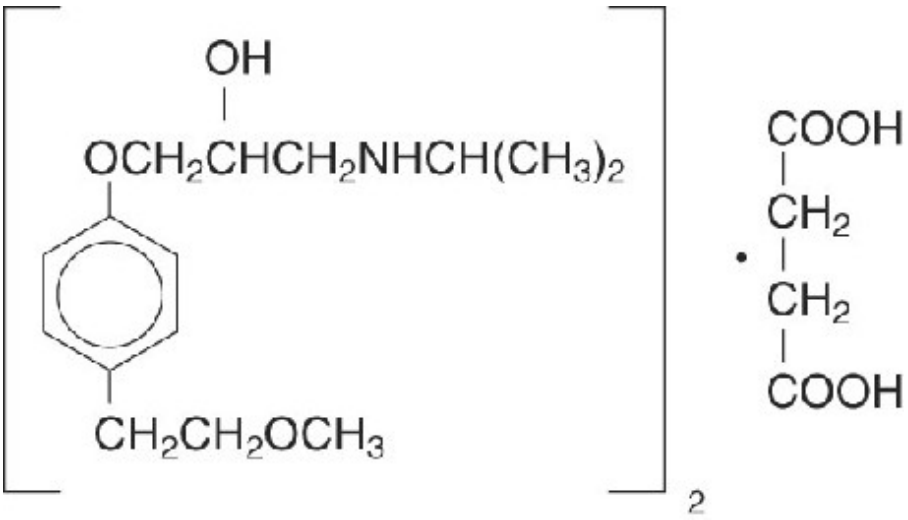
Hypotension: Treat underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine.

Bronchospasm: Administer a $beta_2$-agonist, including albuterol inhalation, or an oral theophylline derivative.

Cardiac Failure: Administer diuretics or digoxin for congestive heart failure. For cardiogenic shock, consider IV dobutamine, isoproterenol, or glucagon.

11 DESCRIPTION

TOPROL-XL, metoprolol succinate, is a $beta_1$-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended-release tablets. TOPROL-XL has been formulated to provide a controlled and predictable release of metoprolol for once-daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 23.75, 47.5, 95 and 190 mg of metoprolol succinate equivalent to 25, 50, 100 and 200 mg of metoprolol tartrate, USP, respectively. Its chemical name is (±)1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). Its structural formula is:



Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptane. Inactive ingredients: silicon dioxide, cellulose compounds, sodium stearyl fumarate, polyethylene glycol, titanium dioxide, paraffin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hypertension: The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites,

leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

Heart Failure: The precise mechanism for the beneficial effects of beta-blockers in heart failure has not been elucidated.

12.2 Pharmacodynamics

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Metoprolol is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

The relative $beta_1$-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the $beta_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV_1 and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent $beta_1$-receptor blocking doses.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using an E_{max} model, the maximum effect is a 30% reduction in exercise heart rate, which is attributed to $beta_1$-blockade. $Beta_1$-blocking effects in the range of 30-80% of the maximal effect (approximately 8-23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations from 30-540 nmol/L. The relative $beta_1$-selectivity of metoprolol diminishes and blockade of $beta_2$-adrenoceptors increases at plasma concentration above 300 nmol/L.

Although beta-adrenergic receptor blockade is useful in the treatment of angina, hypertension, and heart failure there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. $Beta_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

In other studies, treatment with TOPROL-XL produced an improvement in left ventricular ejection fraction. TOPROL-XL was also shown to delay the increase in left ventricular end-systolic and end-diastolic volumes after 6 months of treatment.

12.3 Pharmacokinetics

Adults: In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S- enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity.

Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in metoprolol succinate dosage is usually needed in patients with chronic renal failure.

Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Poor metabolizers and extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity *[see Drug Interactions (7.2)]*.

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of TOPROL-XL are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once-daily administration of TOPROL-XL average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of TOPROL-XL, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24-hour dosing interval, β_1-blockade is comparable and dose-related *[see Clinical Pharmacology (12)]*. The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following TOPROL-XL administration.

Pediatrics: The pharmacokinetic profile of TOPROL-XL was studied in 120 pediatric hypertensive patients (6-17 years of age) receiving doses ranging from 12.5 to 200 mg once daily. The pharmacokinetics of metoprolol were similar to those described previously in adults. Age, gender, race, and ideal body weight had no significant effects on metoprolol pharmacokinetics. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight. Metoprolol pharmacokinetics have not been investigated in patients < 6 years of age.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a *Salmonella*/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient.

14 CLINICAL STUDIES

In five controlled studies in normal healthy subjects, the same daily doses of TOPROL-XL and immediate-release metoprolol were compared in terms of the extent and duration of beta$_1$-blockade produced. Both formulations were given in a dose range equivalent to 100-400 mg of immediate-release metoprolol per day. In these studies, TOPROL-XL was administered once a day and immediate-release metoprolol was administered once to four times a day. A sixth controlled study compared the beta$_1$-blocking effects of a 50 mg daily dose of the two formulations. In each study, beta$_1$-blockade was expressed as the percent change from baseline in exercise heart rate following standardized submaximal exercise tolerance tests at steady state. TOPROL-XL administered once a day, and immediate-release metoprolol administered once to four times a day, provided comparable total beta$_1$-blockade over 24 hours (area under the beta$_1$-blockade versus time curve) in the dose range 100-400 mg. At a dosage of 50 mg once daily, TOPROL-XL produced significantly higher total beta$_1$-blockade over 24 hours than immediate-release metoprolol. For TOPROL-XL, the percent reduction in exercise heart rate was relatively stable throughout the entire dosage interval and the level of beta$_1$-blockade increased with increasing doses from 50 to 300 mg daily. The effects at peak/trough (ie, at 24-hours post-dosing) were: 14/9, 16/10, 24/14, 27/22 and 27/20% reduction in exercise heart rate for doses of 50, 100, 200, 300 and 400 mg TOPROL-XL once a day, respectively. In contrast to TOPROL-XL, immediate-release metoprolol given at a dose of 50-100 mg once a day produced a significantly larger peak effect on exercise tachycardia, but the effect was not evident at 24 hours. To match the peak to trough ratio obtained with TOPROL-XL over the dosing range of 200 to 400 mg, a t.i.d. to q.i.d. divided dosing regimen was required for immediate-release metoprolol. A controlled cross-over study in heart failure patients compared the plasma concentrations and beta$_1$-blocking effects of 50 mg immediate-release metoprolol administered t.i.d., 100 mg and 200 mg TOPROL-XL once daily. A 50 mg dose of immediate-release metoprolol t.i.d. produced a peak plasma level of metoprolol similar to the peak level observed with 200 mg of TOPROL-XL. A 200

mg dose of TOPROL-XL produced a larger effect on suppression of exercise-induced and Holter-monitored heart rate over 24 hours compared to 50 mg t.i.d. of immediate-release metoprolol.

In a double-blind study, 1092 patients with mild-to-moderate hypertension were randomized to once daily TOPROL-XL (25, 100, or 400 mg), PLENDIL® (felodipine extended-release tablets), the combination, or placebo. After 9 weeks, TOPROL-XL alone decreased sitting blood pressure by 6-8/4-7 mmHg (placebo-corrected change from baseline) at 24 hours post-dose. The combination of TOPROL-XL with PLENDIL has greater effects on blood pressure.

In controlled clinical studies, an immediate-release dosage form of metoprolol was an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics at dosages of 100-450 mg daily. TOPROL-XL, in dosages of 100 to 400 mg once daily, produces similar β_1-blockade as conventional metoprolol tablets administered two to four times daily. In addition, TOPROL-XL administered at a dose of 50 mg once daily lowered blood pressure 24-hours post-dosing in placebo-controlled studies. In controlled, comparative, clinical studies, immediate-release metoprolol appeared comparable as an antihypertensive agent to propranolol, methyldopa, and thiazide-type diuretics, and affected both supine and standing blood pressure. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to drug plasma concentration, selection of proper dosage requires individual titration.

14.1 Angina Pectoris

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris.

In controlled clinical trials, an immediate-release formulation of metoprolol has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100 to 400 mg daily. TOPROL-XL, in dosages of 100 to 400 mg once daily, has been shown to possess beta-blockade similar to conventional metoprolol tablets administered two to four times daily.

14.2 Heart Failure

MERIT-HF was a double-blind, placebo-controlled study of TOPROL-XL conducted in 14 countries including the US. It randomized 3991 patients (1990 to TOPROL-XL) with ejection fraction ≤0.40 and NYHA Class II-IV heart failure attributable to ischemia, hypertension, or cardiomyopathy. The protocol excluded patients with contraindications to beta-blocker use, those expected to undergo heart surgery, and those within 28 days of myocardial infarction or unstable angina. The primary endpoints of the trial were (1) all-cause mortality plus all-cause hospitalization (time to first event) and (2) all-cause mortality. Patients were stabilized on optimal concomitant therapy for heart failure, including diuretics, ACE inhibitors, cardiac glycosides, and nitrates. At randomization, 41% of patients were NYHA Class II; 55% NYHA Class III; 65% of patients had heart failure attributed to ischemic heart disease; 44% had a history of hypertension; 25% had diabetes mellitus; 48% had a history of myocardial infarction. Among patients in the trial, 90% were on diuretics, 89% were on ACE inhibitors, 64% were on digitalis, 27% were on a lipid-lowering agent, 37% were on an oral anticoagulant, and the mean ejection fraction was 0.28. The mean duration of follow-up was one year. At the end of the study, the mean daily dose of TOPROL-XL was 159 mg.

The trial was terminated early for a statistically significant reduction in all-cause mortality (34%, nominal p= 0.00009). The risk of all-cause mortality plus all-cause hospitalization was reduced by 19% (p= 0.00012). The trial also showed improvements in heart failure-related mortality and heart failure-related hospitalizations, and NYHA functional class.

The table below shows the principal results for the overall study population. The figure below illustrates principal results for a wide variety of subgroup comparisons, including US vs. non-US populations (the latter of which was not pre-specified). The combined endpoints of all-cause mortality plus all-cause hospitalization and of mortality plus heart failure hospitalization showed consistent effects in the overall study population and the subgroups, including women and the US population. However, in the US subgroup (n=1071) and women (n=898), overall mortality and cardiovascular mortality appeared less affected. Analyses of female and US patients were carried out because they each represented about 25% of the overall population. Nonetheless, subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

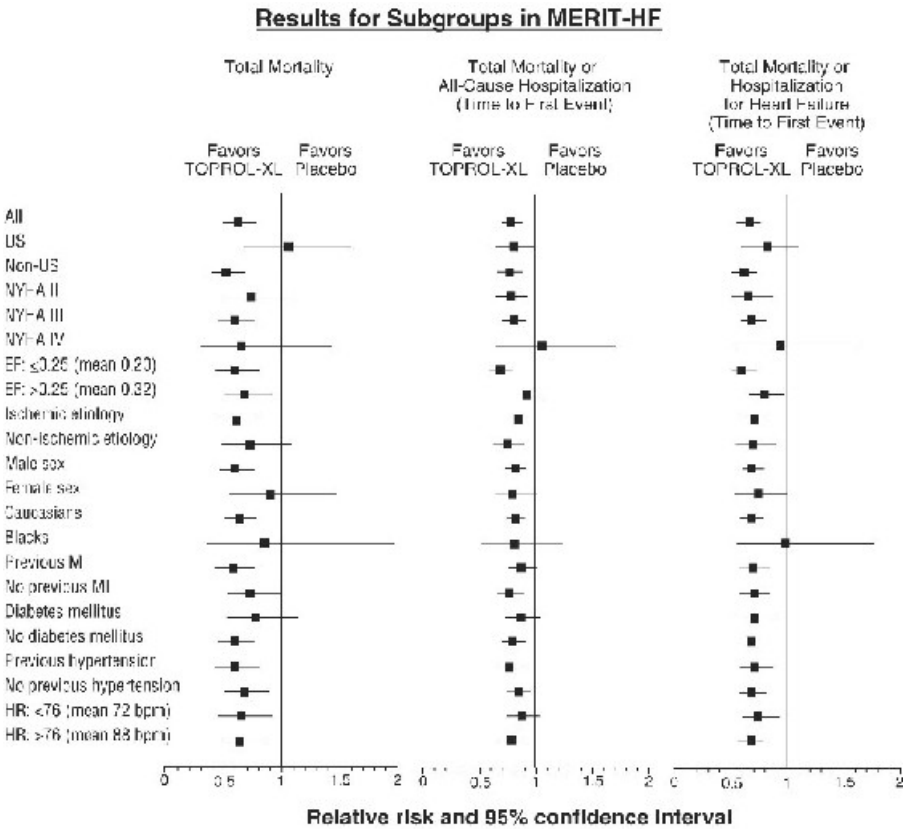
Clinical Endpoints in the MERIT-HF Study

Clinical Endpoint	Number of Patients		Relative Risk (95% Cl)	Risk Reduction With TOPROL-XL	Nominal P-value
	Placebo	TOPROL-			

	n=2001	XL n=1990			
All-cause mortality plus all-caused hospitalization*	767	641	0.81(0.73-0.90)	19%	0.00012
All-cause mortality	217	145	0.66(0.53-0.81)	34%	0.00009
All-cause mortality plus heart failure hospitalization*	439	311	0.69(0.60-0.80)	31%	0.0000008
Cardiovascular mortality	203	128	0.62(0.50-0.78)	38%	0.000022
Sudden death	132	79	0.59(0.45-0.78)	41%	0.0002
Death due to worsening heart failure	58	30	0.51(0.33-0.79)	49%	0.0023
Hospitalizations due to worsening heart failure†	451	317	N/A	N/A	0.0000076
Cardiovascular hospitalization†	773	649	N/A	N/A	0.00028

*Time to first event

†Comparison of treatment groups examines the number of hospitalizations (Wilcoxon test); relative risk and risk reduction are not applicable.



US = United States; NYHA = New York Heart Association; EF = ejection fraction; MI = myocardial infarction; HR = heart rate.

15. REFERENCES:

1. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* 2008; 371:1839-47.

16. HOW SUPPLIED/STORAGE AND HANDLING

Tablets containing metoprolol succinate equivalent to the indicated weight of metoprolol tartrate, USP, are white, biconvex, film-coated, and scored.

Tablet	Shape	Engraving	Bottle of 100 NDC 0186-	Unit Dose Packages of 100 NDC 0186-
25 mg	Oval	A/ β	1088-05	1088-39
50 mg	Round	A/ mo	1090-05	1090-39
100 mg	Round	A/ ms	1092-05	1092-39
200 mg	Oval	A/ my	1094-05	N/A

Store at 25°C (77°F). Excursions permitted to 15-30°C (59- 86°F). (See USP Controlled Room Temperature.)

17. PATIENT COUNSELING INFORMATION

Advise patients to take TOPROL-XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose is missed, the patient should take only the next scheduled dose (without doubling it). Patients should not interrupt or discontinue TOPROL-XL without consulting the physician.

Advise patients (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with TOPROL-XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking TOPROL-XL.

Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.

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