2. Reid JL. Rilmenidine: a clinical overview. *Am J Hypertens* 2000; **13:** 106S–111S.
3. Reid JL. Update on rilmenidine: clinical benefits. *Am J Hypertens* 2001; **14:** 322S–324S.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Hyperium; ***Austria:*** Iterium; ***Braz.:*** Hyperium; ***Cz.:*** Albarel; Tenaxum; ***Fr.:*** Hyperium; ***Hong Kong:*** Iperdix; ***Hung.:*** Hyperlex; Tenaxum; ***Philipp.:*** Hyperdix; ***Pol.:*** Tenaxum; ***Port.:*** Hyperium; ***Rus.:*** Albarel (Альбарел); ***Thai.:*** Hyperdix; ***Turk.:*** Hyperium; ***Venez.:*** Hyperium.

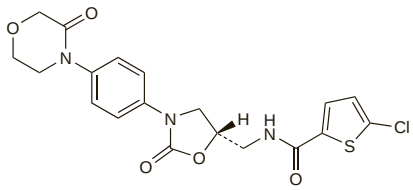
Rivaroxaban *(USAN, rINN)*

Bay-59-7939; Rivaroxabán; Rivaroxabanum. 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide.

Ривароксабан

$C_{19}H_{18}ClN_3O_5S$ = 435.9.

CAS — 366789-02-8.



Profile

Rivaroxaban is an oral direct inhibitor of activated factor X that is under investigation in thromboembolic disorders.

◊ References.

1. Fisher WD, *et al.* Rivaroxaban for thromboprophylaxis after orthopaedic surgery: pooled analysis of two studies. *Thromb Haemost* 2007; **97:** 931–7.
2. Agnelli G, *et al.* Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients with Acute Symptomatic Deep-Vein Thrombosis) study. *Circulation* 2007; **116:** 180–7.
3. Eriksson BI, *et al.* RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; **358:** 2765–75.
4. Lassen MR, *et al.* RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; **358:** 2776–86.
5. Kakkar AK, *et al.* RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008; **372:** 31–9.
6. Piccini JP, *et al.* Rivaroxaban, an oral direct factor Xa inhibitor. *Expert Opin Invest Drugs* 2008; **17:** 925–37.

Rosuvastatin Calcium *(BANM, USAN, rINNM)*

Calcii Rosuvastatinum; Rosuvastatina calcica; Rosuvastatine Calcique; S-4522; ZD-4522 (rosuvastatin). (*E*)-(3*R*,5*S*)-7-{4-(4-Fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid calcium (2:1).

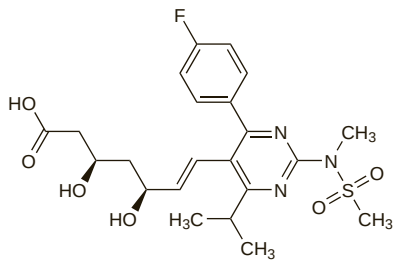
Кальций Розувастатин

$(C_{22}H_{27}FN_3O_6S)_2Ca$ = 1001.1.

CAS — 287714-41-4 (rosuvastatin); 147098-20-2 (rosuvastatin calcium).

ATC — C10AA07.

ATC Vet — QC10AA07.



(rosuvastatin)

Adverse Effects and Precautions

As for Simvastatin, p.1390. Systemic exposure to rosuvastatin may be higher in Asian patients (see Ethnicity under Pharmacokinetics, below) and lower doses are advised in Asians and in other patients at high risk of myopathy (see Uses and Administration, below).

Incidence of adverse effects. An analysis[1] of adverse effects reported to the FDA in the first year of marketing found that rosuvastatin was significantly more likely to be associated with severe adverse effects than some other statins. However, further analyses of data from clinical studies[2] and post-marketing studies[3,4] suggest that the risk of adverse effects is similar for all the statins. Another observational study[5] with a median treatment period of 9.8 months found that rosuvastatin was generally well tolerated, although 17.5% of patients stopped taking the drug, with myalgia being the most common reason. Abnormal liver function tests were more common in patients taking higher doses.

1. Alsheikh-Ali AA, *et al.* The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. *Circulation* 2005; **111:** 3051–7.
2. Shepherd J, *et al.* Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. *Cardiology* 2007; **107:** 433–43.
3. Goettsch WG, *et al.* Results from a rosuvastatin historical cohort study in more than 45 000 Dutch statin users, a PHARMO study. *Pharmacoepidemiol Drug Saf* 2006; **15:** 435–43.
4. McAfee AT, *et al.* The comparative safety of rosuvastatin: a retrospective matched cohort study in over 48 000 initiators of statin therapy. *Pharmacoepidemiol Drug Saf* 2006; **15:** 444–53.
5. Kasliwal R, *et al.* Safety profile of rosuvastatin: results of a prescription-event monitoring study of 11 680 patients. *Drug Safety* 2007; **30:** 157–70.

Interactions

The interactions of statins with other drugs are described under simvastatin, p.1392. Rosuvastatin undergoes limited metabolism, principally by the cytochrome P450 isoenzyme CYP2C9, and may not have the same interactions with enzyme inhibitors as simvastatin. However, increased plasma-rosuvastatin concentrations have been reported with ciclosporin, HIV-protease inhibitors, and, to a lesser extent, with gemfibrozil, and such combinations should be avoided. If they must be given together, lower doses of rosuvastatin should be used (see Uses and Administration, below); in UK licensed product information, rosuvastatin is contra-indicated with ciclosporin.

Pharmacokinetics

Rosuvastatin is incompletely absorbed from the gastrointestinal tract, with an absolute bioavailability of about 20%. Peak plasma concentrations are achieved about 5 hours after an oral dose. It is taken up extensively by the liver, its primary site of action, and undergoes limited metabolism, mainly by the cytochrome P450 isoenzyme CYP2C9. It is about 90% bound to plasma proteins. The plasma elimination half-life of rosuvastatin is about 19 hours. About 90% of an oral dose of rosuvastatin appears in the faeces, including absorbed and non-absorbed drug, and the remainder is excreted in the urine; about 5% of a dose is excreted unchanged in urine.

Ethnicity. A pharmacokinetic study[1] found that plasma exposure to rosuvastatin and its metabolites was significantly higher in Asian (Chinese, Malay, or Indian) than in Caucasian subjects and lower doses should be used (see Uses and Administration, below).

1. Lee E, *et al.* Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther* 2005; **78:** 330–41.

Uses and Administration

Rosuvastatin, a hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p.1394). It is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the management of hyperlipidaemias (p.1169), including primary hypercholesterolaemia (type IIa), mixed dyslipidaemia (type IIb), and hypertriglyceridaemia (type IV), as well as in patients with homozygous familial hypercholesterolaemia. It is also used to reduce the progression of atherosclerosis.

Rosuvastatin is given orally as the calcium salt, although doses are expressed in terms of the base; 10.4 mg of rosuvastatin calcium is equivalent to about 10 mg of base.

The usual initial dose of rosuvastatin is 5 or 10 mg once daily, depending on plasma-cholesterol concentrations, cardiovascular risk factors, and risk factors for adverse effects. The maintenance dose ranges from 5 to 40 mg once daily, although the 40-mg dose is reserved for patients with high cardiovascular risk who do not achieve their target cholesterol concentration at lower doses and who do not have risk factors for adverse effects. Specific dosage recommendations vary; for dosage in renal impairment, see below.

UK licensed product information recommends an initial dose of 5 or 10 mg once daily; elderly patients, Asians, and those at risk of myopathy should be given the 5-mg dose. The dose may be increased at intervals of 4 weeks, if necessary, to a usual maximum of 20 mg once daily. A higher dose of 40 mg once daily may be given under specialist supervision in severe hypercholesterolaemia, but should not be given to patients at high risk of myopathy, including those receiving fibrates, and Asian patients; use with *ciclosporin* is contra-indicated.

US licensed product information recommends a usual initial dose of 10 mg once daily. However, a lower initial dose of 5 mg once daily may be adequate and is recommended for patients at risk of myopathy, including Asian patients; patients with marked hypercholesterolaemia, such as those with homozygous familial hypercholesterolaemia, may be started on 20 mg once daily. The dose should be adjusted after 2 to 4 weeks, to a usual maximum of 20 mg once daily; a dose of 40 mg once daily may be necessary in some patients. Patients receiving *ciclosporin* may be given a maximum of 5 mg once daily, and in those receiving *gemfibrozil* or *ritonavir-boosted lopinavir* the maximum dose is 10 mg once daily; dosage increases should be made with caution in Asian patients.

◊ General reviews.

1. Chong PH, Yim BT. Rosuvastatin for the treatment of patients with hypercholesterolemia. *Ann Pharmacother* 2002; **36:** 93–101.
2. Carswell CI, *et al.* Rosuvastatin. *Drugs* 2002; **62:** 2075–85.
3. White CM. A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. *J Clin Pharmacol* 2002; **42:** 963–70.
4. McKenney JM. Efficacy and safety of rosuvastatin in treatment of dyslipidemia. *Am J Health-Syst Pharm* 2005; **62:**1033–47.
5. Olsson AG. Expanding options with a wider range of rosuvastatin doses. *Clin Ther* 2006; **28:** 1747–63.
6. Kapur NK. Rosuvastatin: a highly potent statin for the prevention and management of coronary artery disease. *Expert Rev Cardiovasc Ther* 2007; **5:** 161–75.
7. Schuster H. The GALAXY Program: an update on studies investigating efficacy and tolerability of rosuvastatin for reducing cardiovascular risk. *Expert Rev Cardiovasc Ther* 2007; **5:** 177–93.
8. Crouse JR. An evaluation of rosuvastatin: pharmacokinetics, clinical efficacy and tolerability. *Expert Opin Drug Metab Toxicol* 2008; **4:** 287–304.

Administration in renal impairment. Patients with renal impairment have an increased risk of developing myopathy and statins should be used with caution, particularly in higher doses. In severe renal impairment plasma-rosuvastatin concentrations may be increased and dosage reduction may be necessary.

UK licensed product information recommends the following oral doses according to creatinine clearance (CC):

- CC 30 to 60 mL/minute: initial oral dose of 5 mg once daily and a maximum dose of 20 mg once daily
- CC below 30 mL/minute: contra-indicated

In the USA usual doses (see above) are allowed in moderate impairment but an initial dose of 5 mg once daily and a maximum dose of 10 mg once daily is recommended in those with CC below 30 mL/minute per 1.73 m^2.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Crestor; Rosuvast; Rovartal; Sinlip; ***Austral.:*** Crestor; ***Austria:*** Crestor; ***Belg.:*** Crestor; ***Braz.:*** Vivacor; ***Canad.:*** Crestor; ***Chile:*** Cresadex; Crestor; Rosumed; ***Cz.:*** Crestor; ***Denm.:*** Crestor; ***Fin.:*** Crestor; ***Fr.:*** Crestor; ***Gr.:*** Crestor; ***Hong Kong:*** Crestor; ***Hung.:*** Crestor; ***India:*** Razel†; Rosuvas; ***Indon.:*** Crestor; ***Irl.:*** Crestor; ***Israel:*** Crestor; ***Ital.:*** Crestor; Provisacor; Simestat; ***Jpn:*** Crestor; ***Malaysia:*** Crestor; ***Mex.:*** Crestor; ***Neth.:*** Cirantan; Crestor; Provisacor; ***Philipp.:*** Crestor; ***Port.:*** Crestor; Visacor; ***Rus.:*** Crestor (Крестор); ***S.Afr.:*** Crestor; ***Singapore:*** Crestor; ***Swed.:*** Crestor; ***Thai.:*** Crestor; ***UK:*** Crestor; ***USA:*** Crestor; ***Venez.:*** Crestor.