Revised: July 2023 (9th version, Section of Careful Administration, etc.)
Revised: August 2022 (8th version)

HMG-CoA Reductase Inhibitor

Prescription-only drug*1)

Japanese Pharmacopoeia (JP)
Rosuvastatin Calcium Tablets

ROSUVASTATIN TABLETS 2.5mg "TOWA" / TABLETS 5mg "TOWA" / TABLETS 10mg "TOWA"

Storage:
Store at room temperature.
Expiration date:
Indicated on the package and label

Standard Commodity Classification No. of Japan 872189			
	2.5mg	5mg	10mg
Approval No.	22900AMX00924	22900AMX00925	22900AMX00926
Date of listing in the NHI reimbursement price	December 2017	December 2017	December 2017
Date of launch in Japan	December 2017	December 2017	December 2017
Date of indication expansion	December 2018	December 2018	December 2018

*1) Caution – Use only pursuant to the prescription of a physician, etc.

CONTRAINDICATIONS (Rosuvastatin Tablets is contraindicated in the following patients.)

1) Patients with a history of hypersensitivity to any of the ingredients of this product.
2) Patients who are considered to have decreased liver function due to any of the following conditions:
Acute hepatitis, acute exacerbation of chronic hepatitis, hepatic cirrhosis, hepatic cancer, and jaundice [Blood concentrations of this product may increase in these patients. This product is distributed mainly to the liver where it exhibits its activity, which may aggravate liver disorders.]
3) Pregnant women, women who may possibly be pregnant or women in lactation [See "Use during Pregnancy, Delivery or Lactation".]
4) Patients under treatment with Ciclosporin [See "Interactions".]

COMPOSITION AND PRODUCT DESCRIPTION

		ROSUVASTATIN TABLETS 2.5mg "TOWA"	ROSUVASTATIN TABLETS 5mg "TOWA"	ROSUVASTATIN TABLETS 10mg "TOWA"
Active ingredient per tablet		JP Rosuvastatin calcium ..... 2.6mg (As Rosuvastatin 2.5mg)	JP Rosuvastatin calcium .....5.2mg (As Rosuvastatin 5mg)	JP Rosuvastatin calcium .....10.4mg (As Rosuvastatin 10mg)
Inactive ingredient		D-Mannitol, Microcrystalline Cellulose, Crospovidone, Sodium Bicarbonate, Light Anhydrous Silicic Acid, Magnesium Stearate, Hypromellose, Triacetine, Titanium Oxide, Yellow Ferric Oxide, Macrogol 6000		
Product description		Yellow film-coated tablets		
Identification mark	Top surface	ロスバ 2.5 スタチン トーワ	ロスバ 5 スタチン トーワ	ロスバ 10 スタチン トーワ
	Bottom surface			
Appearance	Top surface			
	Bottom surface			
	Side surface			
Diameter (mm)		5.7	7.2	9.2
Thickness (mm)		3.2	3.3	4.2
Weight (mg)		80.3	133	262.8

INDICATIONS

Hypercholesterolemia, familial hypercholesterolemia

[PRECAUTIONS CONCERNING INDICATIONS]

1) Consideration should be given to the application of this product only after confirmation of the presence of hypercholesterolemia or familial hypercholesterolemia by prior thorough examinations has been attained.
2) For patients with homozygous familial hypercholesterolemia, the application of this product should be considered as an adjunct to non-drug therapies such as LDL-apheresis or if such therapies are not feasible.

DOSAGE AND ADMINISTRATION

The recommended starting dose for adults is 2.5 mg of rosuvastatin administered once daily. However, for patients requiring prompt lowering of LDL-cholesterol levels, administration of this drug may be started at a dose of 5 mg. The dose may be adjusted appropriately according to patient's age and symptoms, and may be gradually increased to 10 mg if an inadequately decreased LDL-cholesterol level is observed at 4 weeks after the start of treatment or after the dose increase. The dose may be further increased up to 20 mg per day for patients with severe conditions such as patients with familial hypercholesterolemia whose LDL-cholesterol levels are not sufficiently lowered by administration of this product at a dose of 10 mg.

PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

1) For patients with a creatinine clearance of less than 30 mL/min/1.73 m^2, administration of this product should be started at a dose of 2.5 mg, and the maximum daily dose is 5 mg (see "Careful Administration").
2) Renal function may be affected particularly after administration of this product at a dose of 20 mg. Patients receiving this drug at a dose of 20 mg should be closely monitored by renal function tests once a month until Week 12 of treatment and thereafter on a regular basis (e.g., once every 6 months).

PRECAUTIONS

1. Careful Administration

(**Rosuvastatin Tablets** should be administered with care in the following patients.)

1) Patients with renal disorders or with a history of renal disorders [Blood concentrations of this product may increase in patients with severe renal disorders. Generally, Rhabdomyolysis after administration of HMG-CoA reductase inhibitors occurs mostly in patients with renal impairment. Acute exacerbation of renal function may also occur in association with rhabdomyolysis (see "PRECAUTIONS FOR DOSAGE AND ADMINISTRATION").]
2) Patients with alcoholic addiction, and patients with liver disorders or with a history of liver disorders [This product is distributed mainly to the liver where it exhibits its activity, which may aggravate liver disorders. Rhabdomyolysis has been reported to be likely to develop in patients with alcoholic addiction (see "CONTRAINDICATIONS").]
3) Patients receiving fibrates (bezafibrate, etc.), nicotinic acid, azole antifungals (itraconazole, etc.), or macrolide antibiotics (erythromycin, etc.) [In general, concomitant use of this product with HMG-CoA reductase inhibitors is likely to cause rhabdomyolysis (see "INTERACTIONS").]
4) Patients with hypothyroidism, patients with hereditary muscular diseases (e.g., muscular dystrophy) or with a family history of such diseases, and patients with a history of drug-induced muscle disorder [Rhabdomyolysis has been reported to be likely to develop in such patients.]
5) Patients with myasthenia gravis or a history of it [Exacerbation or relapse of myasthenia gravis (ocular or systemic) may occur (see "Clinically significant adverse reactions").]
6) Elderly patients [See "Use in the Elderly".]

2. Important Precautions

1) Diet therapy, the basic treatment for hypercholesterolemia, should be performed in advance. In addition, prior consideration should be carefully given to exercise therapy and reduction of risk factors for ischemic heart diseases such as hypertension and smoking.
2) For patients showing abnormal findings in laboratory test values related to renal function, this product can be coadministered with fibrates only if concomitant use with such drugs is considered essential due to therapeutically unavoidable circumstances. Rhabdomyolysis associated with rapid worsening of renal function is likely to occur. If, due to unavoidable circumstances, this product is coadministered with fibrates, examinations such as renal function tests should be performed periodically. If any symptoms of rhabdomyolysis (myalgia, feelings of weakness) and aggravated renal function such as increases in CK (CPK), blood/urine myoglobin, and serum creatinine are observed, administration of this product must immediately be discontinued.
3) During treatment with this product, blood lipid levels should be examined periodically. If no response to treatment is observed, administration of this drug should be discontinued.
4) There have been case reports of immune-mediated necrotizing myopathy characterized by proximal muscle weakness, increased CK (CPK), muscle fiber necrosis without inflammation, the development of anti-HMG-CoA reductase (HMGCR) antibodies and such, with some cases where such symptoms persists even after discontinuation of this product. Therefore, patients should be closely monitored. It has been reported that, in some cases, the above-mentioned symptoms were alleviated by immunosuppressive therapy (see "Clinically significant adverse reactions").
5) Liver function tests should be performed once a month for the 12 weeks after the start of treatment or after dose increase and thereafter on a regular basis (e.g., once every 6 months).

3. Interactions

This product is the substrate of OATP1B1 and BCRP.

1) Contraindications for co-administration (Do not co-administer with the following.)

Drugs	Signs, Clinical Symptoms and Treatment	Mechanism and Risk Factors
Ciclosporin Sandimmun Neoral, etc.	It has been reported that, concomitant use of this product to heart transplant recipients receiving ciclosporin, blood ciclosporin concentrations were not affected; however, the $AUC_{0\text{-}24h}$ of rosuvastatin was approximately 7 times higher than that following repeated administration of this product alone to healthy adults.	Ciclosporin may inhibit the functions of OATP1B1, BCRP and such.

2) Precautions for co-administration (This drug should be administered with caution when co-administered with the following.)

Drugs	Signs, Clinical Symptoms and Treatment	Mechanism and Risk Factors
Fibrates Bezafibrate, etc.	Concomitant use of this product with fenofibrate did not show influence on blood concentrations of either drug. However, in general, concomitant use of this product with HMG-CoA reductase inhibitors is likely to cause rhabdomyolysis, which is characterized by myalgia, feelings of weakness, increased CK (CPK), and increased blood/urine myoglobin and associated with acute exacerbation of renal function.	Rhabdomyolysis has been reported with both drugs. Risk factor: Patients showing abnormal laboratory test findings related to renal function
Nicotinic acid Azole antifungals Itraconazole, etc. Macrolide antibiotics Erythromycin, etc.	In general, concomitant use of this product with HMG-CoA reductase inhibitors is likely to cause rhabdomyolysis, which is characterized by myalgia, feelings of weakness, increased CK (CPK), and increased blood/urine myoglobin and associated with acute exacerbation of renal function.	Risk factor: Patients with renal impairment

Coumarin anticoagulants Warfarin	The anticoagulant effects of these drugs may be enhanced. If this product is coadministered with such anticoagulants, the prothrombin time-international normalized ratio (INR) and such should be checked frequently at the start of administration and at the time of dose modification of this product, and due precautions should be taken, including dose adjustment of warfarin as necessary.	Mechanism unknown
Antacids Magnesium hydroxide/aluminum hydroxide	Blood rosuvastatin concentrations have been reported to decrease to approximately 50%. Following concomitant use of rosuvastatin with an antacid (when the antacid was administered 2 hours after rosuvastatin administration), the blood rosuvastatin concentration was approximately 80% of that following administration of rosuvastatin alone.	Mechanism unknown
Lopinavir-ritonavir Atazanavir/ritonavir Darunavir/ritonavir Glecaprevir-pibrentasvir	It has been reported that concomitant use of rosuvastatin with lopinavir-ritonavir increased the AUC and Cmax of rosuvastatin by approximately 2 and 5 times, respectively, concomitant use of rosuvastatin with both atazanavir and ritonavir increased the AUC and Cmax of rosuvastatin by approximately 3 and 7 times, respectively, and concomitant use of rosuvastatin with both darunavir and ritonavir increased the AUC and Cmax of rosuvastatin by approximately 1.5 and 2.4 times, respectively. Concomitant use of rosuvastatin with glecaprevir-pibrentasvir Note 2) has been reported to have increased the AUC and Cmax of rosuvastatin by approximately 2.2 times and 5.6 times, respectively.	The drugs listed in the left column may inhibit the functions of OATP1B1 and BCRP.
Daclatasvir Asunaprevir Daclatasvir-asunaprevir-bedabuvir	Concomitant use of rosuvastatin with daclatasvir, asunaprevir, or daclatasvir-asunaprevir-beclabuvir Note 2) has been reported to have increased blood rosuvastatin concentrations.	Daclatasvir and beclabuvir may inhibit the functions of OATP1B1/1B3, and BCRP. Asunaprevir may also inhibit the functions of OATP1B1/1B3.
Grazoprevir/elbasvir	Concomitant use of rosuvastatin with grazoprevir Note 2) and elbasvir has been reported to have increased the AUC and Cmax of rosuvastatin by approximately 2.3 times and 5.5 times, respectively.	
Sofosbuvir/Velpatasvir	Coadministration of rosuvastatin with velpatasvir has been reported to have increased the AUC and Cmax of rosuvastatin by approximately 2.7 times and 2.6 times, respectively.	Velpatasvir may inhibit the function of OATP1B1, 1B3 and BCRP.
Darolutamide	Coadministration of rosuvastatin with darolutamide has been reported to have increased the AUC and Cmax of rosuvastatin by 5.2 times[1)] and 5.0 times, respectively.	Darolutamide may inhibit the function of OATP1B1, 1B3 and BCRP.
Regorafenib	Concomitant use of rosuvastatin with regorafenib has been reported to have increased the AUC and Cmax of rosuvastatin by 3.8 times and 4.6 times, respectively.	Regorafenib may inhibit the function of BCRP.
Capmatinib hydrochloride hydrate	Coadministration of this product with capmatinib hydrochloride hydrate has been reported to have increased the AUC and Cmax of this product by approximately 2.1 times and 3.0 times, respectively.	Blood concentration of this product may be increased due to inhibition of the function of BCRP by capmatinib hydrochloride.
Vadadustat	Coadministration of this product with vadadustat has been reported to have increased the AUC and Cmax of this product by approximately 2.5 times and 2.7 times, respectively.	Blood concentration of this product may be increased due to inhibition of the function of BCRP by vadadustat.
Febuxostat	Coadministration of this product with febuxostat has been reported to have increased the AUC and Cmax of this product by approximately 1.9 times and 2.1 times, respectively.	Blood concentration of this product may be increased due to inhibition of the function of BCRP by febuxostat.
Eltrombopag	Concomitant use of rosuvastatin with eltrombopag has been reported to have increased the AUC of rosuvastatin by approximately 1.6 times.	Eltrombopag may inhibit the functions of OATP1B1 and BCRP.
Fostamatinib sodium hydrate	Coadministration of this product with fostamatinib sodium hydrate has been reported to have increased the AUC and Cmax of this product by 1.96 times and 1.88 times, respectively.	Fostamatinib sodium hydrate may inhibit the function of BCRP.
Roxadustat	Coadministration of this product with roxadustat has been reported to have increased the AUC and Cmax of this product by 2.93 times and 4.47 times, respectively.	Roxadustat may inhibit the functions of OATP1B1 and BCRP.
Tafamidis	Coadministration of this product with tafamidis has been reported to	Tafamidis may inhibit the function of BCRP.

	have increased the AUC and Cmax of this product by 1.97 times and 1.86 times, respectively.	

Note 2) Data based on the results of studies conducted by other pharmaceutical companies, in which these drugs were administered at doses outside the approved dosage.

4. Adverse Reactions

No investigation such as a drug use investigation clearly showing the incidence of adverse reactions has been conducted.

1) Clinically significant adverse reactions (incidence unknown)

(1) **Rhabdomyolysis**: Rhabdomyolysis characterized by myalgia, feelings of weakness, increased CK (CPK), and increased blood/urine myoglobin may occur, and serious renal disorders such as acute kidney injury may occur. In the event of such symptoms occurring, administration of this product must immediately be discontinued.

(2) **Myopathy:** Myopathy may occur. If myalgia involving extensive areas, severe feelings of weakness, and markedly increased CK (CPK) are observed, administration of this product should be discontinued.

(3) **Immune-mediated necrotizing myopathy:** Immune-mediated necrotizing myopathy may occur. Patients should be closely monitored, and if any abnormalities are observed, administration of this product should be discontinued, and appropriate treatment should be given.

(4) **Myasthenia gravis:** Myasthenia gravis (ocular or systemic) may occur or worsen. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

(5) **Hepatitis, Hepatic dysfunction, Jaundice:** Hepatitis, hepatic dysfunction associated with increased AST (GOT), or ALT (GPT) or jaundice may occur. Patients should be carefully monitored by periodical hepatic function tests or other measures, and if any abnormalities are observed, administration of this product should be discontinued and appropriate treatment should be given.

(6) **Thrombocytopenia:** Thrombocytopenia may occur. Patients should be closely monitored by examinations including blood tests. If any such abnormalities are observed, administration of this product should be discontinued, and appropriate treatment should be given.

(7) **Hypersensitivity symptoms:** Hypersensitivity symptoms including angioedema may occur. In the event of such symptoms, administration of this product should be discontinued, and appropriate treatment should be given.

(8) **Interstitial pneumonia:** Interstitial pneumonia may occur. If pyrexia, cough, dyspnea, chest X-ray abnormalities and such are observed, administration of this product should be discontinued even during long-term treatment with this drug, and appropriate treatment should be given, including corticosteroid therapy.

(9) **Peripheral neuropathy:** Peripheral neuropathy such as hypoesthesia or numbness of the limbs, pain, or muscular weakness may occur. If any abnormalities are observed, administration of this product should be discontinued and appropriate treatment should be given.

(10) **Erythema multiforme**: Erythema multiforme may occur. Patients should be closely monitored, and if any abnormalities are observed, administration of this product should be discontinued and appropriate treatment should be given.

2) Other adverse reactions

	Incidence unknown
Dermatologic*3)	Pruritus, rash, urticaria, lichenoid eruption
Gastrointestinal	Abdominal pain, constipation, nausea, diarrhea, pancreatitis, stomatitis
Musculoskeletal system	Increased CK (CPK), asthenia, myalgia, arthralgia, muscle cramps
Psychoneurologic	Headache, dizziness, amnesia, sleep disorder (insomnia, nightmare, etc.), depression
Endocrine	Gynecomastia
Abnormal metabolism	Increased HbA1c, increased blood glucose level
Hepatic	Abnormality of hepatic function (increased AST(GOT), increased ALT(GPT))
Renal	Proteinuria*4), abnormality of renal function (increased BUN, increased serum creatinine level)

*3): If such symptoms are observed, administration of this product should be discontinued.

*4): Proteinuria is usually transient; however, if proteinuria of unknown cause persists, appropriate measures should be taken, including dose reduction of this product.

5. Use in the Elderly

In general, elderly patients often have reduced physiological functions; therefore, this product should be administered to elderly patients under close monitoring of their conditions. Rhabdomyolysis has been reported to be likely to develop in elderly patients.

In clinical studies conducted by other pharmaceutical companies, no notable difference in plasma rosuvastatin concentrations was observed between elderly and non-elderly patients.

6. Use during Pregnancy, Delivery or Lactation

1) This product should not be used in pregnant women or in women who may possibly be pregnant.
[Although the safety of use during pregnancy has not been established, fetal skeletal malformation has been reported in rats given high-dose administration of other HMG-CoA reductase inhibitors. Furthermore, it has been reported that, in humans, congenital fetal malformations occurred following oral administration of other HMG-CoA reductase inhibitors to women during the first trimester.]

2) This product should not be administered to breast-feeding women. [This product has been reported to be excreted in milk in rats.]

7. Pediatric Use

The safety of this product in low birth weight infants, neonates, nursing infants, infants and children has not been established. (No sufficient data in pediatric patients.)

8. Precautions Concerning Use

Precautions regarding dispensing:

For drugs that are dispensed in a PTP (press-through package) sheet, instruct the patient to remove the drug from the package prior to use [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa,

causing perforation and resulting in severe complications such as mediastinitis.]

9. Other precautions

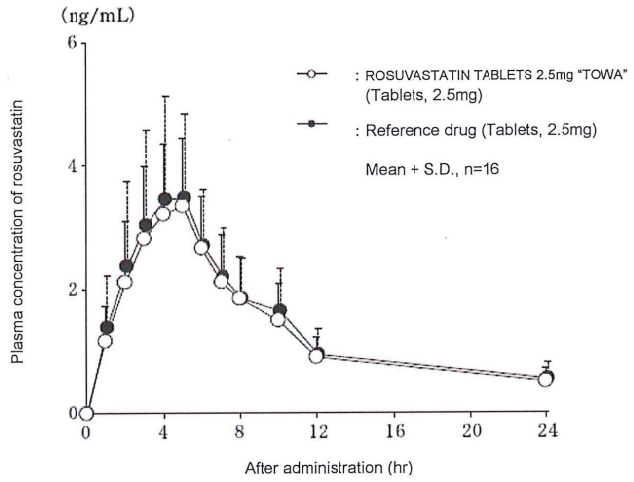
It has been reported in countries outside Japan that patients receiving HMG-CoA reductase inhibitors including rosuvastatin were placed at increased risk of diabetes mellitus.

PHARMACOKINETICS

1. Bioequivalence test

1) ROSUVASTATIN TABLETS 2.5mg "TOWA"

One tablet each of ROSUVASTATIN TABLETS 2.5mg "TOWA" and a reference drug (as 2.5 mg of rosuvastatin) were administered orally as a single dose to healthy adult men under fasting conditions (n=16) in a crossover design to measure each unchanged drug concentration in plasma. Obtained pharmacokinetic parameters (AUC and Cmax) were statistically analyzed in a 90% confidence interval design. The analysis results confirmed the bioequivalence of these drugs within the range between log (0.80) and log (1.25).[2)]



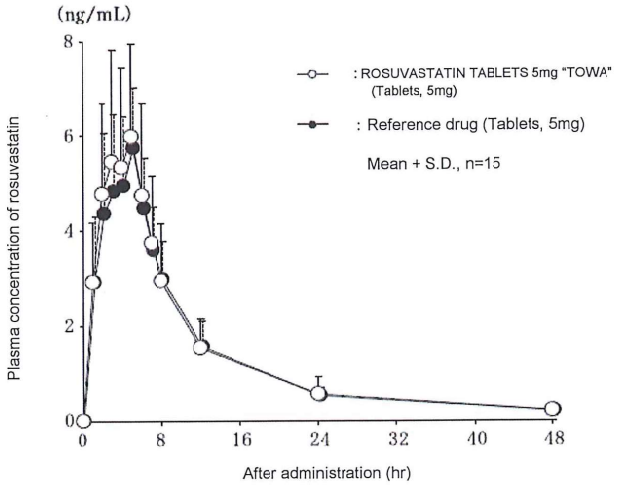
	Determined parameter		Reference parameter	
	AUC_{24} (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	$T_{1/2}$ (hr)
ROSUVASTATIN TABLETS 2.5mg "TOWA" (Tablets, 2.5mg)	32.38±11.41	3.503±1.116	4.7±0.6	9.14±1.47
Reference drug (Tablets, 2.5mg)	34.56±14.27	3.731±1.537	4.7±0.5	9.17±2.24

(Mean ± S.D., n=16)

Plasma concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

2) ROSUVASTATIN TABLETS 5mg "TOWA"

One tablet each of ROSUVASTATIN TABLETS 5mg "TOWA" and a reference drug (as 5 mg of rosuvastatin) were administered orally as a single dose to healthy adult men under fasting conditions (n=15) in a crossover design to measure each unchanged drug concentration in plasma. Obtained pharmacokinetic parameters (AUC and Cmax) were statistically analyzed in a 90% confidence interval design. The analysis results confirmed the bioequivalence of these drugs within the range between log (0.80) and log (1.25).[3)]



	Determined parameter		Reference parameter	
	AUC_{48} (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	$T_{1/2}$ (hr)
ROSUVASTATIN TABLETS 5mg "TOWA" (Tablets, 5mg)	64.4±26.6	6.240±2.139	4.3±1.0	11.71±2.85
Reference drug (Tablets, 5mg)	62.4±16.9	5.841±1.292	4.4±1.0	12.06±2.71

(Mean ± S.D., n=15)

Plasma concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

3) ROSUVASTATIN TABLETS 10mg "TOWA"

The bioequivalence of ROSUVASTATIN TABLETS 10mg "TOWA" was determined by equal dissolution behavior compared with ROSUVASTATIN TABLETS 5 mg "TOWA" as the standard formulation in accordance with the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PFSB/ELD Notification No. 0229-10 dated February 29, 2012).[4)]

2. Dissolution profile

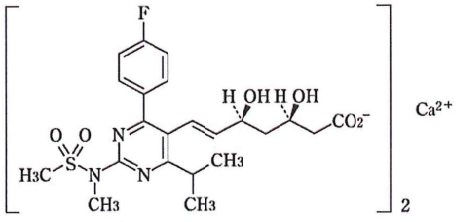
ROSUVASTATIN TABLETS 2.5mg "TOWA" / TABLETS 5mg "TOWA" / TABLETS 10mg "TOWA" have been confirmed to conform to the dissolution specifications for Rosuvastatin Calcium Tablets defined in the official monographs of the Japanese Pharmacopoeia.[5)6)7)]

PHARMACOLOGY

This product competitively inhibits HMG-CoA reductase in the liver, a major organ of cholesterol biosynthesis, thereby inhibiting cholesterol biosynthesis. As a result, LDL receptors in the liver increase, which leads to decreased blood LDL-cholesterol levels.[8)]

PHYSICOCHEMICAL PROPERTIES

Structural formula:



Nonproprietary name:

Rosuvastatin Calcium

Chemical name:

Monocalcium bis[(3*R*,5*S*,6*E*)-7-{4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-encate]

Molecular formula:
$(C_{22}H_{27}FN_3O_6S)_2Ca$

Molecular weight:
1001.14

Description:
Rosuvastatin Calcium occurs as a white powder. It is freely soluble in acetonitrile, soluble in methanol, and slightly soluble in water and in ethanol (99.5). It is hygroscopic.

PRECAUTIONS FOR HANDLING

Stability test

In an accelerated test using final packaged products (at 40°C and 75% relative humidity for 6 months), ROSUVASTATIN TABLETS 2.5mg "TOWA" / TABLETS 5mg "TOWA" / TABLETS 10mg "TOWA" were estimated to be stable for 3 years under normal distribution conditions.[9)10)11)]

PACKAGING

ROSUVASTATIN TABLETS 2.5mg "TOWA":
Boxes of 100 tablets, 500 tablets (PTP)
140 tablets (14 tablets x 10) (PTP)
700 tablets (14 tablets x 50) (PTP)
Polyethylene containers of 300 tablets

ROSUVASTATIN TABLETS 5mg "TOWA":
Boxes of 100 tablets, 500 tablets (PTP)
140 tablets (14 tablets x 10) (PTP)
Polyethylene containers of 300 tablets

ROSUVASTATIN TABLETS 10mg "TOWA":
Boxes of 100 tablets (PTP)

REFERENCES

1) Zurth,C.,et al. : Eur J Drug Metab Pharmacokinet., 44, 747, 2019
2) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test (tablets 2.5mg)
3) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test (tablets 5mg)
4) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test (tablets 10mg)
5) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test (tablets 2.5mg)
6) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test (tablets 5mg)
7) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test (tablets 10mg)
8) Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th Edition, 1134, 2013
9) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test (tablets 2.5mg)
10) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test (tablets 5mg)
11) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test (tablets 10mg)

Manufacturer and Distributor
TOWA PHARMACEUTICAL CO., LTD.
2-11, Shinbashi-cho, Kadoma, Osaka 571-8580
Japan