# FULL PRESCRIBING INFORMATION

## Crestor® 5,10 and 20 mg film coated Tablets

Rosuvastatin Calcium

## 1 INDICATIONS AND USAGE

CRESTOR is indicated:

- To reduce the risk of major adverse cardiovascular (CV) events (CV death, nonfatal myocardial infarction, nonfatal stroke, or an arterial revascularization procedure) in adults without established coronary heart disease who are at increased risk of CV disease based on age, high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L, and at least one additional CV risk factor.
- As an adjunct to diet to:
  - Reduce low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia.
  - Reduce LDL-C and slow the progression of atherosclerosis in adults.
  - Reduce LDL-C in adults and pediatric patients aged 8 years and older with heterozygous familial hypercholesterolemia (HeFH).
- As an adjunct to other LDL-C-lowering therapies, or alone if such treatments are unavailable, to reduce LDL-C in adults and pediatric patients aged 7 years and older with homozygous familial hypercholesterolemia (HoFH).
- As an adjunct to diet for the treatment of adults with:
  - Primary dysbetalipoproteinemia.
  - Hypertriglyceridemia.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 General Dosage and Administration Information

- Administer CRESTOR orally as a single dose at any time of day, with or without food. Swallow the tablets whole.
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating CRESTOR, and adjust the dosage if necessary.

- If a dose is missed, advise patients not to take an extra dose. Resume treatment with the next dose.
- When taking CRESTOR with an aluminum and magnesium hydroxide combination antacid, administer CRESTOR at least 2 hours before the antacid *[see Drug Interactions (7.2)]*.

## 2.2 Recommended Dosage in Adult Patients

- The dosage range for CRESTOR is 5 to 40 mg orally once daily.
- The recommended dose of CRESTOR depends on a patient's indication for usage, LDL-C, and individual risk for CV events.

## 2.3 Recommended Dosage in Pediatric Patients

Dosage in Pediatric Patients 8 Years of Age and Older with HeFH

The recommended dosage range is 5 mg to 10 mg orally once daily in patients aged 8 years to less than 10 years and 5 mg to 20 mg orally once daily in patients aged 10 years and older.

Dosage in Pediatric Patients 7 Years of Age and Older with HoFH

The recommended dosage is 20 mg orally once daily.

## 2.4 Dosing in Asian Patients

Initiate CRESTOR at 5 mg once daily due to increased rosuvastatin plasma concentrations. Consider the risks and benefits of CRESTOR when treating Asian patients not adequately controlled at doses up to 20 mg once daily *[see Warnings and Precautions (5.1), Use in Specific Populations (8.8), and Clinical Pharmacology (12.3)]*.

## 2.5 Recommended Dosage in Patients with Renal Impairment

In patients with severe renal impairment ($CL_{cr}$ less than 30 mL/min/1.73 $m^2$) not on hemodialysis, the recommended starting dosage is 5 mg once daily and should not exceed 10 mg once daily *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

There are no dosage adjustment recommendations for patients with mild and moderate renal impairment.

## 2.6 Dosage Modifications Due to Drug Interactions

Table 1 displays dosage modifications for CRESTOR due to drug interactions *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

**Table 1: CRESTOR Dosage Modifications Due to Drug Interactions**

| Concomitantly Used Drug | CRESTOR Dosage Modifications |
|---|---|
| Cyclosporine | Do not exceed 5 mg once daily. |
| Teriflunomide | Do not exceed 10 mg once daily. |
| Enasidenib | Do not exceed 10 mg once daily. |
| Capmatinib | Do not exceed 10 mg once daily. |
| Fostamatinib | Do not exceed 20 mg once daily. |
| Febuxostat | Do not exceed 20 mg once daily. |
| Gemfibrozil | Avoid concomitant use. If used concomitantly, initiate at 5 mg once daily and do not exceed 10 mg once daily. |
| Tafamidis | Avoid concomitant use. If used concomitantly, initiate at 5 mg once daily and do not exceed 20 mg once daily. |
| Antiviral Medications | |
| o Sofbuvir/velpatasvir/voxilaprevir<br>o Ledipasvir/sofosbuvir | Concomitant use not recommended. |
| o Simeprevir<br>o Dasabuvir/ombitasvir/paritaprevir/ritonavir<br>o Elbasvir/Grazoprevir<br>o Sofosbuvir/Velpatasvir<br>o Glecaprevir/Pibrentasvir<br>o Atazanavir/Ritonavir<br>o Lopinavir/Ritonavir | Initiate at 5 mg once daily. Do not exceed 10 mg once daily. |
| Darolutamide | Do not exceed 5 mg once daily. |
| Regorafenib | Do not exceed 10 mg once daily. |

CRESTOR Administration Modifications Due to Drug Interactions

When taking CRESTOR with an aluminum and magnesium hydroxide combination antacid, administer CRESTOR at least 2 hours before the antacid [see Drug Interactions (7.2)].

# 3 DOSAGE FORMS AND STRENGTHS

CRESTOR tablets:

- Rosuvastatin Calcium 5.2 mg equivalent to Rosuvastatin 5 mg: Round, biconvex yellow, Film-coated tablet, intagliated with 'ZD4522' and '5' on one side and plain on the reverse

- Rosuvastatin Calcium 10.4 mg equivalent to Rosuvastatin 10 mg: Round, pink ,biconvex film-coated tablet, intagliated with 'ZD4522' and '10' on one side and plain on the reverse

- Rosuvastatin Calcium 20.4 mg equivalent to Rosuvastatin 20 mg: Round, pink ,biconvex film-coated tablet, intagliated with 'ZD4522' and '20' on one side and plain on the reverse

Not All concentrations are marketed.

# 4 CONTRAINDICATIONS

CRESTOR is contraindicated in the following conditions:

- Acute liver failure or decompensated cirrhosis *[see Warnings and Precautions (5.3)]*.
- Hypersensitivity to rosuvastatin or any excipients in CRESTOR. Hypersensitivity reactions including rash, pruritus, urticaria, and angioedema have been reported with CRESTOR *[see Adverse Reactions (6.1)]*.

# 5 WARNINGS AND PRECAUTIONS

## 5.1 Myopathy and Rhabdomyolysis

CRESTOR may cause myopathy [muscle pain, tenderness, or weakness associated with elevated creatine kinase (CK)] and rhabdomyolysis. Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis with statins, including CRESTOR.

Risk Factors for Myopathy

Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs (including other lipid-lowering therapies), and higher CRESTOR dosage. Asian patients on CRESTOR may be at higher risk for myopathy *[see Drug Interactions (7.1) and Use in Specific Populations (8.8)]*. The myopathy risk is greater in patients taking CRESTOR 40 mg daily compared with lower CRESTOR dosages.

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

The concomitant use of CRESTOR with cyclosporine or gemfibrozil is not recommended. CRESTOR dosage modifications are recommended for patients taking certain antiviral medications, darolutamide, and regorafenib *[see Dosage and Administration (2.6)]*. Niacin, fibrates, and colchicine may also increase the risk of myopathy and rhabdomyolysis *[see Drug Interactions (7.1)]*.

Discontinue CRESTOR if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations may resolve if CRESTOR is discontinued. Temporarily discontinue CRESTOR in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis (e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or

uncontrolled epilepsy).

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the CRESTOR dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

## 5.2 Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use, including reports of recurrence when the same or a different statin was administered. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase that persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Discontinue CRESTOR if IMNM is suspected.

## 5.3 Hepatic Dysfunction

Increases in serum transaminases have been reported with use of CRESTOR *[see Adverse Reactions (6.1)]*. In most cases, these changes appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or improved on continued therapy or after a brief interruption in therapy. In a pooled analysis of placebo-controlled trials, increases in serum transaminases to more than three times the ULN occurred in 1.1% of patients taking CRESTOR versus 0.5% of patients treated with placebo. Marked persistent increases of hepatic transaminases have also occurred with CRESTOR. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including CRESTOR.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury *[see Use in Specific Populations (8.7)]*.

Consider liver enzyme testing before CRESTOR initiation and when clinically indicated thereafter. CRESTOR is contraindicated in patients with acute liver failure or decompensated cirrhosis *[see Contraindications (4)]*. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue CRESTOR.

## 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 statins, though it was generally transient and was not associated with worsening renal function. Although

the clinical significance of this finding is unknown, consider a dose reduction for patients on CRESTOR therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

## 5.5 Increases in HbA1c and Fasting Serum Glucose Levels

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including CRESTOR. Based on clinical trial data with CRESTOR, in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus *[see Adverse Reactions (6.1)]*. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

## 5.6 Myasthenia gravis

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. Crestor should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

# 6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Myopathy and Rhabdomyolysis *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Necrotizing Myopathy *[see Warnings and Precautions (5.2)]*
- Hepatic Dysfunction *[see Warnings and Precautions (5.3)]*
- Proteinuria and Hematuria *[see Warnings and Precautions (5.4)]*
- Increases in HbA1c and Fasting Serum Glucose Levels *[see Warnings and Precautions (5.5)]*
- Skin and Subcutaneous Tissue Disorders: drug reaction with eosinophilia and systemic symptoms (DRESS), lichenoid drug eruption
- Nervous system disorders: Myasthenia gravis (frequency: not known)
- Eye disorders: Ocular myasthenia (frequency: not known)

## 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 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 2. These studies had a treatment duration of up to 12 weeks.

**Table 2: Adverse Reactions Reported in ≥2% of Patients Treated with CRESTOR and > Placebo in Placebo-Controlled Trials**

| Adverse Reactions | Placebo N=382 % | 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 % |
|---|---|---|---|---|---|---|
| Headache | 5.0 | 5.5 | 4.9 | 3.1 | 8.5 | 5.5 |
| Nausea | 3.1 | 3.8 | 3.5 | 6.3 | 0 | 3.4 |
| Myalgia | 1.3 | 3.1 | 2.1 | 6.3 | 1.9 | 2.8 |
| Asthenia | 2.6 | 2.4 | 3.2 | 4.7 | 0.9 | 2.7 |
| Constipation | 2.4 | 2.1 | 2.1 | 4.7 | 2.8 | 2.4 |

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; elevated creatine phosphokinase, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities.

In the METEOR study, patients were treated with CRESTOR 40 mg (n=700) or placebo (n=281) with a mean treatment duration of 1.7 years. Adverse reactions reported in ≥2% of patients and at a rate greater than placebo are shown in Table 3.

**Table 3: Adverse Reactions Reported in ≥2% of Patients Treated with CRESTOR and > Placebo in the METEOR Trial**

| Adverse Reactions | Placebo N=281 % | CRESTOR 40 mg N=700 % |
|---|---|---|
| Myalgia | 12.1 | 12.7 |
| Arthralgia | 7.1 | 10.1 |
| Headache | 5.3 | 6.4 |
| Dizziness | 2.8 | 4.0 |
| Increased CPK | 0.7 | 2.6 |
| Abdominal pain | 1.8 | 2.4 |
| ALT greater than 3x ULN[1] | 0.7 | 2.2 |

[1] Frequency recorded as abnormal laboratory value.

In the JUPITER study, patients were treated with CRESTOR 20 mg (n=8,901) or placebo (n=8,901) for a mean duration of 2 years. In JUPITER, there was a significantly higher frequency of diabetes mellitus reported in patients taking CRESTOR (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in CRESTOR-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 CRESTOR-treated versus placebo-treated patients *[see Clinical Studies (14)]*.

Adverse reactions reported in ≥2% of patients and at a rate greater than placebo are shown in Table 4.

**Table 4: Adverse Reactions Reported in ≥2% of Patients Treated with CRESTOR and > Placebo in the JUPITER Trial**

| Adverse Reactions | Placebo N=8,901 % | CRESTOR 20 mg N=8,901 % |
|---|---|---|
| Myalgia | 6.6 | 7.6 |
| Arthralgia | 3.2 | 3.8 |
| Constipation | 3.0 | 3.3 |
| Diabetes mellitus | 2.3 | 2.8 |
| Nausea | 2.3 | 2.4 |

Pediatric Patients with HeFH

In a 12-week controlled study in pediatric patients 10 to 17 years of age with HeFH with CRESTOR 5 mg to 20 mg daily *[see Use in Specific Populations (8.4) and Clinical Studies (14)]*, elevations in serum CK greater than 10 x ULN were observed more frequently in CRESTOR-treated patients compared with patients receiving placebo. Four of 130 (3%) patients treated with CRESTOR (2 treated with 10 mg and 2 treated with 20 mg) had increased CK greater than 10 x ULN, compared to 0 of 46 patients on placebo.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of CRESTOR. 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.

*Blood Disorders:* thrombocytopenia

*Hepatobiliary Disorders:* hepatitis, jaundice, fatal and non-fatal hepatic failure

*Musculoskeletal Disorders:* arthralgia, rare reports of immune-mediated necrotizing myopathy associated with statin use

*Nervous System Disorders*: peripheral neuropathy, rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, and confusion) associated with the use of all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom

resolution (median of 3 weeks). There have been rare reports of new-onset or exacerbation of myasthenia gravis, including ocular myasthenia, and reports of recurrence when the same or a different statin was administered.

*Psychiatric Disorders:* depression, sleep disorders (including insomnia and nightmares)

*Reproductive System and Breast Disorders:* gynecomastia

*Respiratory Disorders:* interstitial lung disease

*Skin and Subcutaneous Tissue Disorders:* drug reaction with eosinophilia and systemic symptoms (DRESS), lichenoid drug eruption

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the following Egyptian Pharmacovigilance Center contacts:

- e-mail for reporting: pv.followup@edaegypt.gov.eg
- Website for reporting: www.edaegypt.gov.eg
- Hotline: 15301
- Scan QR code:


Or Via AstraZeneca Patient Safety Email:

patient.safetyegypt@astrazeneca.com

Or via the following link:

https://contactaz.astrazeneca.com/content/astrazeneca-champion/eg/en/amp-form.html

# 7 DRUG INTERACTIONS

## 7.1 Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with CRESTOR

Rosuvastatin is a substrate of CYP2C9 and transporters (such as OATP1B1, BCRP). Rosuvastatin plasma levels can be significantly increased with concomitant administration of inhibitors of CYP2C9 and transporters. Table 5 includes a list of drugs that increase the risk of myopathy and rhabdomyolysis when used concomitantly with CRESTOR and instructions for preventing or managing them *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

**Table 5: Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with CRESTOR**

| | |
|---|---|
| **Cyclosporine** | |
| *Clinical Impact:* | Cyclosporine increased rosuvastatin exposure 7-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with CRESTOR. |
| *Intervention:* | If used concomitantly, do not exceed a dose of CRESTOR 5 mg once daily. |
| **Teriflunomide** | |
| *Clinical Impact:* | Teriflunomide increased rosuvastatin exposure more than 2.5-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use. |
| *Intervention:* | In patients taking teriflunomide, do not exceed a dose of CRESTOR 10 mg once daily. |
| **Enasidenib** | |
| *Clinical Impact:* | Enasidenib increased rosuvastatin exposure more than 2.4-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use. |
| *Intervention:* | In patients taking enasidenib, do not exceed a dose of CRESTOR 10 mg once daily. |
| **Capmatinib** | |
| *Clinical Impact:* | Capmatinib increased rosuvastatin exposure more than 2.1-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use. |
| *Intervention:* | In patients taking capmatinib, do not exceed a dose of CRESTOR 10 mg once daily. |
| **Fostamatinib** | |
| *Clinical Impact:* | Fostamatinib increased rosuvastatin exposure more than 2.0-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use. |
| *Intervention:* | In patients taking fostamatinib, do not exceed a dose of CRESTOR 20 mg once daily. |

| | | |
|---|---|---|
| **Febuxostat** | | |
| *Clinical Impact:* | Febuxostat increased rosuvastatin exposure more than 1.9-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use. | |
| *Intervention:* | In patients taking febuxostat, do not exceed a dose of CRESTOR 20 mg once daily. | |
| **Gemfibrozil** | | |
| *Clinical Impact:* | Gemfibrozil significantly increased rosuvastatin exposure and gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of gemfibrozil with CRESTOR. | |
| *Intervention:* | Avoid concomitant use of gemfibrozil with CRESTOR. If used concomitantly, initiate CRESTOR at 5 mg once daily and do not exceed a dose of CRESTOR 10 mg once daily. | |
| **Tafamidis** | | |
| *Clinical Impact:* | Tafamidis significantly increased rosuvastatin exposure and tafamidis may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of tafamidis with CRESTOR. | |
| *Intervention:* | Avoid concomitant use of tafamidis with CRESTOR. If used concomitantly, initiate CRESTOR at 5 mg once daily and do not exceed a dose of CRESTOR 20 mg once daily. Monitor for signs of myopathy and rhabdomyolysis if used concomitantly with CRESTOR. | |
| **Anti-Viral Medications** | | |
| *Clinical Impact:* | Rosuvastatin plasma levels were significantly increased with concomitant administration of many anti-viral drugs, which increases the risk of myopathy and rhabdomyolysis. | |
| *Intervention:* | • Sofosbuvir/velpatasvir/voxilaprevir<br>• Ledipasvir/sofosbuvir | Avoid concomitant use with CRESTOR. |
| | • Simeprevir<br>• Dasabuvir/ombitasvir/paritaprevir/ritonavir<br>• Elbasvir/grazoprevir<br>• Sofosbuvir/velpatasvir<br>• Glecaprevir/pibrentasvir<br>• Atazanavir/ritonavir<br>• Lopinavir/ritonavir | Initiate with CRESTOR 5 mg once daily, and do not exceed a dose of CRESTOR 10 mg once daily. |
| **Darolutamide** | | |
| *Clinical Impact:* | Darolutamide increased rosuvastatin exposure more than 5-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use. | |

| | |
|---|---|
| *Intervention:* | In patients taking darolutamide, do not exceed a dose of CRESTOR 5 mg once daily. |
| **Regorafenib** | |
| *Clinical Impact:* | Regorafenib increased rosuvastatin exposure and may increase the risk of myopathy. |
| *Intervention:* | In patients taking regorafenib, do not exceed a dose of CRESTOR 10 mg once daily. |
| **Fenofibrates (e.g., fenofibrate and fenofibric acid)** | |
| *Clinical Impact:* | Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with CRESTOR. |
| *Intervention:* | Consider if the benefit of using fibrates concomitantly with CRESTOR outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug. |
| **Niacin** | |
| *Clinical Impact:* | Cases of myopathy and rhabdomyolysis have occurred with concomitant use of lipid-modifying doses (≥1 g/day) of niacin with CRESTOR. |
| *Intervention:* | Consider if the benefit of using lipid-modifying doses (≥1 g/day) of niacin concomitantly with CRESTOR outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug. |
| **Colchicine** | |
| *Clinical Impact:* | Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with CRESTOR. |
| *Intervention:* | Consider if the benefit of using colchicine concomitantly with CRESTOR outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug. |
| **Ticagrelor** | |
| *Clinical Impact:* | Concomitant use of CRESTOR and ticagrelor has been shown to increase rosuvastatin concentrations, which may result in increased risk of myopathy. Cases of myopathy and rhabdomyolysis have been reported in patients using both products concomitantly. Cases have occurred more frequently in patients taking 40 mg of rosuvastatin. |
| *Intervention:* | In patients taking concomitant ticagrelor, especially those with additional risk factors for myopathy and rhabdomyolysis, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of CRESTOR. |

## 7.2 Drug Interactions that Decrease the Efficacy of CRESTOR

Table 6 presents drug interactions that may decrease the efficacy of CRESTOR and instructions for preventing or managing them.

**Table 6: Drug Interactions that Decrease the Efficacy of CRESTOR**

| **Antacids** | |
|---|---|
| *Clinical Impact:* | Concomitant aluminum and magnesium hydroxide combination antacid administration decreased the mean exposure of rosuvastatin 50% *[see Clinical Pharmacology (12.3)]*. |
| *Intervention:* | In patients taking antacid, administer CRESTOR at least 2 hours before the antacid. |

## 7.3 CRESTOR Effects on Other Drugs

Table 7 presents CRESTOR's effect on other drugs and instructions for preventing or managing them.

**Table 7: CRESTOR Effects on Other Drugs**

| **Warfarin** | |
|---|---|
| *Clinical Impact:* | Rosuvastatin significantly increased the INR in patients receiving warfarin *[see Clinical Pharmacology (12.3)]*. |
| *Intervention:* | In patients taking warfarin, obtain an INR before starting CRESTOR and frequently enough after initiation, dose titration or discontinuation to ensure that no significant alteration in INR occurs. Once the INR is stable, monitor INR at regularly recommended intervals. |

## 7.4 Fusidic Acid

Interaction studies with rosuvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with rosuvastatin and fusidic acid given concurrently. Patients should be closely monitored and temporary suspension of rosuvastatin treatment may be appropriate.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

Risk Summary

Discontinue CRESTOR when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient.

CRESTOR decreases synthesis of cholesterol and possibly other biologically active substances derived from cholesterol; therefore, CRESTOR may cause fetal harm when administered to

pregnant patients based on the mechanism of action *[see Clinical Pharmacology (12.1)]*. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.

Available data from case series and prospective and retrospective observational cohort studies over decades of use with statins in pregnant women have not identified a drug-associated risk of major congenital malformations. Published data from prospective and retrospective observational cohort studies with CRESTOR use in pregnant women are insufficient to determine if there is a drug-associated risk of miscarriage *(see Data)*.

In animal reproduction studies, no adverse developmental effects were observed in pregnant rats or rabbits orally administered rosuvastatin during the period of organogenesis at doses that resulted in systemic exposures equivalent to human exposures at the maximum recommended human dose (MRHD) of 40 mg/day, based on AUC and body surface area ($mg/m^2$), respectively *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

*Human Data*

A Medicaid cohort linkage study of 1,152 statin-exposed pregnant women compared to 886,996 controls did not find a significant teratogenic effect from maternal use of statins in the first trimester of pregnancy, after adjusting for potential confounders – including maternal age, diabetes mellitus, hypertension, obesity, and alcohol and tobacco use – using propensity score-based methods. The relative risk of congenital malformations between the group with statin use and the group with no statin use in the first trimester was 1.07 (95% confidence interval 0.85 to 1.37) after controlling for confounders, particularly pre-existing diabetes mellitus. There were also no statistically significant increases in any of the organ-specific malformations assessed after accounting for confounders. In the majority of pregnancies, statin treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. Study limitations include reliance on physician coding to define the presence of a malformation, lack of control for certain confounders such as body mass index, use of

prescription dispensing as verification for the use of a statin, and lack of information on non-live births.

*Animal Data*

In female rats given 5, 15 and 50 mg/kg/day before mating and continuing through to gestation day 7 resulted in decreased fetal body weight (female pups) and delayed ossification at 50 mg/kg/day (10 times the human exposure at the MRHD dose of 40 mg/day based on AUC).

In pregnant rats given 2, 10 and 50 mg/kg/day of rosuvastatin from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred at 50 mg/kg/day (dose equivalent to 12 times the MRHD of 40 mg/day based body surface area).

In pregnant rabbits given 0.3, 1, and 3 mg/kg/day of rosuvastatin from gestation day 6 to day 18, decreased fetal viability and maternal mortality was observed at 3 mg/kg/day (dose equivalent to the MRHD of 40 mg/day based on body surface area).

Rosuvastatin crosses the placenta in rats and rabbits 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. In rabbits, fetal tissue distribution was 25% of maternal plasma concentration after a single oral gavage dose of 1 mg/kg on gestation day 18.

## 8.2 Lactation

Risk Summary

Limited data from case reports in published literature indicate that CRESTOR is present in human milk. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Statins, including CRESTOR, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol and may cause harm to the breastfed infant.

Because of the potential for serious adverse reactions in a breastfed infant, based on the mechanism of action, advise patients that breastfeeding is not recommended during treatment with CRESTOR *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.1)]*.

## 8.4 Pediatric Use

The safety and effectiveness of CRESTOR as an adjunct to diet to reduce LDL-C have been established in pediatric patients 8 years of age and older with HeFH. Use of CRESTOR for this indication is based on one 12-week controlled trial with a 40-week open-label extension period in 176 pediatric patients 10 years of age and older with HeFH and one 2-year open-label, uncontrolled trial in 175 pediatric patients 8 years of age and older with HeFH *[*see *Clinical*

*Studies (14)]*. In the 1-year trial with a 12-week controlled phase, there was no detectable effect of CRESTOR on growth, weight, BMI (body mass index), or sexual maturation in patients aged 10 to 17 years.

The safety and effectiveness of CRESTOR as an adjunct to other LDL-C-lowering therapies to reduce LDL-C have been established in pediatric patients 7 years of age and older with HoFH. Use of CRESTOR for this indication is based on a randomized, placebo-controlled, cross-over study in 14 pediatric patients 7 years of age and older with HoFH *[*see *Clinical Studies (14)]*.

The safety and effectiveness of CRESTOR have not been established in pediatric patients younger than 8 years of age with HeFH, younger than 7 years of age with HoFH, or in pediatric patients with other types of hyperlipidemia (other than HeFH or HoFH).

## 8.5 Geriatric Use

Of the 10,275 patients in clinical studies with CRESTOR, 3,159 (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.

Advanced age (≥65 years) is a risk factor for CRESTOR-associated myopathy and rhabdomyolysis. Dose selection for an elderly patient should be cautious, recognizing the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of myopathy. Monitor geriatric patients receiving CRESTOR for the increased risk of myopathy *[see Warnings and Precautions (5.1)]*.

## 8.6 Renal Impairment

Rosuvastatin exposure is not influenced by mild to moderate renal impairment ($CL_{cr}$ ≥30 mL/min/1.73 $m^2$). Exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment ($CL_{cr}$ <30 mL/min/1.73 $m^2$) who are not receiving hemodialysis *[see Clinical Pharmacology (12.3)]*.

Renal impairment is a risk factor for myopathy and rhabdomyolysis. Monitor all patients with renal impairment for development of myopathy. In patients with severe renal impairment not on hemodialysis, the recommended starting dosage is 5 mg daily and should not exceed 10 mg daily *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)]*.

## 8.7 Hepatic Impairment

CRESTOR is contraindicated in patients with acute liver failure or decompensated cirrhosis. Chronic alcohol liver disease is known to increase rosuvastatin exposure. Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for

hepatic injury *[see Contraindications (4), Warning and Precautions (5.3) 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 White controls. Adjust the CRESTOR dosage in Asian patients *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

## 8.9 Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

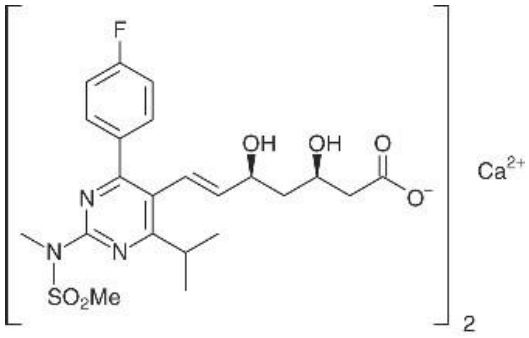
# 10 OVERDOSAGE

No specific antidotes for CRESTOR are known. Hemodialysis does not significantly enhance clearance of rosuvastatin. In the event of overdose, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

# 11 DESCRIPTION

CRESTOR (rosuvastatin) is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA)-reductase inhibitor.

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 1,001.14. 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.

CRESTOR tablets for oral use contain rosuvastatin 5 mg, 10 mg, 20 mg, or 40 mg (equivalent to 5.2mg, 10.4 mg, 20.8 mg, and 41.6 mg rosuvastatin calcium) and the following inactive ingredients:

**Tablet core**
Lactose monohydrate NF
Microcrystalline cellulose NF
Calcium phosphate
Crospovidone NF
Magnesium stearate NF
**Tablet coat**
Hypromellose NF
Glycerol Triacetin NF
Titanium dioxide USP (E171)
tribasic calcium phosphate NF
Ferric oxide, yellow (E172) (5 mg tablet)
Ferric oxide, red NF (E172) (10 mg, 20 mg and 40 mg tablets)

# 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

CRESTOR is an inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol.

## 12.2 Pharmacodynamics

Inhibition of HMG-CoA reductase by rosuvastatin accelerates the expression of LDL-receptors, followed by the uptake of LDL-C from blood to the liver, leading to a decrease in plasma LDL-C and total cholesterol. Sustained inhibition of cholesterol synthesis in the liver also decreases levels of very-low-density lipoproteins. The maximum LDL-C reduction of CRESTOR is usually achieved by 4 weeks and is maintained after that.

## 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%. The AUC of rosuvastatin does not differ following evening or morning drug administration.

*Effect of food*

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

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.

Elimination

*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%). After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route. The elimination half-life of rosuvastatin is approximately 19 hours.

Specific Populations

*Geriatric Patients*

There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥65 years).

*Pediatric Patients*

In a population pharmacokinetic analysis of two pediatric trials involving patients with HeFH 10 to 17 years of age and 8 to 17 years of age, respectively, rosuvastatin exposure appeared comparable to or lower than rosuvastatin exposure in adult patients.

*Male and Female Patients*

There were no differences in plasma concentrations of rosuvastatin between males and females.

*Racial or Ethnic Groups*

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among White, Hispanic or Latino ethnicity, 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 White control group.

*Patients with 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 $m^2$).

Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

*Patients with 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 Interaction Studies

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

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter organic anion-transporting polyprotein 1B1 (OATP1B1) and efflux transporter breast cancer resistance protein (BCRP). Concomitant administration of CRESTOR with medications that are inhibitors of these transporter proteins (e.g., cyclosporine, certain HIV protease inhibitors *[see Dosage and Administration (2.6) and Drug Interactions (7.1)]* and ticagrelor *[see Drug Interactions (7.1)]*) may result in increased rosuvastatin plasma concentrations.

**Table 8: Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure**

| **Coadministered drug and dosing regimen** | **Rosuvastatin** | | |
|---|---|---|---|
| | | **Mean Ratio (ratio with/without coadministered drug) No Effect=1.0** | |
| | **Dose (mg)[1]** | **Change in AUC** | **Change in $C_{max}$** |
| Sofosbuvir/velpatasvir/voxilaprevir (400 mg/100 mg/100 mg) + Voxilaprevir (100 mg) once daily for 15 days | 10 mg, single dose | 7.39[2] (6.68 to 8.18)[3] | 18.88[2] (16.23 to 21.96)[3] |
| Cyclosporine – stable dose required (75 mg – 200 mg BID) | 10 mg, QD for 10 days | 7.1[2] | 11[2] |
| Darolutamide 600 mg BID, 5 days | 5 mg, single dose | 5.2[2] | ~5[2] |
| Regorafenib 160 mg QD, 14 days | 5 mg, single dose | 3.8[2] | 4.6[2] |
| Atazanavir/ritonavir combination 300 mg/100 mg QD for 8 days | 10 mg | 3.1[2] | 7[2] |
| Simeprevir 150 mg QD, 7 days | 10 mg, single dose | 2.8[2] (2.3 to 3.4)[3] | 3.2[2] (2.6 to 3.9)[3] |
| Velpatasvir 100 mg once daily | 10 mg, single dose | 2.69[2] (2.46 to 2.94)[3] | 2.61[2] (2.32 to 2.92)[3] |
| Ombitasvir 25 mg/paritaprevir 150 mg/ ritonavir 100 mg + dasabuvir 400 mg BID | 5 mg, single dose | 2.59[2] (2.09 to 3.21)[3] | 7.13[2] (5.11 to 9.96)[3] |
| Teriflunomide | Not available | 2.51[2] | 2.65[2] |
| Enasidenib 100 mg QD, 28 days | 10 mg, single dose | 2.44 | 3.66 |
| Elbasvir 50 mg/grazoprevir 200 mg once daily | 10 mg, single dose | 2.26[2] (1.89 to 2.69)[3] | 5.49[2] (4.29 to 7.04)[3] |
| Glecaprevir 400 mg/pibrentasvir 120 mg once daily | 5 mg, once daily | 2.15[2] (1.88 to 2.46)[3] | 5.62[2] (4.80 to 6.59)[3] |
| Lopinavir/ritonavir combination 400 mg/100 mg BID for 17 days | 20 mg, QD for 7 days | 2.1[2] (1.7 to 2.6)[3] | 5[2] (3.4 to 6.4)[3] |
| Capmatinib 400 mg BID | 10 mg, single dose | 2.08[2] (1.56 to 2.76)[3] | 3.04[2] (2.36 to 3.92)[3] |
| Fostamatinib 100 mg BID | 20 mg, single dose | 1.96[2] (1.77 to 2.15)[3] | 1.88[2] (1.69 to 2.09)[3] |

**Table 8: Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure**

| **Coadministered drug and dosing regimen** | **Rosuvastatin** | | |
|---|---|---|---|
| | | **Mean Ratio (ratio with/without coadministered drug) No Effect=1.0** | |
| | **Dose (mg)[1]** | **Change in AUC** | **Change in $C_{max}$** |
| Febuxostat 120 mg QD for 4 days | 10 mg, single dose | 1.9[2] (1.5 to 2.5)[3] | 2.1[2] (1.8 to 2.6)[3] |
| Gemfibrozil 600 mg BID for 7 days | 80 mg | 1.9[2] (1.6 to 2.2)[3] | 2.2[2] (1.8 to 2.7)[3] |
| Tafamidis 61 mg BID on Days 1 & 2, followed by QD on Days 3 to 9 | 10 mg | 1.97[2] (1.68 to 2.31)[3] | 1.86[2] (1.59 to 2.16)[3] |
| Eltrombopag 75 mg QD, 5 days | 10 mg | 1.6 (1.4 to 1.7)[3] | 2 (1.8 to 2.3)[3] |
| Darunavir 600 mg/ritonavir 100 mg BID, 7 days | 10 mg, QD for 7 days | 1.5 (1.0 to 2.1)[3] | 2.4 (1.6 to 3.6)[3] |
| Tipranavir/ritonavir combination 500 mg/200 mg BID for 11 days | 10 mg | 1.4 (1.2 to 1.6)[3] | 2.2 (1.8 to 2.7)[3] |
| Dronedarone 400 mg BID | 10 mg | 1.4 | |
| Itraconazole 200 mg QD, 5 days | 10 mg or 80 mg | 1.4 (1.2 to 1.6)[3] 1.3 (1.1 to 1.4)[3] | 1.4 (1.2 to 1.5)[3] 1.2 (0.9 to 1.4)[3] |
| Ezetimibe 10 mg QD, 14 days | 10 mg, QD for 14 days | 1.2 (0.9 to 1.6)[3] | 1.2 (0.8 to 1.6)[3] |
| Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 days | 10 mg | 1.1 | 1.5 |
| Fenofibrate 67 mg TID for 7 days | 10 mg | ↔ | 1.2 (1.1 to 1.3)[3] |
| Rifampicin 450 mg QD, 7 days | 20 mg | ↔ | |
| Aluminum & magnesium hydroxide combination antacid Administered simultaneously Administered 2 hours apart | 40 mg 40 mg | 0.5[2] (0.4 to 0.5)[3] 0.8 (0.7 to 0.9)[3] | 0.5[2] (0.4 to 0.6)[3] 0.8 (0.7 to 1.0)[3] |
| Ketoconazole 200 mg BID for 7 days | 80 mg | 1.0 (0.8 to 1.2)[3] | 1.0 (0.7 to 1.3)[3] |
| Fluconazole 200 mg QD for 11 days | 80 mg | 1.1 (1.0 to 1.3)[3] | 1.1 (0.9 to 1.4)[3] |

**Table 8: Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure**

| **Coadministered drug and dosing regimen** | **Rosuvastatin** | | |
|---|---|---|---|
| | | **Mean Ratio (ratio with/without coadministered drug) No Effect=1.0** | |
| | **Dose (mg)**[1] | **Change in AUC** | **Change in $C_{max}$** |
| Erythromycin 500 mg QID for 7 days | 80 mg | 0.8 (0.7 to 0.9)[3] | 0.7 (0.5 to 0.9)[3] |
| Clopidogrel 300 mg loading, followed by 75 mg at 24 hours | 20 mg, single dose | 2 (1.35-3.01) | 2 (1.14-2.84) |

QD= Once daily, BID= Twice daily, TID= Three times daily, QID= Four times daily
[1] Single dose unless otherwise noted.
[2] Clinically significant *[see Dosage and Administration (2) and Warnings and Precautions (5)]*
[3] Mean ratio with 90% CI (with/without coadministered drug, e.g., 1= no change, 0.7 = 30% decrease, 11=11-fold increase in exposure)

**Table 9: Effect of Rosuvastatin Coadministration on Systemic Exposure to Other Drugs**

| **Rosuvastatin Dosage Regimen** | **Coadministered Drug** | | |
|---|---|---|---|
| | | **Mean Ratio (ratio with/without coadministered drug) No Effect=1.0** | |
| | **Name and Dose** | **Change in AUC** | **Change in $C_{max}$** |
| 40 mg QD for 10 days | Warfarin[1] 25 mg single dose | R- Warfarin 1.0 (1.0 to 1.1)[2] S-Warfarin 1.1 (1.0 to 1.1)[2] | R-Warfarin 1.0 (0.9 to 1.0)[2] S-Warfarin 1.0 (0.9 to 1.1)[2] |
| 40 mg QD for 12 days | Digoxin 0.5 mg single dose | 1.0 (0.9 to 1.2)[2] | 1.0 (0.9 to 1.2)[2] |
| 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 1.3 (1.2 to 1.3)[2] NG 1.3 (1.3 to 1.4)[2] | EE 1.3 (1.2 to 1.3)[2] NG 1.2 (1.1 to 1.3)[2] |

**Table 9: Effect of Rosuvastatin Coadministration on Systemic Exposure to Other Drugs**

| **Rosuvastatin Dosage Regimen** | **Coadministered Drug** | | |
|---|---|---|---|
| | | **Mean Ratio (ratio with/without coadministered drug) No Effect=1.0** | |
| | **Name and Dose** | **Change in AUC** | **Change in $C_{max}$** |

EE = ethinyl estradiol, NG = norgestrel, QD= Once daily

[1] Clinically significant pharmacodynamic effects *[see Drug Interactions (7.3)]*

[2] Mean ratio with 90% CI (with/without coadministered drug, e.g., 1= no change, 0.7=30% decrease, 11=11-fold increase in exposure)

## 12.5 Pharmacogenomics

Disposition of rosuvastatin, involves OATP1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1 (*SLCO1B1* 521T > C). The frequency of this genotype (i.e., *SLCO1B1* 521 C/C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on efficacy and/or safety of CRESTOR has not been clearly established.

# 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, or 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.

# 14 CLINICAL STUDIES

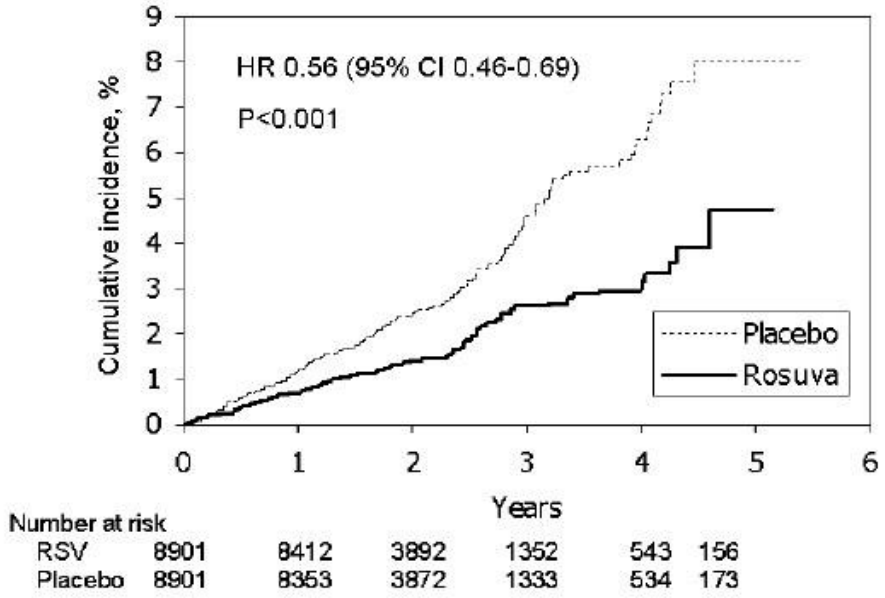
## Primary Prevention of CV Disease

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of CRESTOR on the occurrence of major CV disease events was assessed in 17,802 males (≥50 years) and females (≥60 years) who had no clinically evident CV disease, LDL-C levels <130 mg/dL and hsCRP 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%). Patients had a median baseline LDL-C of 108 mg/dL and hsCRP of 4.3 mg/L. Patients were randomly assigned to placebo (n=8901) or CRESTOR 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 CRESTOR-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.

CRESTOR 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 1). 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 1. Time to First Occurrence of Major CV Events in JUPITER**

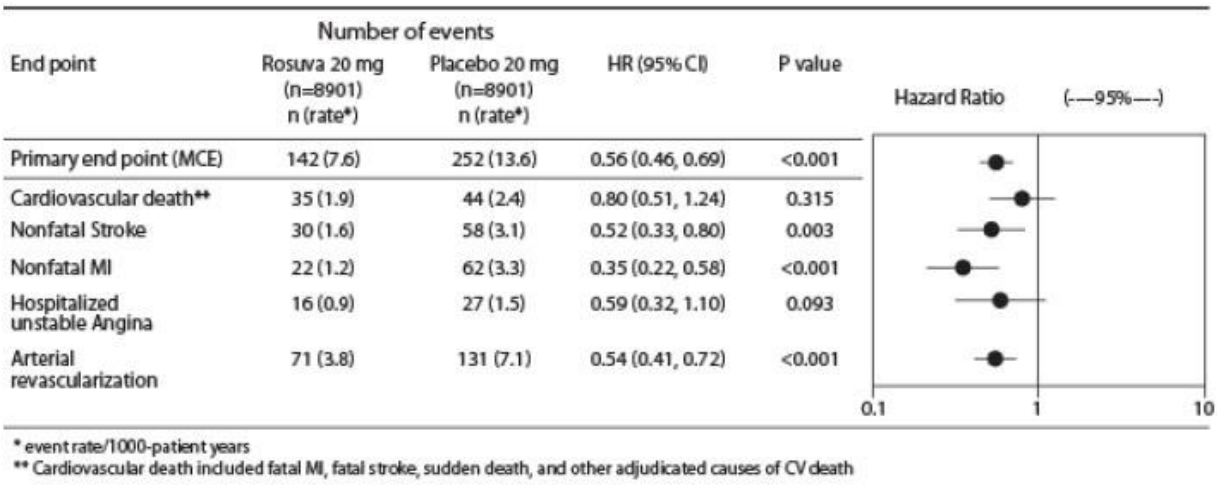



The individual components of the primary end point are presented in Figure 3. CRESTOR significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the CRESTOR and placebo groups for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

CRESTOR 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 CRESTOR-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 CRESTOR-treated subjects).

In a post-hoc subgroup analysis of JUPITER subjects (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 CRESTOR treatment.

**Figure 2. Major CV Events by Treatment Group in JUPITER**




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

## Primary Hyperlipidemia in Adults

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

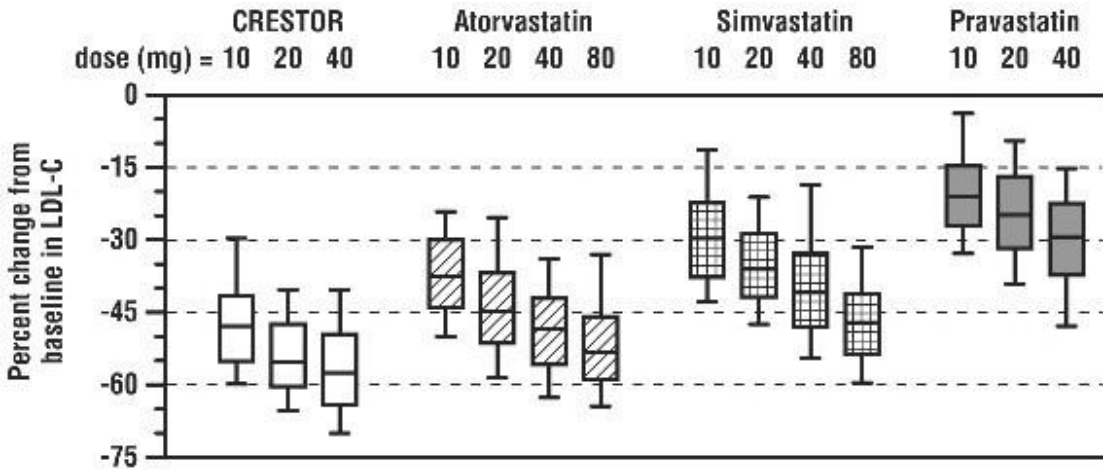
In a multicenter, double-blind, placebo-controlled study in patients with hyperlipidemia, CRESTOR given as a single daily dose (5 to 40 mg) for 6 weeks significantly reduced Total-C, LDL-C, non-HDL-C, and ApoB, across the dose range (Table 10).

**Table 10: Lipid-Modifying Effect of CRESTOR in Adult 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 |

CRESTOR was compared with the statins (atorvastatin, simvastatin, and pravastatin) in a multicenter, open-label, dose-ranging study of 2,240 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 (see Figure 3 and Table 11).

**Figure 3. Percent LDL-C Change by Dose of CRESTOR, Atorvastatin, Simvastatin, and Pravastatin at Week 6 in Adult 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 11: Percent Change in LDL-C by Dose of CRESTOR, Atorvastatin, Simvastatin, and Pravastatin From Baseline to Week 6 (LS Mean[1]) in Adult Patients with Hyperlipidemia or Mixed Dyslipidemia (Sample Sizes Ranging from 156–167 Patients Per Group)**

| | **Treatment Daily Dose** | | | |
|---|---|---|---|---|
| **Treatment** | **10 mg** | **20 mg** | **40 mg** | **80 mg** |
| CRESTOR | -46[2] | -52[3] | -55[4] | --- |
| Atorvastatin | -37 | -43 | -48 | -51 |
| Simvastatin | -28 | -35 | -39 | -46 |
| Pravastatin | -20 | -24 | -30 | --- |

[1] Corresponding standard errors are approximately 1.00.
[2] 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. ($p<0.002$)
[3] 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. ($p<0.002$)
[4] CRESTOR 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg, and 80 mg. ($p<0.002$)

## 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 adult 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.

## HeFH in Adults

In a study of adult patients with HeFH (baseline mean LDL of 291 mg/dL), patients were randomized to CRESTOR 20 mg or atorvastatin 20 mg. The dose was increased at 6-week intervals. Significant LDL-C reductions from baseline were seen at each dose in both treatment groups (see Table 12).

**Table 12: LDL-C Percent Change from Baseline**

| | | **CRESTOR (n=435) LS Mean[1] (95% CI)** | **Atorvastatin (n=187) LS Mean[1] (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%) |

[1] LS Means are least square means adjusted for baseline LDL-C

## HeFH in Pediatric Patients

In a double-blind, randomized, multicenter, placebo-controlled, 12-week study, 176 (97 male and 79 female) pediatric patients with HeFH were randomized to rosuvastatin 5 mg, 10 mg 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 13 below.

**Table 13: Lipid-Modifying Effects of CRESTOR in Pediatric Patients 10 to 17 years of Age with HeFH (Least-Squares Mean Percent Change from Baseline To Week 12)**

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

[1] Median percent change
[2] Difference from placebo not statistically significant

Rosuvastatin was also studied in a two-year open-label, uncontrolled, titration-to-goal trial that included 175 pediatric patients with HeFH who were 8 to 17 years old (79 males and 96 females). All patients had a documented genetic defect in the LDL receptor or in ApoB. Approximately 89% were White, 7% were Asian, 1% were Black or African American, and fewer than 1% were Hispanic or Latino ethnicity. Mean LDL-C at baseline was 236 mg/dL. Fifty-eight (33%) patients were prepubertal at baseline. The starting rosuvastatin dosage for all pediatric patients was 5 mg once daily. Pediatric patients aged 8 to less than 10 years (n=41 at baseline) could titrate to a maximum dosage of 10 mg once daily, and pediatric patients aged 10 to 17 years could titrate to a maximum dosage of 20 mg once daily.

The reductions in LDL-C from baseline were generally consistent across age groups within the trial as well as with previous experience in both adult and pediatric controlled trials.

## HoFH in Adult and Pediatric Patients

In an open-label, forced-titration study, HoFH 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-C 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.

## HoFH in Pediatric Patients

CRESTOR was studied in a randomized, double-blind, placebo-controlled, multicenter, cross-over study in 14 pediatric patients with HoFH. The study included a 4-week dietary lead-in phase during which patients received CRESTOR 10 mg daily, a cross-over phase that included two 6-week treatment periods with either CRESTOR 20 mg or placebo in random order, followed by a 12-week open-label phase during which all patients received CRESTOR 20 mg. Patients ranged in age from 7 to 15 years of age (median 11 years), 50% were male, 71% were White, 21% were Asian, 7% were Black or African American, and no patients were of Hispanic or Latino ethnicity. Fifty percent were on apheresis therapy and 57% were taking ezetimibe. Patients who entered the study on apheresis therapy or ezetimibe continued the treatment throughout the entire study. Mean LDL-C at baseline was 416 mg/dL (range 152 to 716 mg/dL). A total of 13 patients completed both treatment periods of the randomized cross-over phase; one patient withdrew consent due to inability to have blood drawn during the cross-over phase.

CRESTOR 20 mg significantly reduced LDL-C, total cholesterol, ApoB, and non-HDL-C compared to placebo (see Table 14).

**Table 14: Lipid-Modifying Effects of CRESTOR in Pediatric Patients 7 to 15 years of Age with HoFH After 6 Weeks**

| | Placebo (N=13) | CRESTOR 20 mg (N=13) | Percent difference (95% CI) |
|---|---|---|---|
| LDL-C (mg/dL) | 481 | 396 | -22.3% (-33.5, -9.1)[1] |
| Total-C (mg/dL) | 539 | 448 | -20.1% (-29.7, -9.1)[2] |
| Non-HDL-C (mg/dL) | 505 | 412 | -22.9% (-33.7, -10.3)[2] |
| ApoB (mg/dL) | 268 | 235 | -17.1% (-29.2, -2.9)[3] |

% Difference estimates are based on transformations of the estimated mean difference in log LDL measurements between CRESTOR and placebo using a mixed model adjusted for study period
[1] p=0.005, [2] p=0.003, [3] p=0.024

## Primary Dysbetalipoproteinemia in Adults

In a randomized, multicenter, double-blind cross-over study, 32 adult patients (27 with ϵ2/ϵ2 and 4 with apo E mutation [Arg145Cys] with primary dysbetalipoproteinemia 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 for 6 weeks each: rosuvastatin 10 mg followed by rosuvastatin 20 mg or rosuvastatin 20 mg followed by rosuvastatin 10 mg. CRESTOR reduced non-HDL-C (primary end point) and circulating remnant lipoprotein levels. Results are shown in the table below.

**Table 15: Lipid-Modifying Effects of CRESTOR 10 mg and 20 mg in Adult Patients with 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<br>(-46.9, - 37.5) | -47.6<br>(-51.6, -42.8) |
| Triglycerides | 503.5 | -40.1<br>(-44.9, -33.6) | -43.0<br>(-52.5, -33.1) |
| Non-HDL-C | 294.5 | -48.2<br>(-56.7, -45.6) | -56.4<br>(-61.4, -48.5) |
| VLDL-C + IDL-C | 209.5 | -46.8<br>(-53.7, -39.4) | -56.2<br>(-67.7, -43.7) |
| LDL-C | 112.5 | -54.4<br>(-59.1, -47.3) | -57.3<br>(-59.4, -52.1) |
| HDL-C | 35.5 | 10.2<br>(1.9, 12.3) | 11.2<br>(8.3, 20.5) |
| RLP-C | 82.0 | -56.4<br>(-67.1, -49.0) | -64.9<br>(-74.0, -56.6) |
| Apo-E | 16.0 | -42.9<br>(-46.3, -33.3) | -42.5<br>(-47.1, -35.6) |

## Hypertriglyceridemia in Adults

In a double-blind, placebo-controlled study in adult 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 (see Table 16).

**Table 16: Lipid-Modifying Effect of CRESTOR in Adult Patients with Primary Hypertriglyceridemia After Six Weeks by Median (Min, Max) Percent Change from Baseline to Week 6**

| 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) |
| Non-HDL-C | 2 (-13, 19) | -29 (-43, -8) | -49 (-59, -20) | -43 (-74, 12) | -51 (-62, -6) |
| 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) |

# 16 HOW SUPPLIED/STORAGE AND HANDLING

CRESTOR tablets are supplied as :

5mg: Carton box containing (Aluminum foil strip, soft, mat/dull side lacquer laminated against OPA-film, Bright side Aluminum lacquer laminated against PVC-film) strip of 7 film coated tablets and an inner leaflet.

10mg: Carton box containing (Al/Al) blisters, each of 7 film-coated tablets and an inner leaflet.

20mg: Carton box containing (Al/Al) blisters, each of 7 film-coated tablets and an inner leaflet.

For number of blisters see outer pack

**Storage**

Do not store above 30ºC . Protect from moisture .

shelf life: see outer pack

# 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

*Myopathy and Rhabdomyolysis*

Advise patients that CRESTOR may cause myopathy and rhabdomyolysis. Inform patients that the risk is also increased when taking certain types of medication and they should discuss all medication, both prescription and over-the-counter, with their healthcare provider. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever *[see Warnings and Precautions (5.1), and Drug Interactions (7.1)]*.

*Hepatic Dysfunction*

Inform patients that CRESTOR may cause liver enzyme elevations and possibly liver failure. Advise patients to promptly report fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice *[see Warnings and Precautions (5.3)]*.

*Increases in HbA1c and Fasting Serum Glucose Levels*

Inform patients that increases in HbA1c and fasting serum glucose levels may occur with CRESTOR. Encourage patients to optimize lifestyle measures, including regular exercise,

maintaining a healthy body weight, and making healthy food choices *[see Warnings and Precautions (5.5)]*.

*Pregnancy*

Advise pregnant patients and patients who can become pregnant of the potential risk to a fetus. Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if CRESTOR should be discontinued *[see Use in Specific Populations (8.1)]*.

*Lactation*

Advise patients that breastfeeding during treatment with CRESTOR is not recommended *[see Use in Specific Populations (8.2)]*.

*Concomitant Use of Antacids*

When taking CRESTOR with an aluminum and magnesium hydroxide combination antacid, administer CRESTOR at least 2 hours before the antacid *[see Drug Interactions (7.2)]*.

*Missed Doses*

If a dose is missed, advise patients not to take an extra dose. Just resume the usual schedule *[see Dosage and Administration (2.1)]*.



AstraZeneca UK Limited, Macclesfield, Cheshire, United Kingdom.

Manufactured by IPR Pharmaceuticals Inc. Puerto Rico.

## 18 DATE OF TEXT REVISION

07/2024

**معلومات للمريض:**
كريستور
روزيوفاستاتين 5،10،20 مجم
أقراص مغلفة للاستخدام عن طريق الفم

يُرجى قراءة معلومات المريض هذه بعناية قبل البدء في تناول عقار كريستور وكل مرة يُعاد فيها صرف الدَّواء لك. إذا كانت لديك أية أسئلة حول عقار كريستور، استشر مقدم الرعاية الصحية. يُعد مقدم الرعاية الصحيةهو الشخص الوحيد القادر على تحديد ما إذا كان عقار كريستور مناسبًا لك أم لا.

**ما هو عقار كريستور؟**

يُعد عقار كريستور دواءً وصفيًّا يحتوي على دواء مخفض للكوليسترول يُدعى روزيوفاستاتين.

- يُستخدم عقار كريستور في الحالات الآتية:
  - لتقليل خطرحدوث أحداث قلبية وعائية ضارة كبرى، ، مثل الوفاة بسبب أمراض القلب والأوعية الدموية، والنوبة القلبية، الإصابة بالسكتة الدماغية، والحاجة إلى إجراءات لتحسين تدفق الدم إلى القلب يسمى إعادة تكوين الأوعية الدموية الشريانية عند البالغين الذين ليس لديهم مرض بالقلب -معروف ولكن لديهم بعض عوامل الخطر الإضافية.
- يستخدم كريستور مع النظام الغذائي من أجل:
  - خفض مستوى البروتين الدهني منخفض الكثافة (LDL-C) الكولسترول أو "الضار" الكوليسترول لدى البالغين الذين يعانون من فرط شحميات الدم الأولي.
  - إبطاء تراكم الرواسب الدهنية (**لُوَيحَةُ** ) في جدران الأوعية الدموية.
  - علاج البالغين والأطفال بعمر 8 سنوات فيما فوق الذين يعانون من ارتفاع نسبة الكوليسترول في الدم بسبب فرط كوليستيرول الدم العائلي المتغاير الزيجوت (HeFH) (حالة وراثية تسبب مستويات عالية من الكولسترول منخفض الكثافة (LDL -C)).
  - مع علاجات خفض الكولسترول الأخرى أو بمفردها إذا كانت هذه العلاجات موجودة غير متوفر لدى البالغين والأطفال بعمر 7 سنوات فيما فوق والمصابين بعائلي متماثل الزيجوت فرط كوليستيرول الدم(HoFH) (حالة وراثية تسبب مستويات عالية من الكولسترول منخفض الكثافة LDL-C).
  - علاج البالغين الذين يعانون من نوع من ارتفاع الكوليسترول يسمى شُذُوْذُ البروتِينِ الشَّحْمِيّ البيتا فِي الدَّم الأولى (النوع الثالث فرط بروتينات الدم الشَّحْمِيَّة).
  - بالإضافة إلى النظام الغذائي لعلاج البالغين من خلال:
  - فقر الدم الأولي المصحوب بالبروتينات (حالة وراثية تسبب إرتفاع مستويات الكوليسترول والدهون)
  - ارتفاع الدهون الثلاثية

لم يتم إثبات سلامة وفعالية كريستور لدى الأطفال الأصغر من 8 سنوات من العمر مع فرط كوليسترول الدم العائلي المتغاير الزيجوت أو الأطفال الذين تقل أعمارهم عن 7 سنوات مصابين بفرط كوليستيرول الدم العائلي المتماثل الزيجوت أو عند الأطفال الذين يعانون من أنواع أخرى منالكولسترول فرط شحميات الدم (بخلاف فرط كوليسترول الدم العائلي المتغاير الزيجوت HeFH أو فرط كوليستيرول الدم العائلي المتماثل الزيجوت HoFH).

**لا تتناول عقار كريستور في الحالات التالية:**

- اذا كان لديك مشاكل بالكبد
- إذا كنت تعاني من حساسية تجاه روزيوفاستاتين أو تجاه أي من المكونات الأخرى بعقار كريستور. انظر نهاية هذه النَّشرة؛ لمعرفة القائمة الكاملة لمكونات عقار كريستور.
- الرضاعة الطبيعية يمكن لأدوية مثل عقار كريستور أن تصل إلى اللبن لديكِ وقد تضر طفلكِ.

المرضى الذين يعانون من مشاكل وراثية نادرة من عدم تحمل الجالاكتوز، ونقص اللاب لاكتاز أو سوء امتصاص الجلوكوز والجالاكتوز لا ينبغي أن يأخذ هذا الدواء.

**قبل أن تأخذ كريستور ، أخبر الطبيب الخاص بك عن جميع حالاتك الطبية، بما في ذلك:**

- إذا كنت تعاني من أوجاع أو ضعف غير مبرر بالعضلات.
- إذا كنت تعاني أو قد عانيت من مشاكل بالكُلى.
- إذا كنت تعاني أو قد عانيت من مشاكل بالكبد.
- إذا كنت تشرب أكثر من كوبين من الكحوليات يوميًّا.
- إذا كنت تعاني من مشاكل في الغدة الدَّرقية.
- المرضى من أصول آسيوية
- إذا كنتِ حاملًا، أو تعتقدين أنكِ قد تكونين حاملًا أو تخططين للحمل. إذا أصبحت حاملاً أثناء تناول كريستور، فاتصل بمقدم الرعاية الصحية الخاص بك على الفور لمناقشة علاج كريستور الخاص بك.
- إذا كنت ترضعين طفلك رضاعة طبيعية، يمكن أن ينتقل كريستور إلى حليب الثدي وقد يضر طفلك. تحدثي مع مقدم الرعاية الصحية الخاص بك حول أفضل طريقة لإطعام طفلك إذا كنت تتناولين كريستور. لا يوصى بالرضاعة الطبيعية أثناء تناول كريستور *تحدث إلى طبيبك أو الصيدلي قبل تناول كريستور إذا:*

*كنت تعاني أو عانيت من الوهن العضلي (مرض يسبب ضعف عام في العضلات بما في ذلك في بعض الحالات العضلات المستخدمة عند التنفس)، أو الوهن العضلي البصري (مرض يسبب ضعف عضلات العين) لأن الستاتينات قد تؤدي في بعض الأحيان إلى تفاقم الحالة أو تؤدي إلى حدوث الوهن العضلي (انظر القسم 4)*

أخبر مقدم الرعاية الصحية الخاص بك عن جميع الأدوية التي تتناولها، بما في ذلك الأدوية التي تستلزم وصفة طبية والأدوية المتاحة دون وصفة طبية والفيتامينات والمكملات العشبية. أخبر مقدم الرعاية الصحية الذي يصف لك كريستور إذا قام مقدم رعاية صحية آخر بزيادة جرعة دواء آخر تتناوله. قد يؤثر كريستور على طريقة عمل الأدوية الأخرى، وقد تؤثر الأدوية الأخرى على طريقة عمل كريستور.

- على وجه الخصوص، أخبر طبيبك إذا كنت تتناول:
- مضادات التخثر التي تحتوي على الكومارين (أدوية تمنع تجلط الدم، مثل الوارفارين)
- مضادات الحموضة (الأدوية التي تتناولها لعلاج حرقة المعدة والتي تحتوي على هيدروكسيد الألومنيوم والمغنيسيوم)
- قد يؤدي تناول كريستور مع بعض الأدوية إلى زيادة خطر الإصابة بمشاكل العضلات
- على وجه الخصوص، أخبر طبيبك إذا كنت تتناول:
- سيكلوسبورين (دواء لجهازك المناعي).
- تيريفلونوميد (دواء يستخدم لعلاج التصلب المتعدد الانتكاسي المتكرر)
- إيناسيدينيب (دواء يستخدم لعلاج الحالات الحادة لسرطان الدم النخاعي)
- كابماتينيب (دواء لعلاج سرطان الرئة ذو الخلايا غير الصغيرة)
- فوستاماتينيب (دواء يستخدم لعلاج انخفاض عدد الصفائح الدموية)
- فيبوكسوستات (دواء يستخدم لعلاج ومنع ارتفاع مستويات حمض البوليك في الدم)
- جيمفيبروزيل (هو دواء حمض الفيبريك لخفض الكوليسترول)
- تافاميديس [يستخدم لعلاج اعتلال عضلة القلب (تضخم وزيادة سمك عضلة القلب)]
- كلوبيدوجريل
- الأدوية المضادة للفيروسات بما في ذلك فيروس نقص المناعة البشرية أو مثبطات بروتياز التهاب الكبد من النوع "سي" (مثل: لوبينافير، ريتونافير، فوسامبرينافير، تيبرانافير، أتازانافير أو سيمبريفير).

مزيج من:
سوفوسبوفير/فيلباتاسفير/فوكسيلابريفير
داسابوفير/أومبيتاسفير/باريتبريفير/ريتونافير
إلباسفير/غرايزوبريفير
سوفوسبوفير/فيلباتاسفير
جليسابريفير/ بيبرانتاسفير , و
جميع التركيزات الأخرى مع : لديبسفير/ سوفوسبفير

- دارلوتاميد (دواء لعلاج سرطان البروستاتا)
- ريجورافنيب (دواء يستخدم لعلاج سرطان القولون والمستقيم)
- مشتقات حمض الفيبريك (مثل الفينوفايبرات)
- تيكاجريلور (يساعد على تقليل فرصة تكوين جلطة دموية يمكن أن تسد الأوعية الدموية)
- نياسين أو حمض النيكوتينيك
- كُولْشيسين (دواء يستخدم لعلاج النقرس).
- المضادات الحيوية التي تحتوي على حمْض الفُوسيديك.
- قد يؤثر تيكاجريلور على إفراز الكلى للروسوفاستاتين، مما يزيد من خطر تراكم روسوفاستاتين .على الرغم من أن الآلية ا لدقيقة غير معروفة، فقد أدى الاستخدام المصاحب للتيكاجريلور والروسوفاستاتين في بعض الحالات إلى انخفاض وظيفة الكلى وزيادة مستوى انزيم سي بي كي وانحلال الربيدات.

اطلب قائمة بهذه الأدوية من طبيبك أو الصيدلي الخاص بك إذا لم تكن متأكدًا.
كن على دراية بالأدوية التي تتناولها. احتفظ بقائمة بتلك الأدوية لتريها لطبيبك والصيدلي عند وصف دواء جديد لك.

**كيفية تناول عقار كريستور**

- تناول عقار كريستور بالضبط كما أخبر طبيبك.
- تناول عقار كريستور، عن طريق الفم، مرة واحدة كل يوم ، مع أو بدون طعام ابتلع القرص كاملًا.
- يمكن تناول عقار كريستور في أي وقت من اليوم، مع أو بدون طعام.
- **لا** تغير جرعتك أو تتوقف عن تناول عقار كريستور دون التَّحدث إلى طبيبك حتى وإن كنت تشعر بتحسن.
- قد يجري طبيبك اختبارات لك بالدَّم لفحص مستويات الكوليسترول قبل وأثناء العلاج بعقار كريستور. قد يغير طبيبك جرعتك من عقار كريستور إذا لزم الأمر.
- أثناء تناول عقار كريستور ، استمر في اتباع نظامك الغذائي الخافض للكوليسترول وممارسة التمارين الرياضية وفقًا لما أخبرك به مقدم الرعاية الصحية الخاص بك.
- إذا كنت تتناول دواء يسمى مضاد للحموضة والذي يحتوي على مزيج من هيدروكسيد الألومنيوم والمغنيسيوم، تناول كريستور قبل ساعتين على الأقل من تناول مضاد الحموضة.
- إذا أغفلت تناول إحدى جرعات عقار كريستور، تناول الجرعة التالية في الوقت المحدد لها بمجرد أن تتذكر لا تأخذ جرعة إضافية من جرعات كريستور. إذا تناولت كمية كبيرة جدًّا من عقار كريستور أو تناولت جرعة زائدة، فاتصل بطبيبك أو اذهب إلى غرفة الطوارئ بأقرب مستشفى لك فورًا.

ما الآثار الجانبية المُحتمَلة لعقار كريستور؟

إذا واجهت أيًا من الاثار أو االاعراض الجانبية الخطيرة التالية ، فتوقف عن تناول الدواء الخاص بك وأخبر طبيبك على الفور أو اذهب إلى أقرب مستشفى وقسم الطوارىء

**قد يسبب عقار كريستور آثارًا جانبية خطيرة، بما في ذلك:**

- **آلام أو أوجاع أو ضعف بالعضلات (اعتلال عضلي).** قد تكون المشاكل العضلية، بما في ذلك تحلل العضلات، خطيرة لدى بعض الأشخاص ونادرًا ما تسبب تلفًا بالكُلى الذى قد يُؤدي إلى الوفاة. أخبر طبيبك على الفور إذا حدث الآتي:

o **إذا كنت تعاني من آلام أو أوجاع أو ضعف بالعضلات غير مبررة خاصةً إذا كنت مصابًا بحمى أو كنت تشعر بإرهاق أكثر من المعتاد، عند تناولك لعقار كريستور.**

o إذا كنت تعاني من مشاكل عضلية لا تزول حتى بعدما أخبرك طبيبك بالتَّوقف عن تناول عقار كريستور. قد يجري طبيبك اختبارات أو فحوصات إضافية لتشخيص سبب المشاكل العضلية لديك.

o تلون البول باللون الاحمر

ترتفع فرص إصابتك بمشاكل عضلية في الحالات الآتية:

o إذا كنت تتناول بعض الأدوية الأخرى أثناء تناولك عقار كريستور (راجع "أخبر مقدم الرعاية الصحية الخاص بك بشكل خاص إذا كنت تتناول")

o المرضى الذين تبلغ أعمارهم 65 عامًا فأكثر

o من أصل آسيوي

o إذا كنت تعاني من مشاكل في الغدة الدَّرقية (قصور بالغدة الدَّرقية) غير متحكم بها.

o إذا كان لديك مشاكل بالكلى.

o إذا كنت تتناول جرعات مرتفعة من عقار كريستور.

- **مشاكل بالكبد.** قد يقوم طبيبك بإجراء فحوصات الدم لفحص الكبد قبل البدء بتناول عقار كريستوروالتَّحقق مما إذا كان لديك أي أعراض لمشاكل في الكبد أثناء تناولك عقار كريستور أم لا. اتصل بطبيبك فورًا إذا أُصِبت بأيّ من الأعراض التَّالية لمشاكل الكبد:

o شعور غير معتاد بالتَّعب أو الضعف.

o فقدان الشهية.

o ألم في الجزء العلوي من البطن.

o بول داكن.

o اصفرار جلدك أو بياض عينيك.

- البروتين والدم في البول. قد يسبب كريستور وجود بروتين ودم في البول. إذا ظهر لديك بروتين أو دم في البول، فقد يقلل طبيبك جرعتك من كريستور.

o زيادة مستويات السكر في الدم (الجلوكوز). قد يسبب كريستور زيادة في مستويات السكر في الدم.

تم أيضًا الإبلاغ عن الآثار الجانبية التالية ولكن لا يمكن تقدير معدل تكرارها من خلال المعلومات المتاحة (شيوعها غير معروف):

- الوهن العضلي الوبيل (مرض يسبب ضعف عام في العضلات بما في ذلك في بعض الحالات العضلات المستخدمة عند التنفس).
- الوهن العضلي العيني (مرض يسبب ضعف عضلات العين). تحدث إلى طبيبك إذا كنت تعاني من ضعف في ذراعيك أو ساقيك والذي يتفاقم بعد فترات من النشاط، أو الرؤية المزدوجة أو تدلي الجفون، أو صعوبة في البلع، أو ضيق في التنفس.

**قد تتضمن الآثار الجانبية الأكثر شيوعًا الآتي:** صداعًا، غثياناً ،أوجاعًا أو آلامًا بالعضلات، ، ضعفًاو امساك .
أخبر طبيبك إذا كان لديك أي آثار جانبية تزعجك أو لا تزول.

لمزيد من المعلومات، يُرجى استشارة طبيبك أو الصيدلي الخاص بك.

اطلب المشورة الطبية من طبيبك بشأن الآثار الجانبية.

الإبلاغ عن الآثار الجانبية

- يُعد من الهام الإبلاغ عن الآثار الجانبية المُشتبَه بها بعد ترخيص المُنتَج الدوائي. فهو يسمح بالمراقبة المستمرة لتوازن فوائد ومخاطر المُنتَج الدَّوائي. يُطلب من متخصصي الرعاية الصحية الإبلاغ عن أي آثار جانبية مُشتَبه بها من خلال جهات الاتصال التالية الخاصة بمركز اليقظة الدوائية المصري:

- البريد الإلكتروني المُخَصص للإبلاغ: pv.followup@edaegypt.gov.eg
- الموقع الإلكتروني المُخَصص للإبلاغ: www.edaegypt.gov.eg
- الخط الساخن: 15301
- امسح رمز الاستجابة السريعة (QR code):

SCAN ME

- أو عبر البريد الإلكتروني لشركة أسترازينيكا المُخَصص لسلامة المرضى:
- patient.safetyegypt@astrazeneca.com
- أو عبر الرابط التَّالي:
- https://contactazmedical.astrazeneca.com/content/astrazeneca-champion/eg/en/amp-form.html

**كيف يجب عليّ تخزين عقار كريستور؟**

- لا يُخزَّن في درجة حرارة تتعدى 30 درجة مئوية في مكان جاف.

**يحفظ عقار كريستور وجميع الأدوية بعيدًا عن متناول الأطفال.**

مدة الصلاحية :أنظر العبوة الخارجية

**معلومات عامَّة حول أمان وفعالية استخدام عقار كريستور**

أحيانًا يتم وصف الأدوية لأغراض أخرى غير تلك المدرجة في نشرة معلومات المريض. لا تستخدم عقار كريستور لحالة لم يتم وصفه لها. لا تعط عقار كريستور لأشخاص آخرين، حتى وإن كانوا يُعانون من الحالة الطبية نفسها التي تُعاني أنت منها؛ فقد يضر بهم.

يمكنك طلب المزيد من المعلومات حول عقار كريستور المكتوبة من أجل أخصائيي الرعاية من الصيدلي أو الطبيب.

ما هي المكونات في كريستور؟

**المادة الفعالة:** رسيوفاستاتين في هيئة رسيوفاستاتين الكالسيوم

أقراص كريستور:

رسيوفاستاتين الكالسيوم 5.2ملجم مكافئ لروسوفاستاتين 5 ملجم: مستدير، أصفر ثنائي الفوسفات، قرص مغلف بفيلم، مغطى ب 'ZD4522' و'5' على جانب واحد وواضح على الجانب الآخر

رسيوفاستاتين الكالسيوم10.4 ملجم مكافئ لروسوفاستاتين 10 ملجم: قرص مستدير وردي اللون مغلف بالأفلام ثنائيي اللون، مغلف ب 'ZD4522' و '10' على جانب واحد وواضح على الجانب الآخر

رسيوفاستاتين الكالسيوم20.4 ملجم مكافئ لروسوفاستاتين 20 ملجم: قرص مستدير وردي اللون مغلف بالأفلام ثنائيي اللون، مغلف ب 'ZD4522' و '20' على جانب واحد وواضح على الجانب الآخر

لا يتم تسويق جميع التركيزات

*المواد غير الفعالة:*

لاكتوز أحادي التميؤ
سليلوز دقيق التَّبلور
فوسفات الكالسيوم
كروسبوفيدون
ستيرات الماغنسيوم
هيبروميلوز
ثلاثي أسيتات الجليسرول
ثاني أكسيد التيتانيوم
أكسيد الحديد الأصفر(كريستور 5 مجم)
أكسيد الحديد الأحمر (كريستور 10 مجم و20 مجم )

يتم توفير أقراص كريستور على النحو التالي:

5 ملجم: صندوق الكرتون الذي يحتوي على (شريط من رقائق الألومنيوم، وطلاء جانبي ناعم، وسجاجي/قاتم مصقول مصنوع من الألومنيوم، وطلاء مصنوع من الألومنيوم الساطع مصنوع من الألومنيوم مصنوع من مادة البولي فينيل كلورايد) من 7 أقراص مغطاة بالأفلام وورق داخلي.

10 ملجم: صندوق الكرتون الذي يحتوي على شرائط (ألومنيوم/ألومنيوم )، وكل منها من 7 أقراص مغطاة بالأفلام وورقة داخلية.

20 ملجم: صندوق الكرتون الذي يحتوي على شرائط (ألومنيوم/ألومنيوم )، وكل منها من 7 أقراص مغطاة بالأفلام وورقة داخلية.

لعدد الشرائط أنظر العبوة الخارجية

قد لا تتوافر جميع التركيزات بالأسواق.

تم التَّصنيع بواسطة :
شركة آي .بي .آر. للأدوية. بورتو ريكو.

تم اخر مراجعة لهذه النشره بتاريخ 7-2024