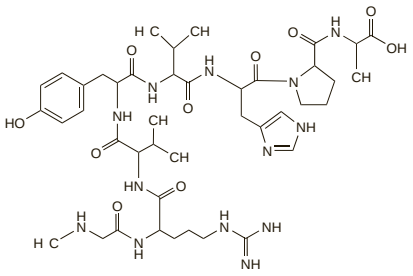
### Saralasin Acetate *(BANM, USAN, rINNM)*

Acetato de sarasalina; P-113; Saralasine, Acétate de; Saralasini Acetas; The acetate of 1-Sar-8-Ala-angiotensin II. The hydrated acetate of Sar-Arg-Val-Tyr-Val-His-Pro-Ala; [1-(*N*-Methylglycine)-5-L-valine-8-L-alanine]-angiotensin II acetate hydrate.

Саралазина Ацетат

$C_{42}H_{65}N_{13}O_{10}$, $xCH_3COOH$,$xH_2O$ = 912.0 (saralasin).

*CAS — 34273-10-4 (saralasin); 54194-01-3 (anhydrous saralasin); 39698-78-7 (saralasin acetate hydrate).*



*(saralasin)*

#### Profile

Saralasin acetate is a competitive antagonist of angiotensin II and thus blocks its pressor action. It is also a partial agonist and causes a transient initial rise in blood pressure. Saralasin has a short half-life and has been used in the differential diagnosis of renovascular hypertension but its use has largely been superseded.

### Sarpogrelate Hydrochloride *(rINNM)*

Hidrocloruro de sarpogrelato; MCI-9042; Sarpogrélate, Chlorhydrate de; Sarpogrelati Hydrochloridum. (±)-2-(Dimethylamino)-1-{[o-(*m*-methoxyphenethyl)phenoxy]methyl}ethyl hydrogen succinate hydrochloride.

Сарпогрелата Гидрохлорид

$C_{24}H_{31}NO_6$,HCl = 466.0.

*CAS — 125926-17-2 (sarpogrelate); 135159-51-2 (sarpogrelate hydrochloride).*

#### Profile

Sarpogrelate is a serotonin 5-$HT_2$-receptor antagonist used as an inhibitor of platelet aggregation in thromboembolic disorders. It is given for occlusive arterial disease (see Peripheral Vascular Disease, p.1178) in oral doses of 100 mg of the hydrochloride three times daily.

#### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Jpn:*** Anplag.

### Saruplase *(BAN, rINN)*

Prourokinase, Non-glycosylated; Recombinant Human Single-Chain Urokinase-type Plasminogen Activator; Saruplasa; Saruplasum; scuPA. Prourokinase (enzyme-activating) (human clone pUK4/pUK18), non-glycosylated.

Саруплаза

$C_{2031}H_{3121}N_{585}O_{601}S_{31}$ = 46343.1.

*CAS — 99149-95-8.*
*ATC — B01AD08.*
*ATC Vet — QB01AD08.*

NOTE. The term prourokinase has been used for both saruplase and nasaruplase (p.1346).

#### Profile

Saruplase is a thrombolytic drug. It is a urokinase-type plasminogen activator with a single chain structure prepared via recombinant DNA technology and is converted to urokinase (p.1420) in the body by plasmin. It also has some intrinsic plasminogen-activating properties. Saruplase has been investigated in acute myocardial infarction.

◊ References.


1. Tebbe U, *et al.* Randomized, double-blind study comparing saruplase with streptokinase therapy in acute myocardial infarction: the COMPASS equivalence trial. *J Am Coll Cardiol* 1998; **31:** 487–93.

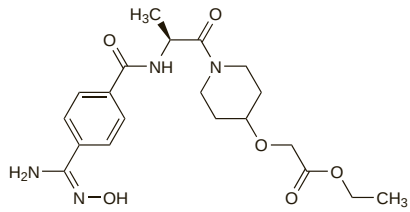

### Sibrafiban *(BAN, USAN, rINN)*

G-7333; Ro-48-3657/001; Sibrafibán; Sibrafibanum. Ethyl (*Z*)-[(1-{*N*-[(*p*-hydroxyamidino)benzoyl]-L-alanyl}-4-piperidyl)oxy] acetate.

Сибрафибан

$C_{20}H_{28}N_4O_6$ = 420.5.

*CAS — 172927-65-0.*



#### Profile

Sibrafiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an oral antiplatelet drug in unstable angina and myocardial infarction but results have been disappointing.

◊ References.


1. Cannon CP, *et al.* Randomized trial of an oral platelet glycoprotein IIb/IIIa antagonist, sibrafiban, in patients after an acute coronary syndrome: results of the TIMI 12 trial. *Circulation* 1998; **97:** 340–9.
2. The SYMPHONY Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. *Lancet* 2000; **355:** 337–45.
3. Second SYMPHONY Investigators. Randomized trial of aspirin, sibrafiban, or both for secondary prevention after acute coronary syndromes. *Circulation* 2001; **103:** 1727–33.

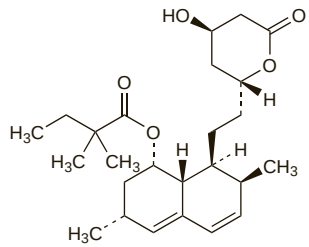

## Simvastatin *(BAN, USAN, rINN)*

L-644128-000U; MK-733; Simvastatiini; Simvastatina; Simvastatinas; Simvastatine; Simvastatinum; Sinvinolina; Synvinolin; Szimvasztatin; Velastatin; Velastatina. (1*S*,3*R*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-{2-[(2*R*,4*R*)-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]ethyl}-1-naphthyl 2,2-dimethylbutyrate.

Симвастатин

$C_{25}H_{38}O_5$ = 418.6.

*CAS — 79902-63-9.*
*ATC — C10AA01.*
*ATC Vet — QC10AA01.*



**Pharmacopoeias.** In *Eur.* (see p.vii) and *US*.

**Ph. Eur. 6.2** (Simvastatin). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol; very soluble in dichloromethane. Store under nitrogen in airtight containers. Protect from light.

**USP 31** (Simvastatin). A white to off-white powder. Practically insoluble in water; freely soluble in alcohol, in chloroform, and in methyl alcohol; sparingly soluble in propylene glycol; very slightly soluble in petroleum spirit. Store at a temperature between 15° and 30°, or at 2° to 8°.

### Adverse Effects

The commonest adverse effects of therapy with simvastatin and other statins are gastrointestinal disturbances. Other adverse effects reported include headache, skin rashes, dizziness, blurred vision, insomnia, and dysgeusia. Reversible increases in serum-aminotransferase concentrations may occur and liver function should be monitored (see Precautions, below). Hepatitis and pancreatitis have been reported. Hypersensitivity reactions including anaphylaxis and angioedema have also occurred. Myopathy, characterised by myalgia and muscle weakness and associated with increased creatine phosphokinase concentrations, has been reported, especially in patients also taking ciclosporin, fibric acid derivatives, or nicotinic acid. Rarely, rhabdomyolysis with acute renal failure may develop.

◊ General references.


1. Farmer JA, Torre-Amione G. Comparative tolerability of the HMG-CoA reductase inhibitors. *Drug Safety* 2000; **23:** 197–213.
2. Davidson MH. Safety profiles for the HMG-CoA reductase inhibitors: treatment and trust. *Drugs* 2001; **61:** 197–206.
3. Pasternak RC, *et al.* ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation* 2002; **106:** 1024–8. Also available at: http://circ.ahajournals.org/cgi/reprint/106/8/1024.pdf (accessed 29/05/08)
4. Karthikeyan VJ. Adverse effects of statins: an update. *Adverse Drug React Bull* 2005; (Aug): 895–8.
5. McKenney JM, *et al.* Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol* 2006; **97** (Issue 8 suppl 1): 89C–94C.
6. Armitage J. The safety of statins in clinical practice. *Lancet* 2007; **370:** 1781–90.


**Incidence of adverse effects.** By February 1992 the UK CSM had received 738 reports of adverse effects associated with simvastatin,[1] from an estimated 257 000 prescriptions. Abnormal hepatic function and myalgia were 2 of the most frequently reported reactions, with 36 and 48 reports respectively, including 5 reports of hepatitis and 2 of jaundice. Other muscle effects included 3 reports of myositis, 10 of myopathy, and 7 reports of asymptomatic increases in serum creatine kinase concentrations. Gastrointestinal adverse effects accounted for 20% of the reports; skin, neurological and musculoskeletal effects for 15% each; psychiatric effects for 10%; liver effects for 7%; and visual effects for 4%. A systematic review[2] of data from clinical studies confirmed that the risk of liver transaminase elevation was increased by statins but there was no significant increase in the incidence of myalgia (reported in about 15% of patients), creatine kinase elevation (0.9%), or rhabdomyolysis (0.2%), compared with placebo. The incidence of adverse effects may be greater with high-dose therapy.[3,4]


1. Committee on Safety of Medicines. Simvastatin. *Current Problems 33* 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Kashani A, *et al.* Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006; **114:** 2788–97.
3. Davidson MH, Robinson JG. Safety of aggressive lipid management. *J Am Coll Cardiol* 2007; **49:** 1753–62.
4. Silva M, *et al.* Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. *Clin Ther* 2007; **29:** 253–60.


**Carcinogenicity.** For discussion of the effects of statins on the risk of cancer, see Malignant Neoplasms under Uses, below.

**Effects on the blood.** *Thrombocytopenia* has been reported rarely with statin therapy. Serious thrombocytopenic purpura has occurred with simvastatin, with the onset ranging from 1 or 2 days[1,2] to 11 or 12 months[3,4] after starting treatment. Platelet counts improved after stopping simvastatin in each case, although most patients were given corticosteroids, immunoglobulins, or plasma exchange. There has also been a similar report with atorvastatin,[5] which recurred on rechallenge; the patient had previously taken simvastatin without developing thrombocytopenia, suggesting an idiosyncratic reaction.

A case of *haemolytic anaemia* has been reported[6] in a patient taking lovastatin; no adverse effect was seen when the patient was given simvastatin.

Statins have effects on coagulation and fibrinolysis but these are generally beneficial (see Action under Uses, below); there have been rare reports of *ocular haemorrhage*,[7] but the association with statins is not established.


1. McCarthy LJ, *et al.* Thrombotic thrombocytopenic purpura and simvastatin. *Lancet* 1998; **352:** 1284–5.
2. Sundram F, *et al.* Thrombotic thrombocytopenic purpura associated with statin treatment. *Postgrad Med J* 2004; **80:** 551–2.
3. Possamai G, *et al.* Thrombocytopenic purpura during therapy with simvastatin. *Haematologica* 1992; **77:** 357–8.
4. Groneberg DA, *et al.* Simvastatin-induced thrombocytopenia. *Am J Hematol* 2001; **67:** 277.
5. González-Ponte ML, *et al.* Atorvastatin-induced severe thrombocytopenia. *Lancet* 1998; **352:** 1284.
6. Robbins MJ, *et al.* Lovastatin-induced hemolytic anemia: not a class-specific reaction. *Am J Med* 1995; **99:** 328–9.
7. Fraunfelder FW. Ocular hemorrhage possibly the result of HMG-CoA reductase inhibitors. *J Ocul Pharmacol Ther* 2004; **20:** 179–82.


**Effects on the eyes.** Studies in *animals* have suggested that some statins could cause cataracts, but this has not been confirmed in humans. Although a study[1] with lovastatin found lens opacities in 13 of 101 patients after treatment for 18 weeks, no deterioration in visual function was found in 11 of these who continued lovastatin and were followed up for an average of 26 months from the start of treatment. Similarly, no differences were found in the development of lens opacities or in changes in visual acuity between patients treated with lovastatin for 48 weeks and patients taking placebo in a study of 8245 patients.[2] A large case-control study[3] found no evidence that use of therapeutic statin doses was associated with the development of cataracts, although the risk did appear to be increased in patients taking simvastatin with erythromycin. Further observational studies have suggested that statins may have beneficial effects; in one study[4] there was no effect on the overall incidence of cataract but the risk of developing nuclear cataract appeared to be decreased, while another study[5] reported a reduction in the overall incidence but this was not significant for any specific cataract type.

For mention of ocular haemorrhage in patients taking statins, see above.


1. Hunninghake DB, *et al.* Lovastatin: follow-up ophthalmologic data. *JAMA* 1988; **259:** 354–5.