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Cerivastatin

A Review of its Pharmacological Properties and Therapeutic Efficacy in the Management of Hypercholesterolaemia

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Data Selection

Sources: Medical literature published in any language since 1966 on Cerivastatin, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International, Auckland, New Zealand). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'Cerivastatin' or 'Cerivastatin sodium' or 'BAY W 6228'. EMBASE search terms were 'Cerivastatin' or 'Cerivastatin sodium' or 'BAY W 6228'. AdisBase search terms were 'Cerivastatin' or 'Cerivastatin sodium' or 'BAY W 6228'. Searches were last updated 20 October 2000.

Selection: Studies in patients with hypercholesterolaemia who received cerivastatin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: cerivastatin, HMG-CoA reductase inhibitors, hypercholesterolaemia, hyperlipidaemia, pharmacodynamics, pharmacokinetics, therapeutic use, drug interactions, tolerability, adverse events, pharmacoeconomics, review.

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Summary

Abstract

Cerivastatin is an HMG-CoA reductase inhibitor used for the treatment of patients with hypercholesterolaemia. The lipid-lowering efficacy of cerivastatin has been demonstrated in a number of large multicentre, randomised clinical trials. Earlier studies used cerivastatin at relatively low dosages of ≤0.3mg orally once daily, but more recent studies have focused on dosages of 0.4 or 0.8 mg/day currently recommended by the US Food and Drug Administration (FDA).

Along with modest improvements in serum levels of triglycerides and high density lipoprotein (HDL)-cholesterol, cerivastatin 0.4 to 0.8 mg/day achieved marked reductions in serum levels of low density lipoprotein (LDL)-cholesterol (33.4 to 44.0%) and total cholesterol (23.0 to 30.8%). These ranges included results of a pivotal North American trial in almost 1000 patients with hypercholesterolaemia. In this 8-week study, US National Cholesterol Education Program (Adult Treatment Panel II) [NCEP] target levels for LDL-cholesterol were achieved in 84% of patients randomised to receive cerivastatin 0.8 mg/day, 73% of those treated with cerivastatin 0.4 mg/day and <10% of placebo recipients. Among patients with baseline serum LDL-cholesterol levels meeting NCEP guidelines for starting pharmacotherapy, 75% achieved target LDL-cholesterol levels with cerivastatin 0.8 mg/day. In 90% of all patients receiving cerivastatin 0.8 mg/day, LDL-cholesterol levels were reduced by 23.9 to 58.4% (6th to 95th percentile). Various subanalyses of clinical trials with cerivastatin indicate that the greatest lipid-lowering response can be expected in women and elderly patients.

Cerivastatin is generally well tolerated and adverse events have usually been mild and transient. The overall incidence and nature of adverse events reported with cerivastatin in clinical trials was similar to that of placebo. The most frequent adverse events associated with cerivastatin were headache, GI disturbances, asthenia, pharyngitis and rhinitis. In the large pivotal trial, significant elevations in serum levels of creatine kinase and transaminases were reported in a small proportion of patients receiving cerivastatin but not in placebo recipients. As with other HMG-CoA reductase inhibitors, rare reports of myopathy and rhabdomyolysis have occurred with cerivastatin, although gemfibrozil or cyclosporin were administered concomitantly in most cases.

Postmarketing surveillance studies in the US have been performed. In 3 mandated formulary switch conversion studies, cerivastatin was either equivalent or superior to other HMG-CoA reductase inhibitors, including atorvastatin, in reducing serum LDL-cholesterol levels or achieving NCEP target levels. Pharmacoeconomic data with cerivastatin are limited, but analyses conducted to date in the US and Italy suggest that cerivastatin compares favourably with other available HMG-CoA reductase inhibitors in terms of its cost per life-year gained.

Conclusion: Cerivastatin is a well tolerated and effective lipid-lowering agent for patients with hypercholesterolaemia. When given at dosages currently recommended by the FDA in the US, cerivastatin achieves marked reductions in

serum levels of LDL-cholesterol, reaching NCEP target levels in the vast majority of patients. Thus, cerivastatin provides a useful (and potentially cost effective) alternative to other currently available HMG-CoA reductase inhibitors as a first-line agent for hypercholesterolaemia.

Pharmacodynamic Properties

Animal and *in vitro* data have shown that cerivastatin has a high affinity for HMG-CoA reductase and that it inhibits hepatic cholesterol synthesis at concentrations around 100 times lower than those of lovastatin. The demethylated (M1) and hydroxylated (M23) metabolites of cerivastatin have inhibitory activity similar to that of the parent compound. Studies in animals and healthy volunteers showed that serum lipid responses to cerivastatin are dose dependent. Mean serum total and low density lipoprotein (LDL)-cholesterol levels were reduced relative to baseline by up to 26.3 and 36.4%, respectively, after 7 days' treatment with cerivastatin 0.1 to 0.4 mg/day in a study in healthy volunteers.

Cerivastatin has shown vascular effects of interest in preclinical studies, most notably attenuation of proliferation of vascular smooth muscle cells, fibroblasts, endothelial cells and myoblasts. In one study, cerivastatin was shown to possess greater potency in terms of drug concentrations required to inhibit cell proliferation than all other commercially available HMG-CoA reductase inhibitors. Antiatherogenic effects such as inhibition of monocyte adhesion to vascular endothelium, and stabilisation of fibrous material in stenotic plaques, have also been reported. Cerivastatin has also been associated with improved endothelial function, shown by markedly and statistically significant increases relative to placebo in forearm blood flow in patients receiving 0.4 mg/day for 2 weeks. The drug has no apparent effect on insulin sensitivity, but has been associated with suppression of serum levels of steroid sex hormones in women.

Pharmacokinetic Properties

Cerivastatin undergoes near-complete GI absorption after oral administration (with no clinically relevant interference by food), but undergoes first-pass metabolism and has an absolute bioavailability of 60%. Maximum plasma concentrations are attained after 2 to 3 hours. The drug exhibits linear pharmacokinetics over the dose range 0.15 to 0.8mg. Cerivastatin is highly bound to plasma proteins (>99%) and has a volume of distribution of approximately 0.3 L/kg.

Metabolism is via hepatic cytochrome P450 (CYP) 3A4 and 2C8 to yield demethylated (M1) and hydroxylated (M23) active major metabolites. These metabolites contribute ≈20 to 25% of the total activity of each dose of cerivastatin. Approximately 70% of a dose is excreted in the faeces, with intact cerivastatin accounting for less than 2% of the total originally administered. The plasma elimination half-life after oral administration is 2 to 3 hours. The pharmacokinetic characteristics of cerivastatin are not affected by advanced age, gender or ethnicity.

Patients with moderate to severe renal impairment have shown an increase in 24-hour area under plasma cerivastatin concentration versus time curve of up to approximately 60% relative to healthy individuals. Mild renal impairment (creatinine clearance 3.7 to 5.4 L/h per 1.73m^2) does not have any clinically relevant effect on the pharmacokinetics of the drug.

As a result of dual hepatic metabolism of cerivastatin, no potentially significant drug interactions with cerivastatin have been noted with the CYP3A4 inhibitors erythromycin and itraconazole. However, the bile acid sequestrant cholestyramine has been shown to impair the absorption of cerivastatin, and a temporal separation of the administration of these 2 drugs has been recommended. Coadministration of the immunosuppressant cyclosporin and cerivastatin

resulted in increased plasma concentrations of the latter in a study in 12 renal transplant recipients. There were no effects on the elimination of cerivastatin or on steady-state plasma concentrations of cyclosporin or its metabolites, however.

Therapeutic Efficacy

The lipid-lowering efficacy of cerivastatin has been demonstrated in a number of large multicentre, randomised studies in patients with hypercholesterolaemia. Earlier studies evaluated cerivastatin at dosages of 0.1 to 0.3 mg/day for 4 to 32 weeks. These studies reported dose-related reductions from baseline in serum levels of total cholesterol ranging from 12.9 to 24.4%, and in LDL-cholesterol ranging from 15.1 to 33.6%. High density lipoprotein (HDL)-cholesterol levels increased by 2.3 to 11.4% with cerivastatin 0.1 to 0.3 mg/day. In general, a treatment response was observed after 1 week of therapy and was maximal by about 3 or 4 weeks.

More recent studies have focused on the lipid-lowering efficacy of cerivastatin at dosages of 0.4 to 0.8 mg/day in patients with hypercholesterolaemia. Cerivastatin 0.4 to 0.8 mg/day was associated with improvements from baseline in serum levels of total cholesterol (–23.0 to –30.8%), LDL-cholesterol (–33.4 to –44.0%), HDL-cholesterol (+3.2 to +8.7%) and triglycerides (–10.4 to –18.4%). These ranges include results of a pivotal multicentre study in almost 1000 patients with primary hypercholesterolaemia. In this 8-week trial, 84% of patients randomised to receive cerivastatin 0.8 mg/day achieved US National Cholesterol Education Program (Adult Treatment Panel II) [NCEP] target levels for LDL-cholesterol compared with 73% of those treated with cerivastatin 0.4 mg/day and <10% of placebo recipients. Among patients with baseline serum LDL-cholesterol levels meeting NCEP guidelines for pharmacotherapy, 75% achieved target LDL-cholesterol levels with cerivastatin 0.8 mg/day. Overall, in 90% of patients receiving cerivastatin 0.8 mg/day, LDL-cholesterol levels were reduced by 23.9 to 58.4% (6th to 95th percentile). One-year follow-up data from this trial showed that the lipid-lowering efficacy of cerivastatin was maintained on a long term basis.

Postmarketing surveillance studies in the US have been performed. In 3 mandated formulary switch conversions, cerivastatin was either equivalent or superior to other HMG-CoA reductase inhibitors, including atorvastatin, in reducing serum LDL-cholesterol levels or achieving NCEP target levels.

Various subanalyses of clinical trials with cerivastatin indicate both age- and gender-related effects. Thus, cerivastatin effectively lowers serum levels of LDL-cholesterol to a greater extent in women than men and in elderly than younger patients.

Tolerability

In general, cerivastatin has been well tolerated in clinical trials, and adverse events have usually been mild and transient. The most frequently reported adverse events with cerivastatin were headache, GI disturbances, asthenia, pharyngitis and rhinitis, although there were essentially no clinically important differences between the overall tolerability profile of cerivastatin and that of placebo. In 2 large pooled analyses, adverse events were reported in approximately 60 to 65% of patients receiving cerivastatin up to 0.4 mg/day or placebo. Discontinuation of therapy because of adverse events occurred in 2.8 and 3.0% of cerivastatin (up to 0.4 mg/day) recipients compared with 2.2 and 2.5% of placebo recipients in the 2 analyses. Adverse events associated with cerivastatin did not appear to be dose related according to pooled results from studies with cerivastatin 0.1 to 0.4 mg/day and data from a pivotal placebo-controlled trial comparing cerivastatin

0.4 and 0.8 mg/day. A small proportion of patients receiving cerivastatin in the pivotal trial had significant elevations in serum levels of creatine kinase and transaminases, whereas these laboratory abnormalities were not reported among placebo recipients.

As with other HMG-CoA reductase inhibitors, postmarketing surveillance data and published case reports indicate that rhabdomyolysis and associated renal failure have been reported (albeit rarely) with cerivastatin, and most cases involved concomitant administration of gemfibrozil or cyclosporin.

Dosage and Administration

The US Food and Drug Administration (FDA) recommends a starting dosage of cerivastatin 0.4mg orally once daily in the evening. The drug may be taken with or without food. If the response to therapy (including continuation of a standard cholesterol lowering diet) is inadequate, cerivastatin dosage may be increased to 0.8 mg/day. Lower dosages are recommended for patients with significant renal impairment. Contraindications to cerivastatin include pregnancy and lactation. The efficacy and tolerability of cerivastatin in paediatric patients have not been established.

1. Cholesterol Synthesis and HMG-CoA Reductase Inhibition

Cholesterol is vital for the maintenance of cell membrane integrity and is required for a number of important physiological functions, including the synthesis of steroid hormones (reviewed by Moghadasian[1]). This and other major plasma lipids such as the triglycerides do not circulate as free molecules in plasma but are bound to proteins and transported as macromolecular complexes known as lipoproteins, the major classes of which are the chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). 60 to 75% of total plasma cholesterol is transported as LDL, the levels of which are directly related to increased risk of cardiovascular disease (notably atherosclerosis and ischaemic heart disease). Plasma levels of HDL, which carries 20 to 25% of the body's total circulating cholesterol,[2] are inversely related to cardiovascular risk.[3,4]

VLDL is converted by the actions of hepatic and endothelial lipase to LDL, much of which is removed from the circulation by the liver. A small proportion, however, appears to be removed by other mechanisms; these include ingestion by macrophages that may migrate into arterial walls where the cholesterol carried contributes to the formation of atherosclerotic plaques. Much of the cholesterol present in the circulation in humans is endogenous and is synthesised in the liver, with small additional amounts being synthesised in the small intestine and the skin. Dietary or exogenous cholesterol forms a minor proportion of the total pool.[1]

Dietary cholesterol is taken up by the liver where elevation of levels suppresses the synthesis of LDL receptors and hence the clearance of circulating LDL and its accompanying cholesterol from plasma. Physiological levels of cholesterol are tightly controlled, however, and restriction of dietary cholesterol leads to an increase in synthesis of endogenous cholesterol from acetate (fig. 1). Suppression of endogenous cholesterol formation under these conditions leads to increased expression of hepatic LDL receptors, which has the effect of drawing LDL-cholesterol out of the bloodstream and into the liver, and reduces plasma levels of cholesterol. This effect represents the rationale behind the use of inhibitors of cholesterol synthesis in the management of hypercholesterolaemia.

Cholesterol is synthesised in a series of chemical reactions as shown in figure 1. The rate-limiting step in this pathway is the conversion of HMG-CoA to mevalonate by HMG-CoA reductase. Since the 1970s, various compounds, including choles-

terol metabolites, bile acids, ketoconazole and the HMG-CoA reductase inhibitors, have been shown to inhibit the activity of HMG-CoA reductase and hence the formation of cholesterol (reviewed by Moghadasian[1]). Cerivastatin (fig. 2) is a synthetic and enantiomerically pure HMG-CoA reductase inhibitor (or 'statin') that is the most recently introduced into clinical practice for the management of hypercholesterolaemia.

2. Pharmacodynamic Properties

Cerivastatin has been shown in animal and *in vitro* studies to have a variety of pharmacodynamic effects. It also has the most potent pharmacodynamic effects among HMG-CoA reductase inhibitors available commercially to date. The pharmacodynamic profile of cerivastatin is summarised in table I and reviewed in more detail in the following discussion.

2.1 Effects on HMG-CoA Reductase and Lipids

Preclinical studies carried out in animals and *in vitro* have shown that cerivastatin has a high affinity for HMG-CoA reductase, and that it inhibits hepatic cholesterol synthesis at concentrations approximately 100 times lower than those required for lovastatin.

Cerivastatin competitively inhibited membrane-bound HMG-CoA reductase (isolated from the native microsomal fraction of rat liver), with an inhibition constant (K_i) of 1.3×10^{-9} mol/L. The K_i for lovastatin in the same *in vitro* system was 150×10^{-9} mol/L.[5] Concentrations required for 50% inhibition of enzyme activity (IC_{50}) in another, similar, experiment were 1.1×10^{-9}, 66×10^{-9}, 77×10^{-9} and 176×10^{-9} mol/L for cerivastatin, simvastatin, lovastatin and pravastatin, respectively.[6]

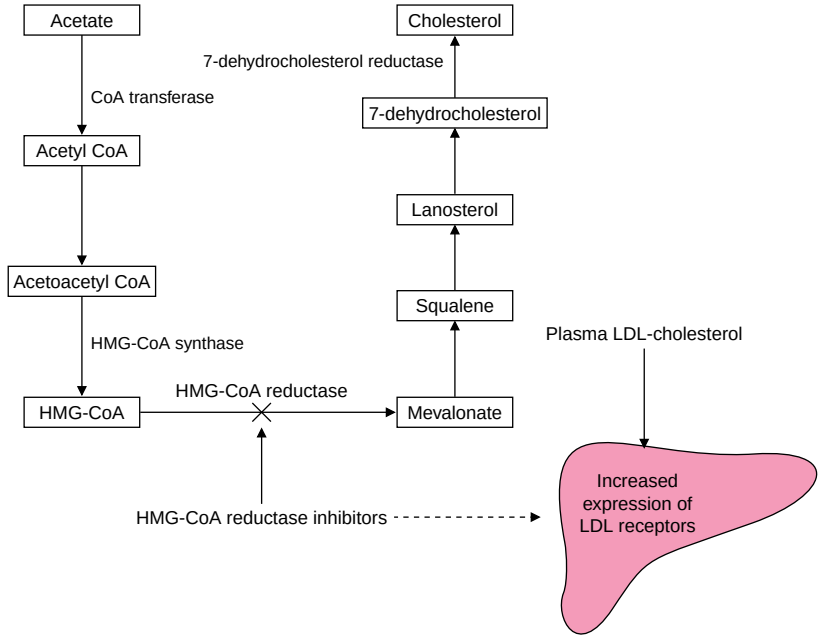
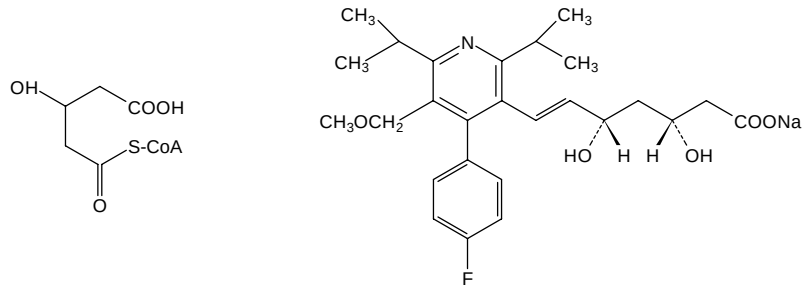


Fig. 1. Hepatic cholesterol synthesis and 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) inhibition. HMG-CoA reductase inhibitors ('statins') such as cerivastatin suppress cholesterol synthesis by blocking mevalonate synthesis as shown. The liver responds to this effect by increasing numbers of surface low density lipoprotein (LDL) receptors and withdrawing LDL-cholesterol from plasma.



HMG-CoA Cerivastatin sodium

Fig. 2. Structural formulae of HMG-CoA and cerivastatin. Cerivastatin is shown as the sodium salt, as presented for formulation and clinical use.

Oral doses of cerivastatin and lovastatin required for 50% inhibition (ED_{50}) of hepatic cholesterol synthesis in rat and dog livers were 0.002 and 0.2 to 0.3 mg/kg, respectively.[7] The demethylated (M1) and hydroxylated (M23) metabolites of cerivastatin were found to possess inhibitory activities similar to that of the parent compound (see section 3.2).[6] Cerivastatin also has high hepatic selectivity: oral ED_{50} values for cholesterol synthesis in rat small intestine and testes were greater than 0.1 mg/kg (at least 50 times that for the liver).[7] The ED_{50} value for the adrenal glands (0.002 mg/kg) was similar to that for the liver.[5]

Relative to control animals, oral dosages of cerivastatin 0.01, 0.03 and 0.1 mg/kg once daily in dogs reduced mean serum total cholesterol levels by 6, 36 ($p < 0.01$) and 41% ($p < 0.001$), respectively, after 13 weeks' treatment.[5] Mean serum levels of LDL- and VLDL-cholesterol were reduced by 52 and 23%, respectively, and triglyceride levels by 24% ($p < 0.001$) by the 0.1 mg/kg dosage. The lipid-lowering effect of cerivastatin has also been shown in the cholestyramine-primed dog (this is a sensitive model of cholesterol metabolism because high doses of bile sequestering agents stimulate hepatic cholesterol synthesis). Oral cerivastatin dosages of 0.01, 0.03 or 0.1 mg/kg/day reduced mean serum triglyceride levels by 50 to 77% ($p < 0.05$) relative to baseline after 20 days.[5] Mean serum total cholesterol levels were reduced by 59% in dogs receiving cerivastatin 0.1 mg/kg/day for 20 days. In both these studies, serum lipid responses to cerivastatin were dosage dependent.

The above findings were confirmed in a double-blind study in healthy volunteers in which 46 participants received cerivastatin 0.1 to 0.4 mg/day (given orally once or twice daily) and 22 received placebo.[8] After 7 days' treatment with cerivastatin, mean serum total cholesterol levels were reduced from baseline by 20.8 to 26.3% and LDL-

Table I. Pharmacodynamic properties of cerivastatin

Inhibition of hepatic cholesterol synthesis via high affinity for and inhibition of HMG-CoA reductase in *in vitro* and animal studies[5-7]
Reduction of serum levels of total and LDL-cholesterol in humans[8]
Suppression of proliferation of vascular smooth muscle cells,[9-12] fibroblasts, endothelial cells and myoblasts[13] in *in vitro* and animal studies
Inhibition of adhesion of monocytes to vascular endothelium *in vitro*[14]
Stimulation of fibrinolytic activity of vascular smooth muscle cells *in vitro*[15]
Potential for stabilisation of existing atherosclerotic plaques in *in vitro* and animal studies[16,17]
Improvement of vascular endothelial function as shown by increases in endothelium-dependent vasodilation and forearm blood flow in patients with hypercholesterolaemia[18]
Reduced levels of circulating steroid hormones (testosterone and estradiol) in women; decreased basal serum cortisol levels after prolonged treatment[19]

LDL = low density lipoprotein.

cholesterol levels by 30.5 to 36.4%. All changes were statistically significant ($p < 0.01$) relative to placebo.

2.2 Vascular Effects

It was originally believed that the benefit of treatment with HMG-CoA reductase inhibitors was related solely to the antihyperlipidaemic effects of these drugs and from atherosclerotic plaque regression. Continuing research shows, however, that other mechanisms may contribute to the therapeutic efficacy of these agents (reviewed by White[20]). Vascular effects are of particular interest because vascular smooth muscle proliferation is involved in atherosclerosis, restenosis and venous bypass graft disease, and the vascular endothelium produces mediators of vascular growth, platelet function and coagulation.

Observations in animal and *in vitro* models have indicated vascular endothelial and smooth muscle effects of interest with cerivastatin. A subcutaneous dosage of 1 mg/kg/day for 2 weeks prevented macrophage accumulation and thereby suppressed balloon catheterisation-induced intimal thickening in rabbits.[9] Furthermore, *in vitro* studies in rat, rabbit, dog and human tissue have demonstrated attenuation of smooth muscle cell migration and proliferation by cerivastatin.[9-12] Results obtained with rat and human arterial myocyte cultures have shown that cerivastatin inhibits cholesterol synthesis and cell proliferation in a dose-dependent manner, and that conditions producing 80 to 90% inhibition of cholesterol synthesis are associated with an approximate 50% inhibition of cell growth.[10]

Further data obtained with human saphenous vein smooth muscle cells indicate inhibition of expression of the cell cycle promotor cellular cyclin-dependent kinase 2 and downregulation of the cell cycle inhibitor $p27^{KIP1}$ by cerivastatin.[21]

Cerivastatin was shown to possess greater potency in terms of drug concentration required to inhibit cell proliferation than all commercially available HMG-CoA reductase inhibitors in a study in which these agents were incubated with cultured human smooth muscle cells, fibroblasts, endothelial cells or myoblasts.[13] Mean drug concentrations at which cell proliferation was inhibited by 25% (IC_{25}) ranged from 0.007 to 0.04 μmol/L for cerivastatin; corresponding ranges for the other drugs tested were 37.6 to >100 μmol/L for pravastatin, 0.4 to >1 μmol/L for lovastatin, 0.2 to 1.2 μmol/L for simvastatin, 0.5 to >1 μmol/L for atorvastatin and 0.3 to 0.4 μmol/L for fluvastatin. Overall, IC_{25} values across cell types were similar for each drug.

2.2.1 Antiatherosclerotic Effects

Of related interest is a preliminary report from an *in vitro* study that shows cerivastatin-mediated reduction of monocyte adhesion to vascular endothelium (a critical step in the development of atherosclerosis).[14] In addition, cerivastatin, lovastatin and simvastatin increased the fibrinolytic potential of human umbilical vein smooth muscle cells *in vitro* by increasing their production of tissue plasminogen activator and decreasing secretion of plasminogen activator inhibitor-1.[15] Cerivastatin has also been associated with suppression of activation of mitogen-activated protein kinases by monocyte chemoattractant protein-1 (a process implicated in atherogenesis) in human umbilical vein endothelial cells.[22]

Reduced serum lipid levels are reported to be associated with stabilisation of atherosclerotic plaques. It has been postulated that lipid lowering reduces localised inflammation and stabilises fibrous material in angiographically detectable stenotic lesions.[23] Data are available to suggest plaque stabilisation and delayed progression of early atherosclerosis with cerivastatin in the WHHL rabbit, an LDL receptor-deficient model with a high prevalence of severe coronary atherosclerosis.[16] In addition, treatment of monocytes with cerivastatin *in vitro* resulted in suppression of secretion of membrane urokinase and of expression of urokinase receptors.[17] This effect is noteworthy because the uptake by monocytes of atherogenic lipoproteins increases expression of urokinase and its receptors, which results in increased plasmin generation and atherosclerotic plaque degradation.

2.2.2 Endothelial Function

Impaired endothelium-dependent vasodilation is important in the pathogenesis of atherosclerosis and acute coronary syndromes in patients with hypercholesterolaemia, and cerivastatin has been shown to improve endothelial function in these individuals. In a double-blind study, 35 patients were randomised to treatment with cerivastatin 0.4 mg/day or placebo.[18] Endothelium-dependent increases in forearm blood flow (measured by plethysmography and intra-arterial infusion of acetylcholine) were markedly and statistically significantly greater in patients receiving cerivastatin than in placebo recipients: mean changes relative to baseline after 2 weeks were 203 and −26%, respectively ($p < 0.05$ between groups).

Further information on the effect of cerivastatin on endothelial function is currently being sought in the Evaluation of Nifedipine and Cerivastatin On Recovery of Endothelial function (ENCORE) studies in patients with coronary artery disease.[24] In the first ENCORE study, 400 patients are to be randomised to treatment with placebo, nifedipine 30 to 60 mg/day, cerivastatin 0.4 mg/day or a combination of the active treatments, and coronary responses to acetylcholine infusions analysed after 6 months. The ENCORE II study is scheduled to last for 2 years and will attempt to correlate endothelial function with atherosclerosis in 200 patients receiving cerivastatin 0.2 mg/day, 200 receiving cerivastatin 0.8 mg/day and 200 receiving a combination of cerivastatin 0.8 mg/day and nifedipine 30 to 60 mg/day.

2.3 Other Effects

Three months' treatment with cerivastatin 0.3 mg/day had no effect on insulin sensitivity in a placebo-controlled study in 20 healthy insulin-resistant immediate relatives of patients with type 2 diabetes mellitus.[25] Reductions relative to baseline in serum levels of total and LDL-cholesterol were apparent after treatment with cerivastatin but not with placebo, but body mass index and glucose disposal under hyperinsulinaemic euglycaemic clamp conditions were unchanged in both groups.

The effect of cerivastatin on circulating steroid hormone levels has been assessed in a study in which 12 women and 19 men with type 2 diabetes mellitus were randomised to treatment with cerivastatin 0.1 or 0.3 mg/day.[19] After 4 weeks, there was a significant ($p = 0.035$) 33% decrease from baseline in the mean serum testosterone level and a nonsignificant 26% decrease in the mean serum estradiol level in female patients receiving cerivastatin 0.3 mg/day. After 4 months, the overall mean basal serum cortisol level was reduced by 16% ($p = 0.04$) in patients receiving 0.3 mg/day.

3. Pharmacokinetic Properties

The pharmacokinetic profile of cerivastatin has been the subject of a number of investigations recently reviewed by Mück,[26] and the reader is referred to that review for detailed information on the pharmacokinetic characteristics of the drug. The following is a brief summary of the major points of interest, including data on the low potential of cerivastatin for drug interactions with other commonly prescribed medications (see section 3.3.3).

3.1 Absorption and Distribution

Studies of radiolabelled cerivastatin in healthy fasting volunteers have shown near-complete GI absorption after oral administration. The drug undergoes moderate first-pass metabolism, with an absolute bioavailability of 60%. More than 80% of an administered dose is absorbed within 6 hours, with an absorption half-life of 1 to 2 hours. Maximum plasma concentrations (C_{max}) are reached after 2 to 3 hours (time to C_{max}, t_{max}).[26] Cerivastatin exhibits linear pharmacokinetics [i.e. for C_{max} and area under the concentration-time curve (AUC)] over the dose range 0.15 to 0.8mg.[27-29] Results from pharmacokinetic studies in patients with hypercholesterolaemia (reviewed by Mück[26]) were similar to those in healthy volunteers, and showed modest interindividual variation only (coefficient of variation approximately 35% for AUC and C_{max}). The presence of food does not appear to influence the GI absorption of cerivastatin to any clinically relevant extent.[30,31]

After absorption, cerivastatin is highly bound to plasma proteins (>99%), predominantly to albumin but also to α_1-acid glycoprotein. This binding is reversible and independent of plasma drug concentration.[26] The volume of distribution at steady-state is approximately 0.3 L/kg, which indicates only moderate penetration into peripheral tissues.[32]

3.2 Metabolism and Elimination

Cerivastatin undergoes 2 major hepatic oxidative transformations: benzylic methyl ether demethylation, which yields metabolite M1, and stereoselective hydroxylation of a methyl group to yield metabolite M23. A third hydroxylated metabolite, M24, is formed as a secondary minor compound that is not detectable in human plasma. Cerivastatin shows high affinity for the hepatic cytochrome P450 (CYP) isoenzyme CYP2C8, which appears to catalyse the formation of both M1 and M23. Affinity of the parent drug for CYP3A4 is considerably lower, and this isoenzyme participates in the formation of M1 but not M23. Both CYP isoforms contribute to the formation of the minor metabolite M24.[26]

Inhibition of HMG-CoA reductase by M1, M23 and M24 is similar to that seen with cerivastatin itself, and the metabolites contribute approximately 20 to 25% of the total activity of each dose of cerivastatin.[26,29,33] Cerivastatin is cleared entirely by the CYP isoenzymes described and subsequent biliary and renal excretion. Approximately 70% of each dose is excreted in faeces, with intact cerivastatin accounting for less than 2% of the total originally administered. No unchanged drug is found in urine. The plasma elimination half-life ($t_{½\beta}$) of cerivastatin after oral administration is 2 to 3 hours,[27] and systemic clearance after an intravenous dose is low (0.2 L/h/kg).[32] Elimination is monoexponential.[26]

After administration of multiple doses, trough concentrations of cerivastatin in plasma show no clinically significant increase after day 3, which indicates the attainment of steady-state conditions. No drug accumulation is seen with repeated once-daily doses, and no time-dependent changes in the pharmacokinetic characteristics of cerivastatin or its metabolites have been observed in multiple-dose studies.[27,28]

3.3 Other Pharmacokinetic Considerations

3.3.1 Demographic Factors

The pharmacokinetics of cerivastatin are not affected by age. Eight healthy men aged 18 to 38 years and 15 men aged 65 to 78 years received oral cerivastatin 0.1mg once daily for 7 days in a double-blind study in which a further 8 young and 7 elderly men received placebo.[34] There were no significant differences between young and elderly participants after 7 days in mean steady-state AUC from 0 to 24 hours after administration (AUC_{24}) [5.71 *vs* 5.98 μg/L · h] or mean C_{max} (0.87 *vs* 1 μg/L). Mean t_{max} and $t_{½\beta}$ were also similar between groups.

Gender has also been shown not to influence the pharmacokinetics of cerivastatin. Mean AUC_{24} values were 15.5 and 17.3 μg/L · h, respectively, after 7 days' treatment with cerivastatin 0.2 mg/day in 16 male and 16 female volunteers who took part in a randomised, double-blind, placebo-controlled study in a total of 49 participants.[35] Mean C_{max} values were 2.3 and 2.5 μg/L, mean $t_{½\beta}$ 3.7 and 3.4 hours, and mean t_{max} 2.4 and 2.7 hours, respectively.

Collated data from clinical studies of cerivastatin in Europe, North America and Japan show no evidence of any clinically relevant differences in pharmacokinetic handling of the drug by different ethnic groups.[36] The studies involved predominantly Caucasian and Japanese individuals, but Black and Hispanic persons were also included.

3.3.2 Renal Impairment

A study in 26 patients with renal insufficiency and 9 healthy individuals showed no difference in the pharmacokinetics of cerivastatin 0.3mg once daily for 7 days between healthy persons [creatinine clearance (CL_{CR}) >5.4 L/h per 1.73m^2] and those with mild renal impairment (CL_{CR} 3.7 to 5.4 L/h per 1.73m^2).[37] Mean AUC_{24} values were, however, approximately 40 to 60% higher in patients with moderate (CL_{CR} 1.8 to 3.6 L/h per 1.73m^2) to severe (CL_{CR} <1.8 L/h per 1.73m^2) renal impairment

than in healthy individuals. Mean $t_{½\beta}$ remained below 5 hours in all groups, which implies that renal dysfunction does not result in accumulation of cerivastatin.

Results of another study in which 6 healthy volunteers and 18 patients with varying degrees of renal insufficiency received single doses of cerivastatin 0.3mg showed mean AUC [extrapolated to infinity (AUC_∞)] and C_{max} values were higher in patients with renal insufficiency than in healthy individuals.[38] Mean AUC_∞ values (for bound and unbound drug) were 13.5, 21.2, 31.7 and 22.5 μg/L · h for participants with CL_{CR} >5.4, 5.4 to 3.6, 3.6 to 1.8 and <1.8 L/h per 1.73m^2, respectively. Corresponding C_{max} values were 3, 3.8, 5.4 and 3.9 μg/L. Mean $t_{½\beta}$ ranged from 2.3 to 3.4 hours. Correlation analysis indicated that the pharmacokinetics of cerivastatin in patients with impaired renal function is related to serum albumin concentration rather than CL_{CR}.

The pharmacokinetics of cerivastatin have not been assessed in studies in children or in patients with hepatic impairment.

3.3.3 Drug Interactions

The pharmacokinetic drug interaction profile of cerivastatin has been analysed in an extensive series of studies, the findings from which have been reviewed in detail elsewhere.[39] Cerivastatin has a number of physicochemical and pharmacokinetic characteristics that are of interest with respect to drug interactions, most notably the possession of a carboxylic acid functional group (potential effects on absorption), extensive binding to plasma proteins, moderate first-pass metabolism and CYP-mediated biotransformation with biliary/renal excretion. Clinically significant pharmacokinetic drug interactions have been reported in patients receiving other HMG-CoA reductase inhibitors in combination with cyclosporin (fluvastatin,[40] pravastatin,[41] lovastatin[42] and simvastatin[43]), fibric acid derivatives (pravastatin[44]), bile acid sequestering agents (fluvastatin[45] and pravastatin[46]) and other drugs. Various reviews have been published on drug interactions with HMG-CoA reductase inhibitors.[47-49]

Changes in gastric pH do not appear to influence the absorption of cerivastatin, as shown by the lack of any interaction with an antacid containing hydroxides of magnesium and aluminium in healthy volunteers.[50] In addition, no interactions between cerivastatin and the proton pump inhibitor omeprazole[51] or the histamine H_2 antagonist and CYP inhibitor cimetidine[50] were apparent in 2 randomised, nonblind 2-way crossover studies in a total of 20 healthy volunteers.

Administration of 12g of the bile sequestering resin cholestyramine with 0.2mg of cerivastatin resulted in a 21% decrease in relative bioavailability and a 41% decrease in mean C_{max} of the latter in a randomised crossover study in 12 healthy men.[52] This may be attributable to irreversible adsorption of the HMG-CoA reductase inhibitor onto the resin, and further investigation showed that the effect can be minimised by administration of the 2 agents at least 1 hour apart.[52] More recent data show no evidence of any interaction between cerivastatin and the GI lipase inhibitor orlistat.[53]

In vitro studies have not shown any evidence of pharmacokinetic interactions between cerivastatin and other drugs [warfarin, clofibrate, ibuprofen, propranolol, imipramine, gemfibrozil, nifedipine, salicylic acid, nicotinic acid, furosemide, phenytoin, digoxin and glibenclamide (glyburide)] that are subject to plasma protein binding (reviewed by Mück[39]).

Concomitant administration of cerivastatin 0.3 mg/day and warfarin had no effect on the pharmacokinetics of either drug in a crossover study in 21 healthy volunteers.[54] Addition of cerivastatin did not result in changes relative to placebo in prothrombin time or clotting factor VII activity. Similar conclusions were reached in a further study in 20 healthy volunteers in which cerivastatin 0.2 mg/day was coadministered with digoxin 0.25 mg/day.[55] There were no clinically significant changes in plasma concentrations or renal clearance of digoxin in the presence of cerivastatin.

As discussed earlier, no pharmacokinetic interactions have been reported between cerivastatin and cimetidine (a nonspecific CYP inhibitor), warfarin

(cleared mainly by CYP2C9-mediated biotransformation) or omeprazole (which is known to inhibit CYP2C19).

As a result of dual hepatic metabolism of cerivastatin, no potentially significant drug interactions with cerivastatin have been noted with the CYP3A4 inhibitors erythromycin and itraconazole. Coadministration of erythromycin 500mg 3 times daily and single doses of cerivastatin 0.3mg in a study in 12 healthy volunteers led to a mean 13% increase in C_{max} and 10% increase in $t_{½\beta}$ of cerivastatin (relative to the drug given alone), with a resultant mean 21% increase in AUC_{∞}.[56] In another study, the mean AUC_{∞} of cerivastatin 0.3mg was increased 15% by the coadministration of itraconazole 200mg once daily.[57] Mean AUC_{24} was increased by 28 and 36% for the M1 and M23 metabolites, respectively (all statistically significant relative to values obtained after administration of cerivastatin alone). In a randomised, 3-way crossover single dose study, 18 healthy volunteers received cerivastatin 0.8mg, pravastatin 40mg or atorvastatin 20mg alone and in combination with itraconazole 200mg.[58] While itraconazole increased cerivastatin and pravastatin AUC_{∞} and C_{max} to a minor extent (1.2- to 1.5-fold), itraconazole significantly elevated the AUC_{∞} and C_{max} of atorvastatin (1.4- to 2.5-fold). No changes in $t_{½}$ and t_{max} were observed with any of the HMG-CoA reductase inhibitors when coadministered with itraconazole.

Coadministration of cerivastatin and the dihydropyridine calcium antagonist nifedipine had no effects on the pharmacokinetics of either drug in a 3-way crossover study in 18 healthy volunteers.[59]

The immunosuppressant cyclosporin is known to interact with HMG-CoA reductase inhibitors, an effect that has resulted in cases of severe rhabdomyolysis in organ transplant recipients.[60] Coadministration of cerivastatin 0.2 mg/day to 12 renal transplant patients who were already receiving cyclosporin and other immunosuppressants, resulted in a 3- to 5-fold increase (relative to control patients receiving cerivastatin alone) in plasma concentrations of cerivastatin and its metabolites.[60] Cerivastatin elimination was not affected, however, and there were no changes in steady-state blood concentrations of cyclosporin or its metabolites. The mechanism behind the interaction between HMG-CoA reductase inhibitors and cyclosporin has not been clarified, but is believed to be related to inhibition by cyclosporin of hepatic transport processes.[60] Preliminary data from a randomised comparative study in renal transplant patients receiving cyclosporin and other immunosuppressants also showed no effect of cerivastatin 0.2 mg/day (n = 10) on trough blood concentrations of cyclosporin after 4 weeks of concomitant therapy; however, atorvastatin 10 mg/day increased trough blood cyclosporin concentrations by >25% in 5 of 10 patients.[61] The mechanism of the possible interaction between atorvastatin and cyclosporin is not known, but may involve the CYP system.[61]

4. Therapeutic Efficacy

Cerivastatin has undergone extensive clinical evaluation and is available in a number of countries for the treatment of patients with lipid disorders. Lipid-lowering efficacy was demonstrated with cerivastatin at daily dosages of 0.1 to 0.3mg in earlier clinical trials, and brief overviews of these data have been published previously in *Drugs*[62,63] and elsewhere.[64] More recent clinical trials have focused on the more efficacious dosages of 0.4 and 0.8 mg/day. These studies were undertaken because of the dose-response curve of cerivastatin (see section 4.1) and its good tolerability profile (see section 5). Results of these trials have led to recent changes in dosage recommendations of cerivastatin by the Food and Drug Administration (FDA) in the US, where the starting dosage is 0.4 mg/day and this may be increased to 0.8 mg/day (section 6). Therefore, this section highlights studies in which cerivastatin was administered at dosages of ≥0.4 mg/day (in at least some randomised patients). The majority of ongoing cerivastatin clinical programme trials (including prevention studies) are using regimens of 0.4 and 0.8 mg/day.[65]

Virtually all published clinical trials with cerivastatin were randomised, double-blind, multicentre

studies of at least 4 weeks' duration (typically ≥8 weeks' duration). Most included a placebo-control group, although several head-to-head comparisons with other HMG-CoA reductase inhibitors did not. The primary end-point in the majority of clinical trials was the percentage reduction in serum levels of LDL-cholesterol from baseline (usually after at least 4 weeks of dietary control, with or without placebo administration) to the end of treatment. Dietary restrictions were continued throughout the study period and patients were not allowed to take other medications that might affect serum lipid levels (e.g. nicotinic acid) or potentially interact with cerivastatin (e.g. cyclosporin; see section 3.3.3). As part of the inclusion criteria, serum LDL-cholesterol levels were, in the majority of clinical trials, ≥160 mg/dl (≥4.1 mmol/L) for patients without definite atherosclerotic disease and <2 cardiovascular risk factors or ≥130 mg/dl (≥3.4 mmol/L) for those with definite atherosclerotic disease or ≥2 cardiovascular risk factors. Patients in most trials had primary hypercholesterolaemia, although some studies involved patients with hypercholesterolaemia associated with diabetes mellitus (section 4.3). Various subanalyses also evaluated age or gender effects on the lipid-lowering efficacy of cerivastatin (section 4.3). To date, clinical end-point data are not available for cerivastatin; however, a full programme of studies evaluating the efficacy of cerivastatin on clinical end-points of cardiovascular mortality or morbidity are ongoing (see section 7).

4.1 Studies Using Lower Dosages of Cerivastatin (≤0.3 mg/day)

Numerous dose-finding and placebo-controlled trials, some of which also included comparator antihyperlipidaemic drugs, have been conducted with cerivastatin ≤0.3 mg/day. The main results of these studies, most of which were large trials involving >250 patients with primary hypercholesterolaemia, are summarised in table II.

Taken together, these studies showed a clear dose-response effect with low dosages of cerivastatin up to 0.3mg administered once daily, usually after the evening meal, for 4 to 32 weeks (table II). Over a more clinically relevant dosage range of 0.1 to 0.3 mg/day, cerivastatin achieved mean reductions from baseline in serum LDL-cholesterol levels of 15.1 to 33.6% (usually in the range of 20 to 30%, as confirmed in a pooled efficacy analysis in >1500 patients receiving cerivastatin 0.1, 0.2 or 0.3 mg/day[78]). Corresponding reductions in serum levels of total cholesterol were 12.9 to 24.4% and changes in serum triglyceride levels ranged between a small increase (3.9%) in 1 trial[67] to more typical moderate reductions of 7.3 to 20.3% in other studies (table II). HDL-cholesterol levels increased modestly by 2.3 to 11.4% in patients receiving cerivastatin 0.1 to 0.3 mg/day.

In all studies which included a placebo-control group,[68-71,73] cerivastatin 0.1, 0.2 and 0.3 mg/day achieved mean reductions from baseline in serum levels of both LDL- and total cholesterol that were significantly greater than those attained with placebo. These parameters were essentially unchanged (approximately –1 to +2%) from baseline in placebo recipients. Improvements in serum levels of triglycerides and HDL-cholesterol were also consistently greater with cerivastatin than placebo (as with other HMG-CoA reductase inhibitors). Statistical significance between groups was not always achieved (table II).

A few of the placebo-controlled trials with cerivastatin ≤0.3 mg/day[70,71,73] as well as several additional studies with low cerivastatin dosages[72,74-76] involved comparisons with other antihyperlipidaemic agents (simvastatin, atorvastatin, lovastatin, fluvastatin, pravastatin and gemfibrozil; see table II). Statistically significant differences favouring the comparator agent over cerivastatin ≤0.3 mg/day were achieved in some studies.[72,75] However, these comparisons are of relatively minor importance in view of the US FDA dosage recommendations for cerivastatin (section 6), although data from comparative clinical trials using higher cerivastatin dosages are also still limited (see section 4.2). In addition, even at a dosage of 0.3 mg/day, cerivastatin achieved significantly ($p \leq 0.01$) greater improvements in se-

Table II. Double-blind, randomised, multicentre studies with low-dose cerivastatin (CER) ≤0.3 mg/day in patients with primary hypercholesterolaemia. Most results are for evaluable patients in efficacy analyses; those results from intention-to-treat analyses are indicated by ITT

Reference	No. of patients	Dosage regimen (mg/day)[a]	Mean change (%) in serum lipid/lipoprotein levels at end of study *vs* baseline				
			total-C	LDL-C	HDL-C	TG	atherogenic index (as specified)
Dose-finding and placebo-controlled studies							
Goto et al.[66]b,c	294[d]	CER 0.05[e]	–11.4	–17.6	+4.8		
		CER 0.1[e]	–14.5	–20.6	+7.3		
		CER 0.15[e]	–18.0	–26.7	+6.6		
		CER 0.2[e]	–18.6	–26.5	+4.2		
Sasaki et al.[67]	33	CER 0.15 x 12wk	–21.6**	–31.2**	+3.3	+3.9	–26.7** (LDL-C:HDL-C)
	40	CER 0.3 x 12wk	–24.4**††	–33.6**†	+11.4**††	–7.3†	–36.4**†† (LDL-C:HDL-C)
Stein et al.[68]	89	CER 0.2 x 4wk [0.1mg bid]	–18.9*	–25.7*	+5.3*	–11.6	
	88	CER 0.2 x 4wk [0.2mg qpm]	–21.9*†	–29.4*†	+2.3*†	–11.6	
	86	CER 0.2 x 4wk [0.2mg hs]	–22.1*†	–30.4*†	+3.2*	–10.9	
	45	Placebo	unchanged	+1.4	–1.2	–3.1	
Tao et al.[69]	103	CER 0.1 x 8wk	–15.8**	–21.5**	+8.7*	–8.8**	
	101	CER 0.2 x 8wk	–18.7**	–25.8**	+8.5*	–10.8**	
	96	CER 0.3 x 8wk	–21.7**	–29.5**	+7.8	–11.7**	
	100	Placebo	+1.3	+0.7	+3.4	+6.6	
Comparisons with other drugs							
Betteridge et al.[70]f,g [ITT]	193	CER 0.025 x 12wk	–8.8*	–11.5*	+0.2	–0.2*	
	187	CER 0.05 x 12wk	–11.9*	–15.5*	+1.4	–5.7*	
	190	CER 0.1 x 12wk	–17.8*	–23.6*	+3.7	–10.4*	
	191	CER 0.2 x 12wk	–21.8*	–29.1*	+3.2	–10.9*	
	183	SIM 20 x 12wk	–28.2‡	–38.3‡	+5.2†	–12.8†	
	187	Placebo	–0.5	–0.3	–1.1	+5.7	
Farnier et al.[71]	131	CER 0.1 x 16wk	–14.1*	–15.1**	+9.7	–14.8*	
	142	CER 0.2 x 16wk	–18.5*	–23.0**	+10.0	–11.7*	
	139	CER 0.3 x 16wk	–19.8*	–24.2**	+11.3**	–20.3*	
	121	GEM 600mg bid x 16wk	–12.6*	–7.5*	+13.3*	–50.3*	
	59	Placebo	+1.2	–0.6	+4.8	+2.1	
Hunninghake et al.[72]b,c	107	CER 0.3 x 6wk	–22.2	–30.2	+4.3		
	108	ATO 10 x 6wk	–27.5††	–37.7††	+6.8†		
Insull et al.[73]b	939[d]	CER 0.05 x 24wk	–9.6**	–13.5**			
		CER 0.1 x 24wk	–12.9**	–18.9**			
		CER 0.2 x 24wk	–17.8**	–25.6**			
		CER 0.3 x 24wk	–19.9**	–28.5**			
		LOV 40 x 24wk	–23.8**	–33.3**			
		Placebo	+1.7	+1.9			
Isaacsohn et al.[74]b	165	CER 0.3 x 12wk[h]	–21.1**††	–30.3**††	+9.3**††	–14.1**††	
	170	FLU 40 x 12wk[h]	–16.5**	–23.6**	+4.0**	–3.7	
Leiter et al.[75] [ITT]	257	CER ≤0.3 x 32wk[i]	–15.9	–22.5	+8.8	–8.8	–22.0 (total-C: HDL-C)
	126	SIM ≤40 x 32wk[i]	–22.5†	–31.8†	+11.0	–9.5	–28.8† (total-C: HDL-C)
Saunders et al.[76]b	202	CER 0.3 x 8wk	–21.1††	–31.1††	+6.5	–8.5	
	200	PRA 20 x 8wk	–17.8	–26.0	+4.7	–9.1	

a Administered as a single daily dose (after the evening meal or at bedtime) unless specified otherwise.
b Study published only as an abstract; full statistical data may not be reported.
c Type of hypercholesterolaemia not specified but assumed to be primary in all patients.
d Total number of patients in all groups combined.
e Duration of treatment not specified.
f Some statistically significant dose-response effects were demonstrated with CER but specific statistical comparisons are not shown in the table.
g Data from early pilot studies of similar design showed broadly similar results (data not included in table).[77]
h During the first 6 weeks of the 12-week forced-titration study, patients received CER 0.2 mg/day or FLU 20 mg/day (data not presented in table).
i Forced-titration study to achieve plasma LDL-C level < 3.36 mmol/L (130 mg/dl); mean dosage at end-point: CER 0.242 mg/day, SIM 21.7 mg/day; statistical comparison *vs* baseline not reported.

ATO = atorvastatin; **bid** = twice daily; **C** = cholesterol; **FLU** = fluvastatin; **GEM** = gemfibrozil; **HDL** = high density lipoprotein; **hs** = at bedtime; **LDL** = low density lipoprotein; **LOV** = lovastatin; **od** = once daily; **PRA** = pravastatin; **qpm** = every evening meal; **SIM** = simvastatin; **TG** = triglyceride; **wk** = weeks; statistically significant change *vs* baseline or placebo: ***** $p \leq 0.05$, ****** $p < 0.001$; statistically significant difference *vs* CER 0.025, 0.05, 0.15, 0.3, ≤0.3mg od or CER 0.1mg bid or FLU or PRA:† $p \leq 0.05$; †† $p \leq 0.01$; statistically significant difference *vs* all CER regimens: ‡ $p \leq 0.05$.

rum levels of LDL- and total cholesterol than those attained with fluvastatin 40 mg/day.[74] or pravastatin 20 mg/day[76] As might be expected, a trend towards greater reductions in serum LDL- and total cholesterol levels was demonstrated with cerivastatin ≤0.3 mg/day versus gemfibrozil 1200 mg/day, whereas gemfibrozil tended to produce greater improvements in serum levels of triglycerides and HDL-cholesterol (table II).[71]

Additional clinical data comparing lower dosages of cerivastatin with other antihyperlipidaemic agents (prior to their use in combined therapy) are presented in section 4.4.

In general, a treatment response was noted by 1 week of therapy with cerivastatin and effects were maximal by about 3 or 4 weeks and then maintained throughout the study period.[68,70] Some of the trials summarised in table II included extensions beyond the double-blind randomised period to evaluate the longer term effects of therapy with cerivastatin for up to 2 years.[67,70,71,75,79] Although not all patients completing the randomised study periods participated in the follow-up extensions, these evaluations generally showed that the beneficial effects on the serum lipid profile achieved by cerivastatin in the short term were maintained in the long term.

4.2 Studies Including Higher Dosages of Cerivastatin (0.4 and 0.8 mg/day)

Several clinical trials have evaluated the lipid-lowering efficacy of cerivastatin 0.4 or 0.8 mg/day in patients with primary hypercholesterolaemia, and results of these studies are summarised in table III. Cerivastatin 0.4 to 0.8 mg/day was associated with reductions from baseline in serum levels of total cholesterol (23.0 to 30.8%), LDL-cholesterol (33.4 to 44.0%) and triglycerides (10.4 to 18.4%), as well as rises in HDL-cholesterol (3.2 to 8.7%) after 4 to 26 weeks of therapy.[29,80-84]

In dose-finding studies, most of which included a placebo-control group, significantly greater reductions in serum levels of LDL- and total cholesterol were achieved with cerivastatin 0.4 versus 0.2 or 0.3 mg/day,[80,82,83] and with cerivastatin 0.8 versus 0.4 mg/day.[81] All comparisons between cerivastatin (0.3, 0.4 and 0.8 mg/day) and placebo showed significantly greater reductions from baseline with cerivastatin for at least these 2 key lipid parameters (table III).[29,80,81] Similarly, the percentage reduction from baseline for the ratio of total cholesterol to HDL-cholesterol was significantly greater with cerivastatin (0.3, 0.4 and 0.8 mg/day) than placebo,[29,80,81] and a dose-response relationship was demonstrated (see table III).[81,82]

Table III. Double-blind, randomised studies in patients with primary hypercholesterolaemia in which at least some randomised groups received cerivastatin (CER) at dosages ≥0.4 mg/day. Most results are for evaluable patients in efficacy analyses; those results from intention-to-treat analyses are indicated by ITT

Reference	No. of patients	Dosage regimen (mg/day)[a]	Mean change (%) in serum lipid/lipoprotein levels at end of study *vs* baseline				
			total-C	LDL-C	HDL-C	TG	atherogenic index (total-C: HDL-C)
Dose-finding and placebo-controlled studies							
Hanefeld et al.[80] [ITT]	140	CER 0.3 x 8wk	–24.3**	–32.5**	+5.8*	–17.3**	–27.8**
	138	CER 0.4 x 8wk	–26.8**†	–35.8**†	+4.1*	–14.8**	–28.9**
	71	Placebo	+0.6	+0.2	–0.3	+8.4	+2.0
Insull et al.[81]	164	CER 0.4 x 8wk	–25.0**	–35.6**	+7.9**	–13.7**	–30.0**
	656	CER 0.8 x 8wk	–29.9**††	–41.8**††	+8.7**	–18.4**†	–35.6**††
	177	Placebo	+0.9	+0.2	+2.8	+3.6	–1.8
Ose et al.[82]b	141	CER 0.2 x 24wk	–21.6	–31.5	+7.4	–11.5	–27.8
	302	CER 0.4 x 24wk	–26.0††	–38.4††	+8.1	–11.1	–32.5†
Stein et al.[29]	28	CER 0.8 x 4wk	–30.8**	–44.0**	+3.2	–11.2*	
	13	Placebo	+2.1	+1.2	–1.2	+15.9	
Comparisons with other drugs							
Hunninghake et al.[83]c,d	194	CER 0.3 x 26wk	–20.3‡	–30.0‡	+6.6	–4.1	
	385	CER 0.4 x 26wk	–23.0†‡	–33.4†‡	+7.7‡	–10.4†‡	
	185	FLU 40 x 26wk	–16.0	–23.0	+4.6	–4.9	
Rubinstein et al.[84]c [ITT]	81	CER 0.8 x 12wk[e]	–29.6‡‡	–38.9‡‡			
	83	PRA 40 x 12wk[e]	–25.2	–33.2			

a Administered as a single daily dose (after the evening meal or at bedtime) unless specified otherwise.

b Statistical analysis *vs* baseline not provided.

c Study published only as an abstract; full statistical data may not be reported.

d Patients in FLU arm received placebo for 8wk then FLU for 16wk; type of hypercholesterolaemia not specified but assumed to be primary in all patients.

e During the first 4 weeks of the 12-week forced titration study, patients received CER 0.2 mg/day or PRA 10 mg/day; this was followed by CER 0.4 mg/day or PRA 20 mg/day for the next 4-week period (data not presented in table), then the final dosage regimens of CER 0.8 mg/day or PRA 40 mg/day for the last 4 weeks of the trial.

C = cholesterol; **FLU** = fluvastatin; **HDL** = high density lipoprotein; **LDL** = low density lipoprotein; **PRA** = pravastatin; **TG** = triglyceride; **wk** = weeks; statistically significant change *vs* placebo: * $p < 0.05$, ** $p < 0.001$; statistically significant difference *vs* lower dosage of CER: † $p < 0.05$; †† $p < 0.001$; statistically significant difference *vs* FLU or PRA: ‡ $p < 0.05$, ‡‡ $p < 0.01$.

Results of a pivotal study comparing cerivastatin 0.8 and 0.4 mg/day and placebo, which was conducted at 59 centres in the US and Canada,[81] are presented in table III and highlighted in figure 3. The efficacy analysis included approximately 1000 patients with primary hypercholesterolaemia. Randomisation of patients in a ratio of 4:1:1 provided a large patient population for evaluation of the efficacy and tolerability of cerivastatin 0.8 mg/day.

At the end of the 8-week treatment period, US National Cholesterol Education Program (Adult Treatment Panel II) [NCEP] target levels for LDL-cholesterol were achieved by 84% of patients receiving cerivastatin 0.8 mg/day.[81] This compares with 73% of those receiving cerivastatin 0.4 mg/day and <10% of placebo recipients. (Specific NCEP treatment goals for serum levels of LDL-cholesterol are provided in section 7.) This rank order (cerivastatin 0.8 mg/day > cerivastatin 0.4

mg/day > placebo) also applied across all 3 NCEP risk groups. For example, in patients at high risk [i.e. those with coronary heart disease (CHD)] the proportion of patients who successfully achieved NCEP target levels for LDL-cholesterol were 59, 41 and 0%, respectively. In hypercholesterolaemic patients at low (<2 cardiovascular risk factors but without CHD) or medium risk (≥2 cardiovascular risk factors but without CHD), NCEP target levels for LDL-cholesterol were achieved in approximately 85 to 90% of those receiving cerivastatin 0.8 mg/day compared with about 80% of patients treated with cerivastatin 0.4 mg/day. In 90% of all patients receiving cerivastatin 0.8 mg/day in this pivotal trial, LDL-cholesterol levels were reduced by 23.9 to 58.4% (6th to 95th percentile).

While the vast majority of patients in the large pivotal trial achieved NCEP goals for LDL-cholesterol with cerivastatin 0.8 mg/day, it is noteworthy that the LDL-cholesterol level criteria for study inclusion across all risk groups were lower than the NCEP-specified guidelines for introducing pharmacological treatment.[81] Thus, it was appropriate that a subgroup analysis was also conducted for those patients whose serum LDL-cholesterol levels met NCEP guidelines (rather than study entry criteria) for pharmacological treatment.[81] For example, according to NCEP guidelines, patients without definite atherosclerotic disease and fewer than 2 cardiovascular risk factors require drug therapy if serum LDL-cholesterol levels are ≥190 mg/dl (4.9 mmol/L), whereas entry criterion in the pivotal trial was ≥160 mg/dl (4.1 mmol/L) for this patient group. There were similar differences between NCEP guidelines and study entry criteria for medium and high risk groups as well. Overall, in the subgroup with serum LDL-cholesterol levels meeting NCEP guidelines for drug treatment, 75% of patients achieved target LDL-cholesterol levels with cerivastatin 0.8 mg/day. The corresponding result for only high risk patients (with definite atherosclerotic disease, a group usually more difficult to treat) was 59% at this dosage level.

Data are also available from 2 randomised trials comparing cerivastatin ≥0.4 mg/day with other

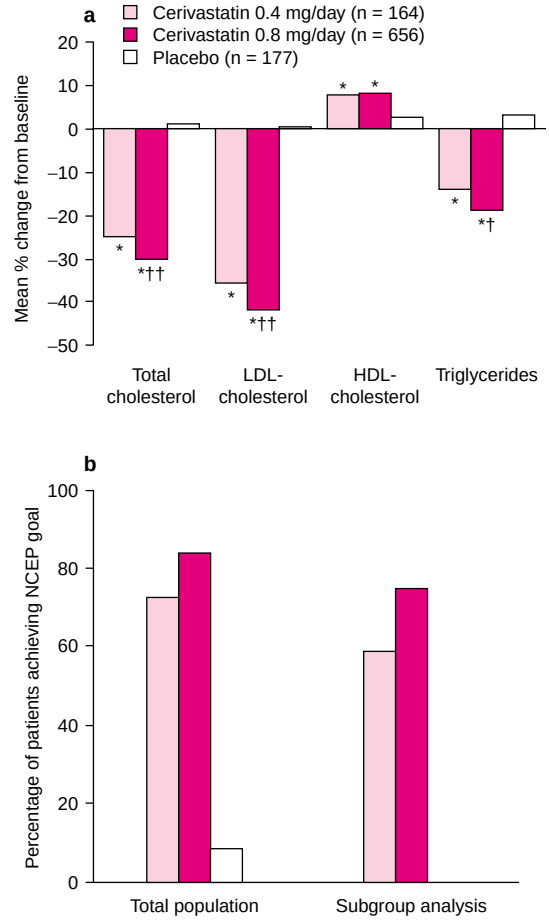


Fig. 3. Main results of a pivotal double-blind, randomised, multicentre trial of cerivastatin in 997 patients with primary hypercholesterolaemia.[81] Mean percentage change from baseline in serum lipid and lipoprotein levels (**a**), and percentage of patients achieving US National Cholesterol Education Program (Adult Treatment Panel II) [NCEP] target low density lipoprotein (LDL)-cholesterol levels (**b**) after 8 weeks of therapy with cerivastatin 0.4 or 0.8 mg/day or placebo. Subgroup analysis included patients whose baseline LDL-cholesterol was greater than the levels at which the NCEP recommends initiation of lipid-lowering therapy (data for placebo and specific patient numbers not provided for subanalysis). **HDL** = high density lipoprotein; * $p < 0.001$ *vs* placebo; † $p < 0.05$, †† $p < 0.001$ *vs* cerivastatin 0.4 mg/day; statistical analysis not reported for data in fig. 3b.

HMG-CoA reductase inhibitors in patients with hypercholesterolaemia, although these studies have been published only as abstracts.[83,84] Reductions from baseline in serum levels of LDL-cholesterol and total cholesterol were significantly greater with cerivastatin 0.3 or 0.4 mg/day than fluvastatin 40 mg/day in a large (n = 764) 26-week trial,[83] and with cerivastatin 0.8 mg/day than pravastatin 40 mg/day in a smaller (n = 164) 12-week study (see table III).[84]

The pivotal 8-week randomised trial conducted in the US and Canada[81] included a 44-week extension period (52 weeks in total) during which patients who had been randomised to receive placebo were placed on pravastatin 40 mg/day.[85] Patients who had been randomised to receive cerivastatin 0.4 or 0.8 mg/day continued with their therapy during the extension phase. Overall, results showed that the lipid-lowering effects of cerivastatin were maintained during long term administration. At 1 year, reductions from baseline in serum levels of LDL-cholesterol were 33.6 and 40.8%, respectively, for cerivastatin 0.4 and 0.8 mg/day, and 31.5% for pravastatin 40 mg/day. The difference between cerivastatin 0.8 mg/day and pravastatin 40 mg/day was statistically significant, as was the difference between the 2 cerivastatin dosage regimens ($p < 0.05$ for both comparisons).

4.2.1 Postmarketing Formulary Conversion Studies

Postmarketing surveillance studies of cerivastatin have been performed within the context of mandated formulary conversion protocols at 3 Veterans Affairs (VA) or Department of Defense (DOD) institutions in the US.[86-88] Cerivastatin was either equivalent or superior to other HMG-CoA reductase inhibitors, including atorvastatin, in reducing serum levels of LDL-cholesterol or achieving NCEP target levels (analyses available as abstracts only).

Among 451 patients who met all study criteria in one of the retrospective analyses at a VA hospital, 54.5% were at the NCEP target level for LDL-cholesterol prior to conversion to cerivastatin compared with 74.3% after conversion ($p < 0.001$).[86] Patients were switched to cerivastatin from fluvastatin (48.6%), atorvastatin (34.8%), pravastatin (11.5%) or '>1 sequential statin' (5.1%) [dosages not reported]. Cerivastatin provided additional LDL-cholesterol and total cholesterol reductions, as well as HDL-cholesterol elevations, that were statistically significantly greater than pre-conversion HMG-CoA reductase inhibitor therapy in secondary prevention patients, and in primary prevention populations who were diabetic, high-risk nondiabetic or low-risk nondiabetic. A similar retrospective analysis at another VA hospital involved conversion from simvastatin to cerivastatin at specified dosages.[88] Results showed that cerivastatin at dosages of 0.2, 0.3 and 0.4 mg/day was equivalent to simvastatin at dosages of 10, 20 and 40 mg/day, respectively, in reducing serum levels of LDL-cholesterol and elevating HDL-cholesterol levels.

The third postmarketing study was a prospective analysis of 980 volunteer DOD beneficiaries (mean age 68 years; secondary prevention 41%, diabetes mellitus 25%).[87] In this study, patients were switched from their pre-conversion HMG-CoA reductase inhibitor therapy (primarily atorvastatin or pravastatin) to cerivastatin or simvastatin. Overall, 80.6% of patients were switched to cerivastatin 0.4 mg/day and 92.8% were switched to cerivastatin at any dosage. Prior to conversion, 69% of patients had achieved NCEP target LDL-cholesterol levels and this increased to 77.5% after conversion ($p < 0.001$). Mean LDL-cholesterol levels of the cohort decreased from 115 mg/dl (2.97 mmol/L) pre-conversion to 106 mg/dl (2.74 mmol/L) post-conversion ($p < 0.001$); HDL-cholesterol and triglyceride levels were not significantly changed.

4.3 Evaluations in Specific Subpopulations

There appears to be a difference in the lipid-lowering efficacy of cerivastatin between men and women. This gender effect was demonstrated in a pooled analysis of data from 2275 patients with primary hypercholesterolaemia treated with cerivastatin 0.1, 0.2, 0.3 or 0.4 mg/day and 546 patients receiving placebo.[78] After 8 weeks of therapy, improvements from baseline in serum levels of LDL-cholesterol were greater in women than in men at

all cerivastatin dosage levels (statistical analysis not provided). The pooled analysis also showed an age-related response, with the greatest reductions in serum LDL-cholesterol levels occurring in elderly patients (≥65 years) at all dosage levels (statistical analysis not provided). Figure 4 illustrates the age- and gender-related effects for cerivastatin 0.4 mg/day (n = 788) in the pooled analysis.

Subanalyses of specific clinical trials with cerivastatin in patients with hypercholesterolaemia have also shown gender-[68,69,81,89] and/or age-related effects.[68,81] For example, a subanalysis of the gender effect of cerivastatin 0.4 mg/day[89] from a 24-week study comparing cerivastatin 0.2 and 0.4 mg/day (see table III)[82] showed that 73 of 102 women (71.6%) and 76 of 200 men (38.0%) had reductions in serum LDL-cholesterol levels >40% from baseline (statistical analysis not provided). Likewise, other studies demonstrated somewhat greater lipid-lowering effects with cerivastatin in women than in men over a wide range of dosages.[68,69,81] An age-related response was also demonstrated with relatively low dosages of cerivastatin 0.1 or 0.2 mg/day,[68] which was similar to that shown in the pooled analysis[78] at this dosage level.

Rubinstein and colleagues[90] evaluated the lipid-lowering efficacy of 12 weeks of treatment with cerivastatin 0.1 and 0.3 mg/day in a placebo-controlled study in 252 hypercholesterolaemic patients with type 2 diabetes mellitus. Results were similar to those reported in table II from clinical trials using cerivastatin at these dosages in patients without diabetes mellitus or relatively nonselective patient populations. Reductions in serum levels of total cholesterol and LDL-cholesterol from baseline to the end of the 12-week treatment period were 13.7 and 20.2%, respectively, for cerivastatin 0.1 mg/day and 23.5 and 33.8%, respectively, for cerivastatin 0.3 mg/day. A large primary prevention clinical outcome trial (Lipids in Diabetes Study) in patients with type 2 diabetes mellitus but without hypercholesterolaemia is also under way (see section 7),[91] and results are awaited with interest.

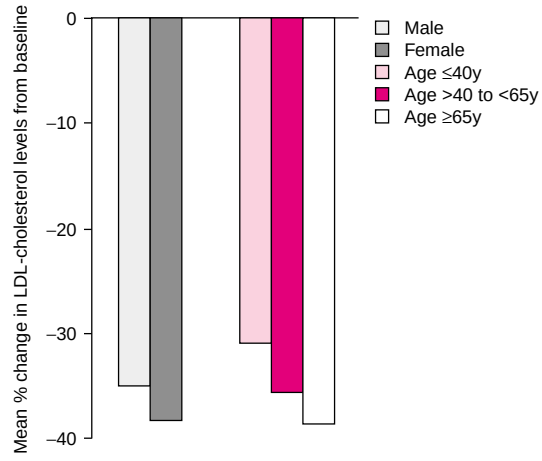


Fig. 4. Age- and gender-related effects on the efficacy of cerivastatin in lowering serum levels of low density lipoprotein (LDL)-cholesterol.[78] Pooled data from 788 patients with hypercholesterolaemia treated for 8 weeks with cerivastatin 0.4 mg/day in clinical trials (statistical analysis not provided).

4.4 Use in Combination with Other Antihyperlipidaemic Drugs

Three trials have examined the efficacy of cerivastatin (0.2 or 0.3 mg/day) in combination with other antihyperlipidaemic drugs.[92-94] Two of these studies have been published only as abstracts and also included periods of monotherapy during which cerivastatin was compared with the drug later used concomitantly.[92,93] In these 2 analyses, 8 weeks of therapy with cerivastatin 0.3 mg/day combined with either bezafibrate 400 mg/day (n = 116)[92] or micronised fenofibrate 200 mg/day (n = 115)[93] achieved significantly greater reductions from baseline in serum levels of total cholesterol and LDL-cholesterol than monotherapy with either drug in the respective studies (n > 100 for each monotherapy group). As might be expected, cerivastatin monotherapy was significantly better at improving these lipid parameters than either fibrate, whereas improvements in serum levels of trigly-

cerides and HDL-cholesterol were greater with the fibrates than the HMG-CoA reductase inhibitor.[92,93] In both studies, combined therapy led to mean reductions in serum LDL-cholesterol levels of >40% from baseline; reductions with cerivastatin monotherapy were approximately 28 to 35% compared with about 20% with fibrate monotherapy. Neither study showed significantly greater reductions in triglycerides with combined therapy than with fibrate monotherapy. It is important to note that the combined use of fibrates and HMG-CoA reductase inhibitors is generally not recommended because of the potential for increased risk of myopathy (including rhabdomyolysis and associated renal failure; section 5).[95]

A relatively low dosage of cerivastatin 0.2 mg/day was used as monotherapy, or combined with cholestyramine 8 g/day or probucol 1 g/day, in a small study of 20 patients with heterozygous familial hypercholesterolaemia [mean baseline serum LDL-cholesterol level ≈265 mg/dl (6.85 mmol/L)].[94] Cerivastatin 0.2 mg/day for 4 weeks achieved reductions from baseline in serum levels of total cholesterol ranging from 18 to 22% and in serum levels of LDL-cholesterol of 25%. The addition of either cholestyramine or probucol for 12 weeks reduced serum levels of total cholesterol by 32 to 34% versus baseline and by 34 to 44% versus baseline for LDL-cholesterol. Thus, combined therapy was more effective than monotherapy with cerivastatin in this patient population.

5. Tolerability

In general, cerivastatin has been well tolerated in clinical trials. Data from US placebo-controlled studies, for example, showed broadly similar tolerability profiles between cerivastatin up to 0.4 mg/day and placebo.[95] In these trials adverse events were reported in 65.3% of patients receiving cerivastatin (n = 1263) compared with 64.5% of placebo recipients (n = 504), and discontinuation due to adverse events occurred in 2.8 and 2.2% of patients, respectively. Overall, the most frequently reported adverse events were headache, pharyngitis and rhinitis. Adverse events reported with cerivastatin have usually been mild and transient.[95]

Similar results were noted in a larger pooled analysis of double-blind randomised studies of at least 8 weeks' duration.[78] Tolerability was assessed in a total of 3532 patients who received at least 1 dose of cerivastatin (n = 2816) or placebo (n = 716). Again, there were essentially no clinically important differences between the adverse event profiles of cerivastatin (up to 0.4 mg/day) and placebo. The incidence of adverse events among patients receiving cerivastatin ≤0.4 mg/day was not dose related (fig. 5). Headache, GI disturbances (e.g. dyspepsia, abdominal pain, diarrhoea) and asthenia were among the most common treatment-related adverse events reported. Discontinuation of therapy because of adverse events was reported in 3.0% of patients receiving cerivastatin and 2.5% of those treated with placebo. Overall, there were no differences between cerivastatin and placebo recipients with respect to clinically significant changes in laboratory parameters. Serum levels of creatine kinase were elevated to >10 times the upper limit of normal (ULN) in 0.3% of patients treated with cerivastatin 0.4 mg/day and 0.4% of those who received placebo.

As in the pooled analysis,[78] the incidence of adverse events among patients receiving cerivastatin was similar to that among placebo recipients and did not appear to be dose related in the pivotal trial comparing cerivastatin 0.4 and 0.8 mg/day.[81] Adverse events were reported in 58 and 61% of those receiving cerivastatin 0.4 and 0.8 mg/day, respectively, compared with 59% of placebo recipients during the 8-week randomised period. The most frequently reported adverse events were headache, pharyngitis and rhinitis. Adverse events leading to discontinuation of therapy occurred in 3.1 and 3.9% of patients treated with cerivastatin 0.4 and 0.8 mg/day, respectively, compared with 1.5% of those who received placebo. A small proportion of patients receiving cerivastatin in the pivotal trial had significant elevations in serum levels of creatine kinase and transaminases, whereas

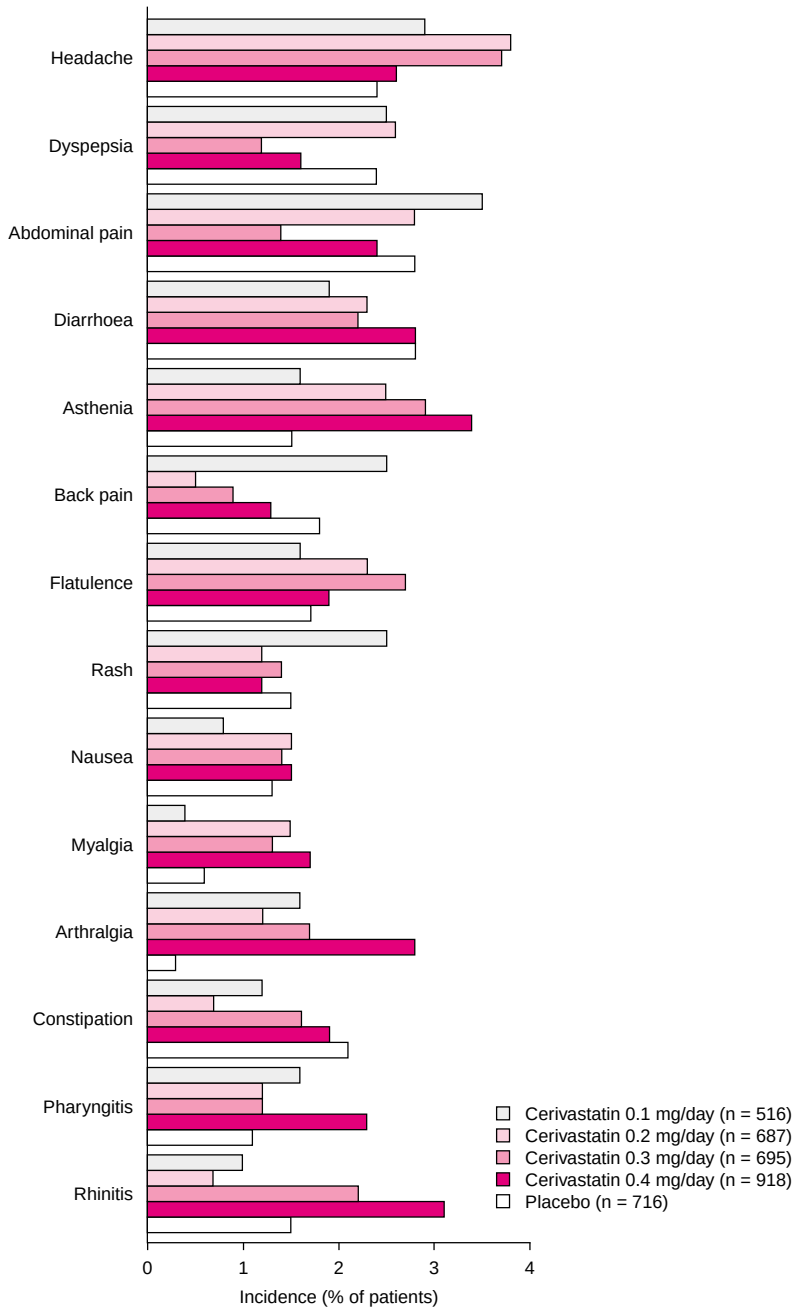


Fig. 5. Pooled tolerability data from double-blind randomised trials with cerivastatin in patients with primary hypercholesterolaemia.[78] Studies were placebo-controlled or comparative and involved ≥8 weeks of treatment. Tolerability was assessed in patients who received at least 1 dose of cerivastatin or placebo (statistical analysis not conducted).

these laboratory abnormalities were not reported among placebo recipients.

Myopathy and rhabdomyolysis have been reported, albeit rarely, with all currently available HMG-CoA reductase inhibitors, although the mechanism of these myotoxic reactions has not been clearly elucidated.[96] Clinically, myopathy involves muscle pain, tenderness and muscle weakness, accompanied by abnormal elevations in serum levels of creatine kinase (>10 times ULN). Rhabdomyolysis is an acute fulminating condition characterised by destruction of skeletal muscle, as evidenced by serum creatine kinase levels >10 times the ULN, myoglobinaemia and myoglobinuria. Renal failure and other serious complications can occur following acute rhabdomyolysis, and the condition can be fatal.[96] Postmarketing surveillance data indicate that cerivastatin (as with other HMG-CoA reductase inhibitors) has been associated with rhabdomyolysis and associated renal failure; most cases involved concomitant administration of gemfibrozil.[95,96]

In the few published case reports of patients developing rhabdomyolysis while receiving cerivastatin, concomitant drug therapy included gemfibrozil[97,98] or cyclosporin.[99] The combined use of fibrates (or lipid-lowering dosages of nicotinic acid) and HMG-CoA reductase inhibitors is generally not recommended because of the potential for increased risk of myopathy including rhabdomyolysis and associated renal failure.[95] Likewise, drugs that may inhibit the metabolism of HMG-CoA reductase inhibitors, including cyclosporin, azole antifungal agents and erythromycin (section 3.3.3),[96] are generally not recommended for concomitant therapy in patients receiving HMG-CoA reductase inhibitors because of an increased risk of myopathy.[95]

6. Dosage and Administration

Patients with hypercholesterolaemia should be placed on a standard cholesterol lowering diet before drug therapy is implemented. If nonpharmacological measures are inadequate to control serum cholesterol levels, patients should continue on their diet during drug treatment.

Cerivastatin is administered orally and may be taken with or without food. The recommended dosage of cerivastatin currently varies between countries. The US FDA recommends a starting dosage of cerivastatin 0.4mg orally once daily in the evening. The maximal lipid-lowering effect of cerivastatin is usually seen within 4 weeks. If response is inadequate, cerivastatin dosage may be increased to 0.8 mg/day (US FDA recommendation), also administered once daily in the evening. For patients with significant renal impairment [creatinine clearance ≤60 ml/min/1.73m^2 (3.6 L/h/1.73m^2)] lower dosages <0.4 mg/day are recommended.[95,100]

HMG-CoA reductase inhibitors affect cholesterol biosynthesis, and this could have an adverse effect on fetal development, including synthesis of steroids and cell membranes. Cerivastatin is contraindicated during pregnancy and (because it is secreted in breast milk) in nursing mothers. Other contraindications include active liver disease or unexplained persistent elevations of serum transaminases.[95] The efficacy and tolerability of cerivastatin in paediatric patients have not been established.

7. Place of Cerivastatin in the Management of Hypercholesterolaemia

Hypercholesterolaemia is a common problem in industrialised countries. For example, it has been estimated that more than 50 million adults in the US may be candidates for at least dietary treatment of hypercholesterolaemia according to NCEP guidelines.[101] In Northern and Southern Europe an estimated 45 and 25%, respectively, of individuals aged 40 to 59 years are thought to have elevated [>250 mg/dl (>6.5 mmol/L)] serum levels of total cholesterol.[102]

It is well established that elevated serum levels of total and LDL-cholesterol are associated with atherogenic effects and an increased risk of CHD, the leading cause of death among men and women in the US. There is also convincing evidence from

clinical trials, including studies evaluating angiographic progression, that improving the serum lipid profile with diet and drug therapy reduces the risk of atherosclerosis in patients with and without cardiovascular disease (reviewed by Illingworth[4]). These data are reflected in the NCEP guidelines which focus on the importance of achieving and maintaining specific target serum levels of LDL-cholesterol.[103]

In particular, there have been 5 major long term (≈5-year) clinical trials with HMG-CoA reductase inhibitors showing that treatment with these drugs (primarily aimed at reducing serum LDL-cholesterol levels) significantly reduces cardiovascular end-points compared with diet alone. These studies include 3 secondary prevention trials with simvastatin [Scandinavian Simvastatin Survival Study (4S)[104]] and pravastatin [Cholesterol and Recurrent Events Trial (CARE),[105] and Long Term Intervention with Pravastatin in Ischemic Disease (LIPID)[106]] as well as 2 primary prevention studies with pravastatin [West of Scotland Coronary Prevention Study (WOSCOPS)[107]] and lovastatin [Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS)[108]]. Not only did the trials provide clear evidence of the beneficial effects of HMG-CoA reductase inhibitors on cardiovascular events, but they also showed that these drugs are generally well tolerated during long term administration over several years.

Although the effects of cerivastatin on cardiovascular morbidity and mortality have not been evaluated, a large (n = 10 000) study will evaluate the effects of cerivastatin in the primary prevention of stroke in patients at risk. In this trial [Risk Evaluation and Stroke Prevention in the Elderly – Cerivastatin Trial (RESPECT)], cerivastatin will be administered at a dosage of up to 0.8 mg/day for ≥4 years.[109] A large primary prevention clinical outcome trial (Lipids in Diabetes Study) in patients with type 2 diabetes mellitus but without hypercholesterolaemia is also under way.[91] Patients recruited in 30 UK centres will be randomised to receive cerivastatin 0.4 mg/day or micronised fenofibrate 200 mg/day, or a combination of cerivastatin and fenofibrate or placebo according to a two-by-two factorial design. Other studies evaluating the effects of cerivastatin on cardiovascular morbidity and mortality are also in progress, including the Prevention of Re-INfarction with early treatment by CErivaStatin Study (PRINCESS) in patients with acute myocardial infarction and the Cerivastatin Heart Outcomes in Renal Disease: Understanding Survival (CHORUS) trial in patients with renal failure recently started on haemodialysis.[65]

Together, these data support and validate therapeutic guidelines for the treatment of hypercholesterolaemia, such as those of the NCEP in the US[103] and a joint task force in Europe.[110] The European guidelines focus on an evaluation of risk factors to determine the patient's 10-year risk of cardiovascular death, with treatment recommended beyond a threshold level of increased risk. NCEP guidelines also consider concurrent cardiovascular risk factors but focus on defined serum levels of LDL-cholesterol as the primary target for treatment to reduce the risk of cardiovascular events. Specifically, NCEP guidelines suggest the following treatment goals for serum levels of LDL-cholesterol:

- <160 mg/dl (<4.1 mmol/L) for patients without CHD and <2 risk factors
- <130 mg/dl (<3.4 mmol/L) for patients without CHD and ≥2 risk factors
- ≤100 mg/dl (≤2.6 mmol/L) for patients with CHD.

While fibrates are the most effective drugs available for reducing serum triglyceride levels, HMG-CoA reductase inhibitors have the greatest effect on lowering serum levels of LDL-cholesterol.[111] This, combined with their good tolerability profile (particularly compared with older agents such as bile acid sequestrants and nicotinic acid), has established HMG-CoA reductase inhibitors as first-line agents for patients with hypercholesterolaemia (increased LDL-cholesterol levels). The HMG-CoA reductase inhibitors have additional beneficial effects on the serum lipid profile (e.g. reductions in serum

triglycerides) and can also be used, for example, in patients with combined hyperlipidaemia.[111]

There are currently 6 commercially available HMG-CoA reductase inhibitors (cerivastatin, lovastatin, pravastatin, simvastatin, fluvastatin and atorvastatin). Differences between the agents in terms of pharmacokinetic properties, dosage regimens, drug interaction potential, availability of clinical end-point data and other features have been recently reviewed by Knopp.[111])

Several multicentre double-blind studies with cerivastatin 0.4 or 0.8 mg/day showed reductions in serum levels of LDL-cholesterol ranging from 33.4 to 44.0%. Marked reductions were also noted for serum levels of total cholesterol, which were typically accompanied by modest reductions in serum triglycerides and small to moderate increases in HDL-cholesterol levels (section 4.2). In particular, recent data are available from a pivotal placebo-controlled trial which included a large group of patients (n = 656) who received cerivastatin 0.8 mg/day.[81] Cerivastatin 0.8 mg/day for 8 weeks was associated with a mean reduction from baseline of 41.8% in serum LDL-cholesterol levels, which was sufficient to achieve NCEP target LDL-cholesterol levels in 84% of patients (see section 4.2 and table III). Overall, in the subgroup with serum LDL-cholesterol levels meeting NCEP guidelines for drug treatment, 75% of patients achieved target LDL-cholesterol levels with cerivastatin 0.8 mg/day. Subpopulation analyses indicate that cerivastatin lowers serum levels of LDL-cholesterol to a greater extent in women than men and in elderly than younger patients (section 4.3). The overall tolerability profile of cerivastatin (section 5) was broadly similar to that of other HMG-CoA reductase inhibitors.[111] Available data suggest that cerivastatin has a low potential for drug-drug interactions (section 3.3.3), which is an important consideration in secondary prevention patients who are typically receiving multiple drugs.

Interestingly, while 84% of patients receiving cerivastatin 0.8 mg/day achieved NCEP target LDL-cholesterol levels after 8 weeks of therapy in the randomised, double-blind, pivotal trial of cerivastatin,[81] data from the Lipid Treatment Assessment Project (L-TAP) showed less promising results with various other HMG-CoA reductase inhibitors used in a naturalistic (or 'real world') setting.[112] Evaluation of data from L-TAP included 4888 patients with hypercholesterolaemia seen by primary care physicians in 5 regions in the US. Patients were eligible for inclusion if they were being treated with the same dietary therapy and/or lipid-lowering drug therapy for at least 3 months. Details were collected regarding each patient's medical history, cardiovascular risk factors, dietary counselling and current lipid-lowering therapy. A single (fasting) blood sample was collected from each patient to analyse their serum lipid profile. Approximately 64% of patients (n = 3136) were receiving monotherapy with an HMG-CoA reductase inhibitor (fluvastatin, lovastatin, pravastatin or simvastatin). In terms of achieving LDL-cholesterol target levels, the success rate was 40% overall in this group, ranging from 32% (with fluvastatin) to 46% (with simvastatin). However, these results cannot be readily compared with those of the large controlled trial of cerivastatin because of major differences in study designs. Results do indicate, though, that the management of hypercholesterolaemia may be more difficult in clinical practice than in randomised, controlled clinical trials.

Numerous pharmacoeconomic studies have evaluated lipid-lowering treatment interventions including HMG-CoA reductase inhibitors, and several recent reviews on this topic have been published.[113-116] In general, results showed a wide range of cost-effectiveness ratios (cost per life-year gained) for lipid-lowering therapy depending on specific CHD risk factors and treatment. For example, HMG-CoA reductase inhibitors appear to be very cost effective when used as secondary prevention in patients with pre-existing CHD, but their cost effectiveness in primary prevention of CHD has varied widely in pharmacoeconomic analyses, depending to a great extent on the patient population.

To date, only a few pharmacoeconomic analyses have included cerivastatin,[117-119] and 2 of

these have not been published in full reports.[117,118] A US analysis[118] and subsequent reevaluation using a Markov model and a more efficacious (0.4 mg/day) cerivastatin dosage regimen[117] compared the cost effectiveness of all HMG-CoA reductase inhibitor dosages approved in the US as of January 2000. Among available agents, cerivastatin 0.4 mg/day had the lowest cost per life-year gained relative to no therapy ($US7200 for high-risk men with CHD and $US248 000 for low-risk women), but atorvastatin was the most efficient agent for patients requiring more aggressive CHD risk reduction. The only other economic evaluation of cerivastatin used a Markov model incorporating epidemiological, efficacy and other data from various sources to compare the drug with simvastatin and pravastatin in Italy [all costs in 1998 Italian lire (L) and converted to Euros (Eur)].[119] As primary prevention, the incremental cost per life-year gained with cerivastatin 0.4 mg/day versus pravastatin 20 mg/day ranged from L11.1 million to L31.8 million (Eur5733 to Eur16 423) depending on the patient cohort and study perspective (Italian National Health Service, which included direct costs only, or societal, which included direct and indirect costs). The incremental cost per life-year gained with simvastatin 40 mg/day versus cerivastatin 0.4 mg/day was >L317 million to >L650 million (Eur163 717 to Eur335 697).

In conclusion, cerivastatin is a well tolerated and effective lipid-lowering agent for patients with hypercholesterolaemia. When given at dosages currently recommended in the US, cerivastatin achieves marked reductions in serum levels of LDL-cholesterol, reaching NCEP target levels in the vast majority of patients. Thus, cerivastatin provides a useful (and potentially cost effective) alternative to other currently available HMG-CoA reductase inhibitors as a first-line agent for hypercholesterolaemia.

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