**Revised in July 2023 (29th edition)
*Revised in March 2022 (28th edition)

SIMÿTÿÿ

Storage method: Store at room temperature, in an airtight container (avoid moisture after opening.) Expiration date: Use within the expiration date indicated on the outer box.

HMG-CoA reductase inhibitor -
Hyperlipidemia treatment
- Prescription drug Note 1)

日本薬局方 シンバスタチン錠
シンバスタチン錠5mg「オーハラ」
シンバスタチン錠10mg「オーハラ」
シンバスタチン錠20mg「オーハラ」
SIMVASTATIN TABLETS 5mg「OHARA」
SIMVASTATIN TABLETS 10mg「OHARA」
SIMVASTATIN TABLETS 20mg「OHARA」

Japanese standard product classification number			
872189			
	Simvastatin Tablets 5 mg "Ohara" Approval number 22500AMX01227000	Simvastatin Tablets 10mg "Ohara" 22500AMX01225000	Simvastatin Tablets 20mg "Ohara" 22500AMX01226000
NHI drug price listing	December 2013	December 2013	December 2013
Sales start	July 2003	July 2004	July 2004

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[Contraindications] (Do not administer to the following patients)

(1) Patients with a history of hypersensitivity to the components of this drug (2) Patients with severe liver damage [Since this drug is mainly metabolized and acts in the liver, it may worsen liver damage. There is.] (3) Pregnant or potentially pregnant women and lactating women (see section 6. Administration to pregnant women, parturient women, lactating women, etc.) (4) Itraconazole, miconazole, posaconazole, atazanavir, saquinavir mecil Patients receiving preparations containing cobicistat (see section 3. Interactions)

<Precautions related to usage and administration>

(1) In addition to dietary therapy, which is the basis of hyperlipidemia treatment , in addition to exercise therapy and reduction of risk factors for ischemic heart disease such as hypertension and smoking, etc. Please give sufficient consideration.

(2) Time of administration: It has been reported that cholesterol biosynthesis increases at night, and clinical trials have confirmed that administration after dinner is more effective than after breakfast. Therefore, when applying this drug, it is preferable to administer it once a day after dinner.

ÿComposition•Characterÿ

Sales name	Simvastatin Tablets 5 mg "Ohara"	Simvastatin Tablets 10mg "Ohara"	Simvastatin Tablets 20mg "Ohara"
Ingredients and content	1 tablet contains 5 mg of Simvastatin	1 tablet contains 10mg of Simvastatin	1 tablet contains 20mg of Simvastatin
Additives	Lactose hydrate, partially pregelatinized starch, hydroxypropylcellulose, ascorbic acid, butylated hydroxyanisole, magnesium stearate		
Color and shape	White, single-sided tablet with score lines	White to yellowish white naked tablets	White to yellowish white naked tablets
shape	Front Back Side Side  Diameter: 6.5mm Thickness: 2.3mm	Front Back Side Side  Diameter: 8.0mm Thickness: 3.0mm	Front Back Side Side  Long axis: 14.0mm Short axis: 7.5mm Thickness: 4.5mm
Weight 100mg		200mg	400mg
Identification code	simvastatin 5 OHARA	simvastatin 10 OHARA	simvastatin 20 OHARA

[Efficacy/Efficacy]

Hyperlipidemia, familial hypercholesterolemia

[Dosage and

Administration] The usual adult dose is 5 mg of simvastatin orally administered once a day. The dose may be increased or decreased as appropriate depending on your age and symptoms, but if the reduction in LDL cholesterol levels is insufficient, the dose may be increased up to 20mg per day.

[Precautions for use]

ÿÿ **1. Careful administration (Administer with caution to the following patients)** (1) Alcoholics, patients with liver disorder or a history thereof [This drug is mainly metabolized and acts in the liver, so there is a risk of worsening liver disorder. There is. Additionally, it has been reported that rhabdomyolysis is more likely to occur in alcoholics. (Refer to section 4. Adverse reactions (1) Serious adverse reactions)] (2) Patients with renal impairment or a history of renal impairment [Many reported cases of rhabdomyolysis are in patients with renal impairment. In addition, rapid deterioration of renal function has been observed with rhabdomyolysis.]

(3) Patients with hypothyroidism, patients with inherited muscle diseases (muscular dystrophy, etc.) or a family history thereof, patients with a history of drug-induced myopathy [rhabdomyolysis is likely to occur] There is a report that. (Refer to section ``4. Side effects (1) Serious side effects'')] (4) Elderly patients (refer to section 5. Administration to the elderly) (5) Patients receiving fibrate drugs (bezafibrate, etc.) Patients [prone to rhabdomyolysis]. (See section “3. Interaction”)]

(6) Patients with myasthenia gravis or a history thereof [myasthenia gravis (ocular muscle type, generalized type) may worsen or recur. (Refer to “4. Side effects (1) Serious side effects”)] **2. Important basic precautions** When applying this drug, pay careful attention to the following points.

(1) Before application, conduct sufficient tests to prevent hyperlipidemia and familial hyperlipidemia.

Note 1) Caution: Use with prescription from a doctor, etc.

Consider applying this drug after confirming that the patient has cholesterolemia. This drug responds well to hyperlipidemia, where hypercholesterolemia is the main abnormality.

(2) During administration, blood lipid levels should be checked periodically, and administration should be discontinued if no response to treatment is observed. (3) Immune-mediated necrotizing myopathy, characterized by proximal muscle weakness, high CK (CPK) levels, muscle fiber necrosis without inflammation, and anti-HMG-CoA reductase (HMGCR) antibody positivity, appears. There have been reports of cases of symptoms persisting even after discontinuation of administration, so patients should be closely monitored. In addition, there are reports of improvement with the administration of immunosuppressants. (Refer to “4. Side effects (1) Serious side effects”) (4) If this drug is used in combination with a fibrate drug in patients with abnormal clinical test values related to renal function, if it is unavoidable for therapeutic reasons. This drug should be used in combination only when it is determined that the drug is safe, and the dosage of this drug should not exceed 10 mg/day. Rhabdomyolysis, which is accompanied by rapid deterioration of renal function, is likely to occur. If concomitant use is unavoidable, kidney function tests should be conducted periodically to check for the onset of subjective symptoms (muscle pain, weakness), etc. If worsening of renal function such as increased CK (CPK), increased blood and urinary myoglobin, or increased serum creatinine is observed, administration should be immediately discontinued. **3. Interaction**

* This drug is mainly metabolized by the liver metabolic enzyme cytochrome P450 3A (4 CYP3A4). The active metabolite of this drug, the open acid form, is a substrate of OATP1B11). Additionally, this drug is a substrate for breast cancer resistance protein (BCRP)2). ** **(1) Contraindications for concomitant use (do not use together)** *

Drug name, etc.	Clinical symptoms/measures	Mechanism/risk factors
Itraconazole Itorizole Miconazole Florid Posaconazole Noxafil	Rhabdomyolysis, which is accompanied by rapid deterioration of renal function, is likely to occur.	These drugs inhibit CYP3A4, suppressing the metabolism of this drug.
Atazanavir Reyataz Saquinavir mesylate Invirase Preparations containing cobicistat Staribild Genvoya Prezicobix Simtuza _____ _____ _____	Serious side effects such as myopathy including rhabdomyolysis may occur.	These drugs inhibit CYP3A4, suppressing the metabolism of this drug.

(2) Caution in combination (be careful when using in combination)

Drug name, etc.	Clinical symptoms/measures	Mechanism/risk factors
Coumarin anticoagulant warfarin potassium	Slightly enhances anticoagulant effect. If coumarin anticoagulants are used concomitantly, monitor prothrombin time and adjust the dose of anticoagulants.	Mechanism unknown

Drug name, etc.	Clinical symptoms/measures	Mechanism/risk factors
Fibrate drugs Bezafibrate, etc.	Rhabdomyolysis, which is accompanied by rapid deterioration of renal function, is likely to occur. If concomitant use is necessary, the dose of this drug should not exceed 10 mg/day. [Administration should be discontinued immediately if subjective symptoms (muscular pain, weakness), worsening of renal function such as increased CK (CPK), increased blood and urinary myoglobin, and increased serum creatinine are observed.]	These drugs are also known to cause rhabdomyolysis. Risk factor: Patients with abnormal clinical test values related to renal function
Danazol		Be especially careful in patients with renal impairment.
cyclosporine		Cyclosporine inhibits CYP3A4, and concomitant use may inhibit the metabolism of this drug. ciclosporin Due to the OATP1B1 inhibitory effect, hepatic uptake of the open acid form of this drug may be suppressed, leading to an increase in plasma concentration. Be especially careful in patients with renal impairment.
Erythromycin Clarithromycin HIV protease inhibitors ritonavir etc.	Rhabdomyolysis, which is accompanied by rapid deterioration of renal function, is likely to occur. [If you notice the onset of subjective symptoms (muscle pain, weakness), increased CK (CPK), increased myoglobin in blood or urine, or increased serum creatinine, discontinue administration immediately. thing.]	These drugs inhibit CYP3A4, and concomitant use may inhibit the metabolism of this drug. Be especially careful in patients with renal impairment.
nicotinic acid		Be especially careful in patients with renal impairment.
It has been reported that the plasma concentration of this drug decreased when used in combination with efavirenz.		of efavirenz Metabolism of this drug may be accelerated due to CYP3A4 induction.
amiodarone amlodipine verapamil	Concomitant use may increase the AUC of this drug and cause rhabdomyolysis or myopathy.	Mechanism unknown
diltiazem		Diltiazem may inhibit CYP3A4-mediated metabolism of this drug.
grapefruit juice	There are reports that the AUC of this drug increases when used together. Avoid drinking grapefruit juice while taking this drug.	Grapefruit juice inhibits CYP3A4 and may inhibit the metabolism of this drug.
Concomitant use with grazoprevir may increase the plasma concentration of this drug.		Grazoprevir inhibits intestinal CYP3A and Inhibits BCRP.
ÿ vadadustat		Vadadustat inhibits BCRP.
If used concomitantly with daptomycin, CK (CPK) may increase, so consider discontinuing this drug while receiving daptomycin.		Mechanism unknown

ÿÿ ÿ **Four.**

Adverse reactions This drug has not been subjected to use results surveys or other studies to clarify the frequency of adverse reactions. **(1)**

Serious side effects (incidence unknown) 1) Rhabdomyolysis, myopathy: Rhabdomyolysis, which is characterized by muscle pain, weakness, increased CK (CPK), and increased myoglobin in blood and urine, occurs. , severe kidney damage such as acute kidney injury may occur. In addition, myopathy may occur, so be careful of widespread muscle pain, muscle tenderness, or marked CK (CPK) increase. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

2) Immune-mediated necrotizing myopathy: Immune-mediated necrotizing myopathy may occur, so patients should be carefully observed, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. **3)** Hepatitis, liver dysfunction, jaundice: Hepatitis, jaundice, and other liver dysfunction may occur. In addition, in rare cases it may lead to liver failure, so please conduct thorough monitoring such as liver function tests on a regular basis, and if any abnormalities are observed, discontinue administration and take appropriate measures. **4)** Peripheral neuropathy: Sensory disorders such as hypoesthesia in the extremities, numbness and coldness, or peripheral neuropathy such as muscle weakness may occur. If any abnormalities are observed, administration should be discontinued. Appropriate measures should be taken.

5) Thrombocytopenia: Thrombocytopenia may occur, so carefully monitor blood tests, etc., and if any abnormalities are found, discontinue administration and take appropriate measures. **6)** Hypersensitivity syndrome: Hypersensitivity syndrome including lupus-like syndrome, vasculitis, etc. has been reported. If such symptoms occur, administration should be discontinued and appropriate measures should be taken. **7)** Interstitial pneumonia: Interstitial pneumonia may occur, so even after long-term administration, if fever, cough, difficulty in breathing, abnormal chest X-rays, etc. are observed, administration should be discontinued. , take appropriate measures such as administering corticosteroids. **8)** Myasthenia gravis: Myasthenia gravis (ocular muscle type, generalized type) may develop or worsen. Therefore, the patient should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate

ÿ treatment should be carried out. To carry out Do treatment. **(2)Other side effects**

If the following symptoms or abnormalities occur, take appropriate measures such as discontinuing administration.

	Frequency of side effects Frequency unknown
digester	Abdominal pain, nausea, diarrhea, indigestion, vomiting, loss of appetite, constipation, flatus, abdominal distention, stomatitis, glossitis, pancreatitis
increase, liver	AST (GOT) increase, ALT (GPT) increase, Al-P LDH increase, ÿ-GTP increase, total bilirubin level increase
skin	Pruritus, rash, urticaria, hair loss, erythema, photosensitivity, lichen planus
muscle	CK (CPK) increase, myoglobin increase, muscle pain, muscle spasm
Blood anemia, leukopenia	
mental nervous system	Headache, insomnia, dizziness, numbness, cognitive dysfunction (memory disorder, confusion, etc.), depression
others	Decreased testosterone, fatigue, increased BUN, edema, dry mouth, joint pain, tinnitus, fever, hot flashes, chest pain, abnormal taste, heart palpitations, frequent urination, erectile dysfunction, increased HbA1c, increased blood sugar levels

Five. Administration to the elderly

Physiological functions generally decline in elderly people, so care should be taken to reduce the amount taken. [There are reports that rhabdomyolysis is more likely to occur.] (Refer to “4. Side effects (1) Serious side effects”)]

6. Administration to pregnant women, parturient women, lactating women, etc. (1) Do not administer to pregnant women or women who may be pregnant. [Fetal skeletal malformations have been reported in rats following large doses of the active metabolite (open acid form) of simvastatin and other HMG-CoA reductase inhibitors. (2) Do not administer to breastfeeding women. [In milk in rats A transition has been observed.]

7. Administration to children, etc.

Safety in low birth weight infants, neonates, infants, infants, or children has not been established.

8. Precautions for application : When delivering drugs: For drugs packaged in PTP, instruct patients to take them out of the PTP sheet before taking them. [It has been reported that if a PTP sheet is accidentally ingested, the hard, sharp edges may penetrate the esophageal mucosa and even perforate the sheet, resulting in serious complications such as mediastinal sinusitis.]

9. Other precautions It has been reported overseas that patients taking HMG-CoA reductase inhibitors, including this drug, had a higher risk of developing diabetes.

[Drug kinetics]

1. Bioequivalence test

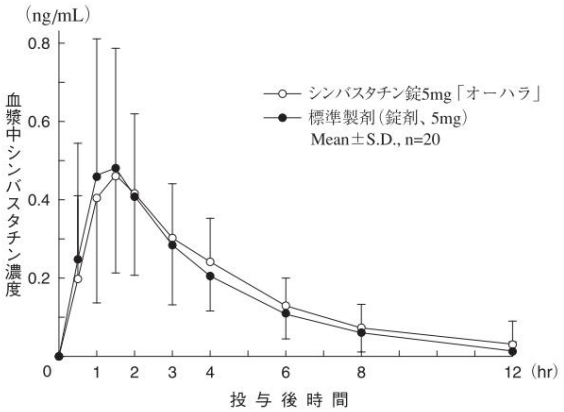
Simvastatin tablets 5 mg, 10 mg, and 20 mg "OHHARA" and each standard formulation were administered orally in a single dose to healthy male adults using a crossover method (5 mg, 10 mg, and 20 mg of simvastatin). The plasma concentration of the unchanged drug was measured using

As a result of statistical analysis of Cmax), bioequivalence of both drugs was confirmed3), 4). (1) Simvastatin tablets 5 mg “Ohara”

Pharmacokinetic parameters

	n	AUC0ÿ12 ÿng•hr/mLÿ	Cmax (ng/mL)	tmax ÿhrÿ	t1/2 ÿhrÿ
Simvastatin Tablets “Ohara” 5mg	20	2.04±0.88	0.51±0.24	2.2±2.5	3.4±2.6
standard formulation (tablets, 5mg)	20	1.89±0.95	0.55±0.33	1.6±0.7	2.8±1.5

ÿMean±S.D.ÿ



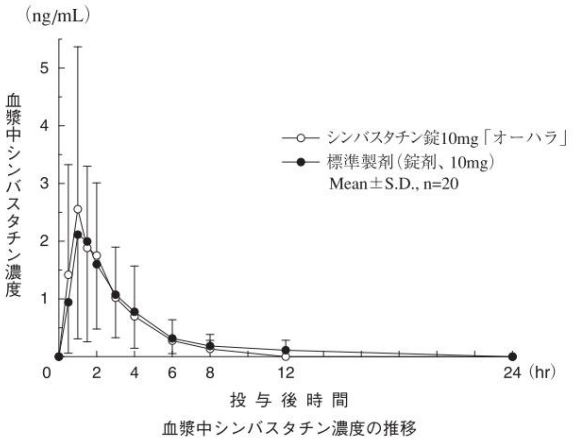
血漿中シンバスタチン濃度の推移

(2)Simvastatin tablets 10mg “Ohara”

Pharmacokinetic parameters

	n	AUC0ÿ24 ÿng•hr/mLÿ	Cmax (ng/mL)	tmax ÿhrÿ	t1/2 ÿhrÿ
Simvastatin Tablets “Ohara”	10mg 20	7.50±5.78	2.70±2.76	1.3±0.6	2.1±1.2
standard formulation (tablet, 10mg)	20	8.07±6.62	2.48±1.82	1.5±0.8	3.1±2.4

ÿMean±S.D.ÿ



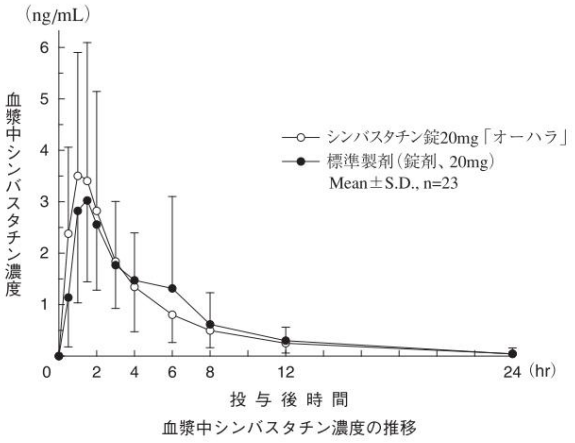
血漿中シンバスタチン濃度の推移

(3) Simvastatin tablets 20mg “Ohara”

Pharmacokinetic parameters

	n	AUC0ÿ24 ÿng•hr/mLÿ	Cmax (ng/mL)	tmax ÿhrÿ	t1/2 ÿhrÿ
Simvastatin tablets “Ohara”	20mg 23	15.61±7.96	4.31±2.98	1.1±0.6	4.0±2.1
standard formulation (tablet, 20mg)	23	16.11±9.00	3.97±1.74	2.0±1.5	3.7±2.4

ÿMean±S.D.ÿ



血漿中シンバスタチン濃度の推移

Plasma concentrations and parameters such as AUC and Cmax may vary depending on test conditions such as subject selection and number and time of blood sampling. **2.**

Dissolution

behavior It has been confirmed that simvastatin tablets 5 mg “OHHARA”, simvastatin tablets 10 mg “OHHARA” and simvastatin tablets 20 mg “OHHARA” conform to the dissolution standards for simvastatin tablets stipulated in the Japanese Pharmacopoeia monograph. 5).

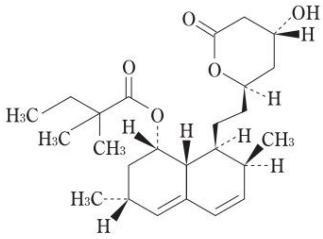
[Efficacy and

Pharmacology] Suppresses cholesterol biosynthesis by selectively inhibiting HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis6).

[Physical and chemical knowledge about

active ingredients] Generic name: Simvastatin

Chemical name: (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-Hydroxy 6-oxotetrahydro-2H -pyran-2-yl]ethyl}-3,7- dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate **structural formula:**



Molecular formula:

C25H38O5 Molecular

weight: 418.57 Properties: This product is a white crystalline powder. This product is easily soluble in acetonitrile, methanol or ethanol (99.5), and almost insoluble in water.

[Handling Precautions]

As a result of a long-term storage test (at normal temperature and humidity, 3 years) using the final packaged product, the appearance, content, etc. were within the standard range, and simvastatin tablets 5 mg "OHHARA" It was confirmed that simvastatin tablets 10mg ``OHHARA'' and simvastatin tablets 20mg ``OHHARA'' are stable for 3 years under normal market distribution7).

[Packaging]

Simvastatin Tablets 5 mg “Ohara”:
(PTP) 100 tablets (10 tablets x 10 x 1 bag)

Simvastatin tablets 10mg "Ohara":
(PTP) 100 tablets (10 tablets x 10 x 1 bag)

Simvastatin tablets 20mg "Ohara":
(PTP) 100 tablets (10 tablets x 10 x 1 bag)

ÿ **[Key documents]**

1) Niemi M.: Pharmacogenomics, 8 (7): 787 (2007) 2) Niemi M.: Clin Pharmacol Ther, 87: 130 (2010) 3) Ohara Pharmaceutical Co., Ltd. Internal materials: Biological Bioequivalence study (2002) 4) Ohara Pharmaceutical Co., Ltd. Internal document: Bioequivalence study (2003)

5) Ohara Pharmaceutical Co., Ltd. Internal material: Dissolution test (2013) 6) 18th edition Japanese Pharmacopoeia commentary (Hirokawa Shoten) C-2495 (2021) 7) Ohara Pharmaceutical Co., Ltd. Internal material: Long-term stability test

[Request for literature/Inquiries for product

information] Please contact the following for requests for in-house materials listed in the main literature. Ohara Pharmaceutical Co., Ltd.

Customer Service Office 36th floor, St. Luke's Tower, 8-1 Akashicho, Chuo-ku, Tokyo 104-6591 0120-419-363 FAX 03-6740-7703 URL https://www.ohara-ch.co .jp

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