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Cerivastatin

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Contents

Summary

▲ Cerivastatin is a synthetic HMG-CoA reductase inhibitor with high liver selectivity, which lowers plasma cholesterol levels by inhibiting endogenous cholesterol synthesis.

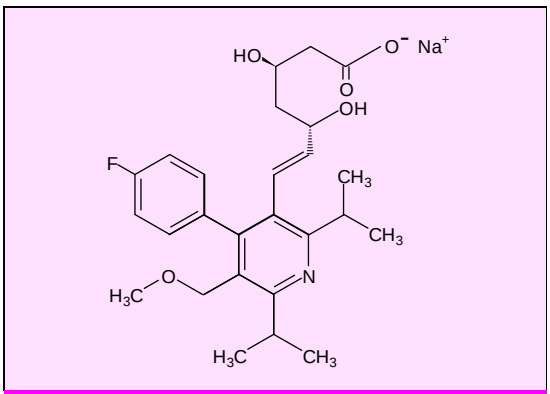
▲ *In vitro*, the affinity of cerivastatin for HMG-CoA reductase was higher than that of lovastatin, simvastatin and pravastatin. This higher enzyme affinity was reflected *in vivo*, with a lower ED_{50} (dose causing 50% inhibition) for cerivastatin in rats and beagle dogs compared with lovastatin.

▲ Cerivastatin 0.2 mg/day significantly reduced low density lipoprotein (LDL)-cholesterol, total cholesterol and triglyceride levels, and increased high density lipoprotein (HDL)-cholesterol levels, in patients with type IIa hypercholesterolaemia.

▲ Available data indicate that cerivastatin has a tolerability profile similar to that of other HMG-CoA reductase inhibitors.

▲ No drug interactions were observed when cerivastatin was coadministered with digoxin, warfarin, cimetidine or the antacid magnesium/aluminium hydroxide.

Features and properties of cerivastatin (BAY W 6228)	
Indications	
Primary hypercholesterolaemia (types IIa and IIb)	Launched
Mechanism of action	
Lipid-lowering	HMG-CoA reductase inhibitor
Dosage and administration	
Usual dosage in clinical trials	0.1-0.3 mg/day
Route of administration	Oral
Frequency of administration	Once daily in the evening
Pharmacokinetic profile (0.2mg dose)	
Peak plasma concentration	0.002 mg/L
Time to peak plasma concentration	2.5-3h
Area under the plasma concentration-time curve	0.01 mg/L • h
Bioavailability	60%
Clearance	13 L/h
Elimination half-life	2.1-3.1h
Adverse events	
Serious events	Potential myopathy



Cerivastatin (BAY W 6228)

Cerivastatin is a synthetic inhibitor of HMG-CoA reductase, the enzyme which catalyses the rate-limiting step of cholesterol biosynthesis. The resulting reduction in intracellular cholesterol causes up-regulation of low density lipoprotein (LDL)-cholesterol receptors, thereby increasing clearance of plasma LDL-cholesterol.

Elevated LDL-cholesterol levels are a well established risk factor for coronary heart disease. Primary and secondary prevention studies using other HMG-CoA reductase inhibitors have clearly demonstrated that lowering LDL-cholesterol levels is an effective treatment strategy for reducing coronary morbidity and mortality.[1-4]

1. Pharmacodynamic Profile

Lipid-Lowering Effects

- Cerivastatin has high affinity for HMG-CoA reductase. *In vitro*, the drug inhibited isolated rat enzyme at concentrations significantly lower than those of simvastatin, lovastatin and pravastatin (fig. 1).[5,6]

- A 0.002 mg/kg oral dose of cerivastatin caused 50% inhibition (ED_{50}) of hepatic cholesterol synthesis in Wistar rats and beagle dogs; the ED_{50} for lovastatin was 0.2 to 0.3 mg/kg.[7] Cerivastatin was about 50-fold less active against cholesterol synthesis in nonhepatic versus hepatic rat tissue (ED_{50} values were >0.1 mg/kg in small intestine and testes).[6]

- The main human cerivastatin metabolites M1, M23 and M24 inhibited hepatic cholesterol synthesis in rats after intravenous administration; ED_{50} values were similar to that of the parent drug (0.001 to 0.006 mg/kg).[5,8]

- In cholestyramine-primed dogs, 20 days' treatment with oral cerivastatin (0.01 to 0.1 mg/kg) dose-dependently reduced serum total cholesterol levels by up to 59% from baseline. In addition, the drug reduced serum triglyceride levels by up to 77% from baseline.[6]

- In beagle dogs fed standard chow, oral cerivastatin 0.1 mg/kg/day for 13 weeks significantly reduced serum levels of total cholesterol (–41%; $p < 0.001$), LDL-cholesterol (–52%), very low density lipoprotein (VLDL)-cholesterol (–23%) and triglycerides (–24%; $p < 0.001$) after adjustment for vehicle-treated controls (fig. 2).[6]

- Seven days' treatment with cerivastatin 0.1 to 0.4 mg/day (given once or twice daily) reduced total cholesterol by up to 26% and LDL-cholesterol by up to 36% in 46 healthy volunteers. All re-

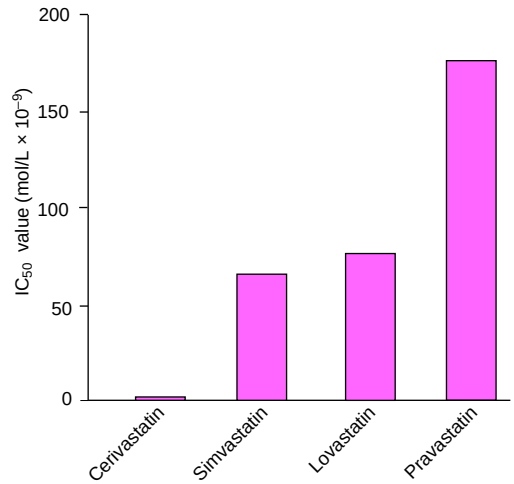


Fig. 1. Effects of various HMG-CoA reductase inhibitors on rat enzyme activity *in vitro*. Concentrations of cerivastatin, simvastatin, lovastatin and pravastatin causing 50% inhibition (IC_{50}) of isolated rat HMG-CoA reductase.[5]

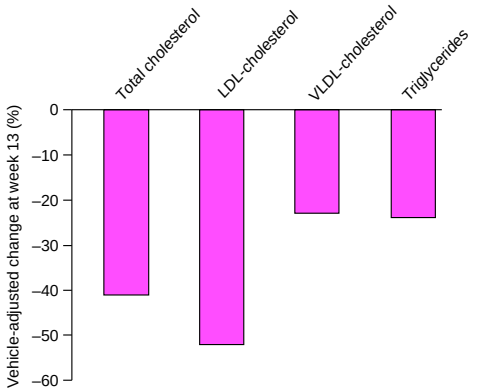


Fig. 2. Lipid-lowering effects of cerivastatin in standard chow-fed beagle dogs. 12 dogs received oral cerivastatin 0.1 mg/kg/day once daily for 13 weeks; results were adjusted for those reported in vehicle-treated controls (n = 8).[6] *Abbreviations:* LDL = low density lipoprotein; VLDL = very low density lipoprotein.

gimens produced a statistically significant reduction in total and LDL-cholesterol compared with placebo ($p < 0.01$).[9]

Other Effects

- Cerivastatin dose-dependently inhibited human smooth muscle cell migration and proliferation *in vitro*.[10,11] At the concentrations used, cerivastatin was more effective than simvastatin, fluvastatin, atorvastatin, lovastatin and pravastatin.[11]

- Nine weeks' treatment with cerivastatin 0.1 mg/kg/day reduced cholesterol ester accumulation in the aortic arch of cholesterol-fed rabbits by 73% compared with untreated hypercholesterolaemic rabbits ($p < 0.01$).[6]

- Subcutaneous cerivastatin 1 mg/kg/day for 2 weeks suppressed balloon catheterisation-induced intimal thickening in rabbits by attenuating smooth muscle cell proliferation and macrophage infiltration. The intima/media thickness ratio in the cerivastatin group was reduced to 45% of that in controls ($p < 0.05$).[12,13]

2. Pharmacokinetic Profile

- After a single 0.2mg dose of cerivastatin in healthy volunteers, maximum plasma concentrations (C_{max}; about 0.002 mg/L) were reached in 2.5 to 3 hours, and the area under the plasma cerivastatin concentration-time curve (AUC) was approximately 0.01 mg/L · h.[14-16] Preliminary data indicate that cerivastatin exhibits linear pharmacokinetics over the dose range 0.02 to 0.4mg.[17] The absolute bioavailability of oral cerivastatin is about 60%, and the relative bioavailability (tablet compared with solution) is 100%.[15]

- Cerivastatin is highly bound to plasma proteins (≈99%)[18] and has a low volume of distribution at steady state (approximately 0.3 L/kg), which indicates that cerivastatin penetrates only moderately into peripheral tissues.[15]

- The elimination half-life ($t_{½}$) of cerivastatin after a single 0.2mg dose ranges from 2.1 to 3.1 hours.[14-16] Total body clearance is about 13 L/h.[15]

- Cerivastatin is eliminated via cytochrome P450 3A–mediated biotransformation.[19] Demethylation of the benzylic methylether leads to active metabolite M1, and hydroxylation of a methyl group in the 6′-isopropyl moiety leads to active metabolite M23. The combination of both transformation reactions results in the minor metabolite M24.[19]

- Approximately 30% of a dose is excreted as metabolites (M1, M23 and M24) in urine; the remainder is excreted in the faeces.[20]

- The pharmacokinetics of cerivastatin are not affected by ethnicity,[21] age,[22] gender[23] or the presence of food.[24] Furthermore, a study in 18 patients with varying degrees of renal insufficiency showed that renal dysfunction did not have a clinically significant effect on the plasma pharmacokinetics of cerivastatin or its metabolites.[20]

- The pharmacokinetics of cerivastatin were not affected by concomitant administration of cimetidine or magnesium/aluminium hydroxide.[14] Coadministration of cholestyramine reduced the bioavailability of cerivastatin by up to 21%; how-

ever, this effect is unlikely to be clinically relevant if the drugs are administered at least 1 hour apart.[25]

- Unlike some other statins, coadministration of cerivastatin does not affect the pharmacokinetics of digoxin[16] or warfarin.[26]

- Pre- and co-treatment with erythromycin 500mg 3 times daily reduced the clearance of a 0.3mg cerivastatin dose in 12 male volunteers. This resulted in increases in C_{max} (by a mean 13%), $t_{½}$ (by approximately 10%) and AUC (by 21%).[27] However, these changes were not considered sufficient to warrant dosage adjustment.[27]

3. Therapeutic Trials

- Four weeks' treatment with cerivastatin 0.2 mg/day reduced LDL-cholesterol levels by up to 30% ($p < 0.05$ *vs* placebo) in a study of 319 patients with type IIa hypercholesterolaemia.[28] Total cholesterol and triglyceride levels were reduced by up to 22% ($p < 0.05$ *vs* placebo) and 12%, respectively, whereas high density lipoprotein (HDL)-cholesterol levels increased by up to 5% ($p < 0.05$ *vs* placebo). An initial response was seen by week 1 of treatment, with maximal responses observed by week 3. The reductions in total and LDL-cholesterol were significantly greater after once daily administration (in the evening or at bedtime) than after twice daily administration.[28]

- Cerivastatin 0.025 to 0.2 mg/day significantly and dose-dependently reduced LDL-cholesterol levels after 12 weeks' treatment in a study involving 894 evaluable patients with type IIa hypercholesterolaemia ($p \leq 0.05$).[29] The highest cerivastatin dosage reduced LDL-cholesterol levels by 30.6% compared with a 2% reduction with placebo ($p \leq 0.05$).[29] An adequate response (LDL-cholesterol levels reduced by >15%) occurred in 94% of patients treated with cerivastatin 0.2 mg/day and 99% of those treated with simvastatin 20 mg/day compared with 9% of those who received placebo.[30]

- The lipid-lowering efficacy of cerivastatin 0.3 mg/day was similar to that of lovastatin 40 mg/day when either drug was administered once daily for 24 weeks in a study involving 939 patients with type IIa hypercholesterolaemia.[31] LDL- and total cholesterol levels were reduced by 29 and 20%, respectively, with cerivastatin ($p < 0.001$ *vs* placebo) and by 33 and 24% with lovastatin ($p < 0.001$ *vs* placebo).

- In a study involving 751 patients with type IIb hypercholesterolaemia, treatment with cerivastatin 0.1, 0.2 and 0.3 mg/day for up to 16 weeks significantly and dose-dependently reduced levels of LDL-cholesterol (by 15.1, 23.0 and 24.2%, respectively) and triglycerides (by 14.8, 11.7 and 20.3%, respectively) from baseline ($p < 0.01$ *vs* placebo). Corresponding reductions from baseline achieved with gemfibrozil 1200 mg/day were 7.5 and 50.3% ($p < 0.01$ *vs* placebo).[32] The efficacy of cerivastatin was maintained during a 1-year extension phase.[33]

4. Tolerability

- Oral cerivastatin 0.2 mg/day for 4 weeks was well tolerated in 273 patients with hypercholesterolaemia, the most common adverse events being rhinitis, headache, pharyngitis, flu syndrome, sinusitis, arthralgia, chest pain and insomnia (fig. 3).[28] The tolerability profile of cerivastatin was not significantly different from that of placebo with regard to creatine kinase, serum aspartate aminotransferase and serum alanine aminotransferase levels, or with regard to ophthalmological changes.[28] Only 2 treatment-related withdrawals (skin rash and arm pain) were reported. Although serum creatine kinase levels increased slightly in 9 to 12% of patients, drug-induced myopathy was not apparent.[28]

- An unpublished meta-analysis of 9 studies involving >4000 patients with primary hypercholesterolaemia showed that the tolerability profile of cerivastatin 0.025 to 0.3 mg/day was not significantly different from that of lovastatin, simvastatin, gemfibrozil or placebo.[34] However, 1.6% of patients treated with cerivastatin 0.1 to 0.3 mg/day withdrew because of adverse events, com-

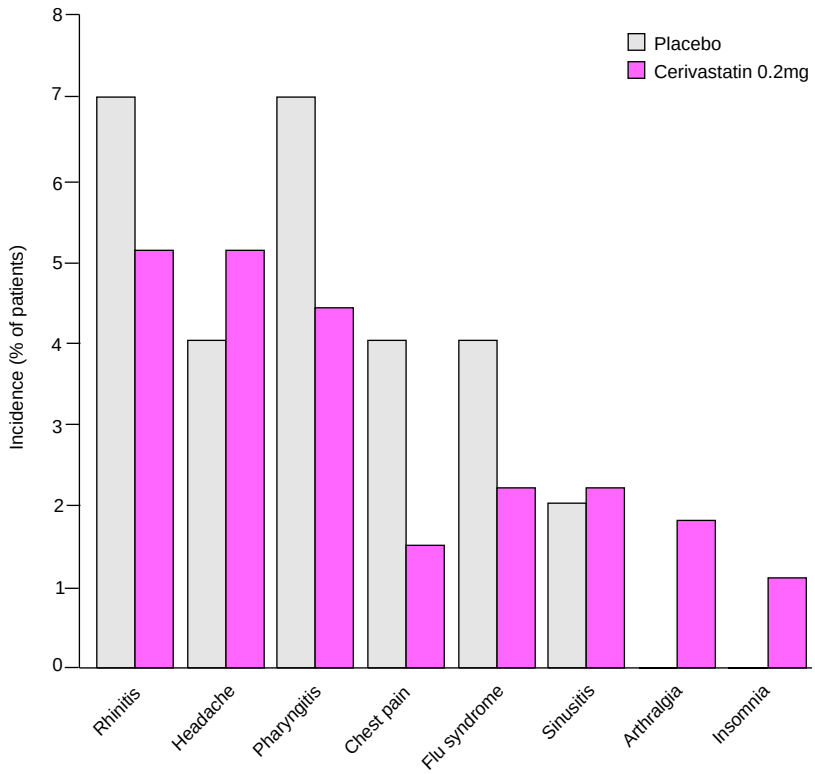


Fig. 3. Tolerability profile of cerivastatin. Most commonly reported adverse events in patients with type IIa hypercholesterolaemia who received cerivastatin 0.2 mg/day (n = 273) or placebo (n = 46) for 4 weeks.[28]

pared with 3.2% of patients taking lovastatin or simvastatin and 2.3% taking placebo.[34]

- Unpublished data have reported that cerivastatin and simvastatin were associated with a similar incidence of ophthalmological changes over a 2-year treatment period (8 *vs* 11% for new nuclear opacities and 6 *vs* 8% for new posterior subcapsular abnormalities).[35]

5. Cerivastatin: Current Status

Cerivastatin is an HMG-CoA reductase inhibitor which has been launched in a number of European countries (including the UK, Germany, the Netherlands and Sweden) and the USA for the treatment of patients with type IIa or IIb hypercholesterolaemia who have not responded adequately to diet. In addition, it has been approved in most other European countries.

Clinical trials indicate that cerivastatin is as effective and as well tolerated as other HMG-CoA reductase inhibitors in patients with type IIa hypercholesterolaemia and as effective as gemfibrozil in patients with type IIb hypercholesterolaemia.

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