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Rational Assessment of the Interaction Profile of Cerivastatin Supports its Low Propensity for Drug Interactions

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Abstract

Pharmacokinetic drug-drug interactions influence drug efficacy, tolerability, and compliance. Such interactions are both more common and of more clinical relevance than often appreciated. The US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products have recently issued guidelines setting out *in vitro* and *in vivo* investigations to be conducted during drug development. These guidelines reflect the increasing interest of public health authorities in this topic.

Cerivastatin is a novel, potent HMG-CoA reductase inhibitor that effectively reduces serum cholesterol levels at low daily doses. It is completely absorbed after oral administration, undergoes moderate first-pass metabolism and high plasma protein binding, and is cleared exclusively via hepatic cytochrome P450 (CYP). Unlike other drugs of its class, cerivastatin has a dual metabolic pathway, with the involvement of more than one CYP isozyme. Metabolites are cleared via both biliary and renal excretion.

On the basis of this pharmacokinetic profile and a knowledge of the target population, the formal *in vivo* interaction programme for cerivastatin investigated many important potential cerivastatin drug-drug interactions. Cerivastatin appears to lack clinically relevant interactions with digoxin, warfarin, antacid, cimetidine, nifedipine, omeprazole, erythromycin and itraconazole.

Pharmacokinetic drug-drug interactions are those affecting the absorption, distribution, metabolism or excretion of one or more drugs (the so-called ADME interactions). Such an interaction may lead either to increased drug exposure, with the potential for increased toxicity, or to reduced drug exposure, with the potential for decreased therapeutic efficacy. A drug interaction is considered clinically relevant when it occurs between 2 commonly coadministered agents and results in the need for dosage adjustment or other medical intervention.[1]

The potential for clinically important drug-drug interactions to reduce tolerability and patient compliance, and to increase treatment costs and the incidence of serious adverse events is more common and of greater significance than is often appreciated or expected. For example, when the medication data of 2547 hospitalised patients were combined in a computerised system with a rule-based drug interactions programme, 173 (6.8%) patients had received one or several drug combinations that might have resulted in serious clinical adverse effects.[2] Similar frequencies for interactions are listed by Stockley.[3]

Patients with hyperlipidaemia are generally

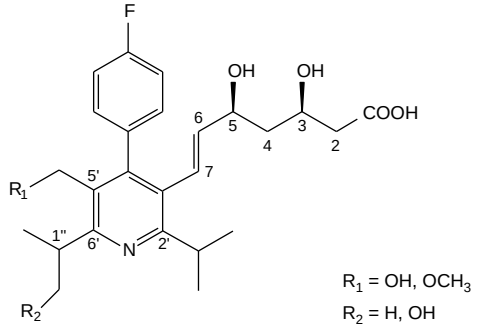

Fig. 1. Structural formula of cerivastatin (R_1 = OCH_3; R_2 = H) and its pharmacodynamically active metabolites M-1 (R_1 = OH; R_2 = H), M-23 (R_1 = OCH_3; R_2 = OH), and M-24 (R_1 = OH; R_2 = OH).

middle-aged or older and often have other cardiovascular risk factors such as hypertension or diabetes and/or other conditions such as gastric reflux, which necessitate taking medication. Moreover, antihyperlipidaemic therapy is usually prescribed over a long period of time, often a lifetime, and thus the likelihood of patients taking concomitant medication at some stage, even if only briefly, is high.[4] The potential for drug-drug interactions in these patients is therefore also high and needs to be minimised when possible.

Clinical experience indicates that the HMG-CoA reductase inhibitors are well tolerated, with a favourable risk-benefit profile. The only potentially serious adverse effect is myopathy, which in rare instances may lead to rhabdomyolysis. However, drug-drug interactions have been reported with currently available HMG-CoA reductase inhibitors when administered with, for example, antacids, cimetidine, cyclosporin, warfarin, propranolol and digoxin.[4] The considerable variations between HMG-CoA reductase inhibitors with regard to drug-drug interactions are related to their differing pharmacokinetic and biopharmaceutical characteristics.[5,6]

Drug-drug interactions are therefore important in therapeutic use, and a detailed assessment of the interaction profile is necessary for any new drug. Guidelines defining detailed *in vitro* and *in vivo* investigations to be conducted during drug development have recently been issued by both the European Agency for the Evaluation of Medicinal Products and the US Food and Drug Administration.[1,7] Both sets of guidelines emphasise the importance of conducting mechanism-based drug interaction studies that will have predictive power for other agents.

Cerivastatin (rivastatin; BAY-W-6228) is a new, fully synthetic and highly potent HMG-CoA reductase inhibitor (fig. 1).[8-10] At the recommended once-daily dosage of 0.1 to 0.3mg, cerivastatin is safe and well tolerated.[11]

This review outlines the pharmacokinetic properties of cerivastatin (section 1), and discusses the results and the underlying rationale of the carefully chosen programme of *in vitro* and *in vivo* drug interaction studies conducted with the drug (section 2).

1. Pharmacokinetic Properties of Cerivastatin

Cerivastatin has a well defined profile with respect to bioavailability and pharmacokinetics: cerivastatin is almost completely absorbed after oral administration, reaching a maximum plasma concentration (C_{max}) 2 to 3 hours postdose.[12] Values for C_{max} and area under the concentration-time curve (AUC) increase in proportion to dosage over the range of 0.05 to 0.4mg.[13,14] No accumulation is observed with repeated administration.[15] The absolute oral bioavailability of cerivastatin is about 60%.[12] The pharmacokinetics of cerivastatin are not influenced by concomitant administration of food, or by the time of day at which the dose is given.[16,17] None of the following had any clinically significant effect on the pharmacokinetics of cerivastatin: age, gender, ethnic group and disease.[18-24] Representative plasma concentration *vs* time profiles of cerivastatin and one of its major metabolites, M-23, are presented in figure 2.

Cerivastatin is highly bound (>99%) to plasma proteins, mainly albumin.[25] Its volume of distribution at steady-state of about 0.3 L/kg indicates that the drug penetrates only moderately into pe-

ripheral tissues.[25,26] Preclinical experiments have indicated that cerivastatin has a high affinity for liver tissue, the target site of action.[25]

The metabolic pathways of cerivastatin in humans have been elucidated, and *in vitro* experiments using human hepatic microsomes and cells expressing human cytochrome P450 (CYP) isozymes have provided a complete CYP isoform profile. Cerivastatin is principally metabolised via 2 oxidative biotransformation reactions: demethylation of the benzylic methyl ether results in the formation of the metabolite M-1, and stereoselective hydroxylation of one methyl group in the 6-isopropyl substituent results in metabolite M-23 (fig. 1). M-24, a secondary, minor metabolite not detectable in plasma, results from the combination of both reactions.[27] Cerivastatin shows high affinity for CYP 2C8, which catalyses the formation of M-1 and M-23 almost to the same extent. Affinity for CYP 3A4 is considerably lower; CYP 3A4 contributes only to the formation of M-1. Formation of the secondary metabolite, M-24, is catalysed by the same CYP isozymes.[28] Metabolites M-1, M-23 and M-24 are similar to the parent drug in terms of HMG-CoA reductase inhibitory activity.[29]

Cerivastatin is cleared exclusively via biotransformation and subsequent biliary/renal excretion of the formed metabolites. No unchanged drug is excreted. 70% of the administered dose is excreted as metabolites via the faeces, with 30% excreted in the urine. The plasma half-life ($t_{1/2}$) of cerivastatin is approximately 2 to 3 hours.[26]

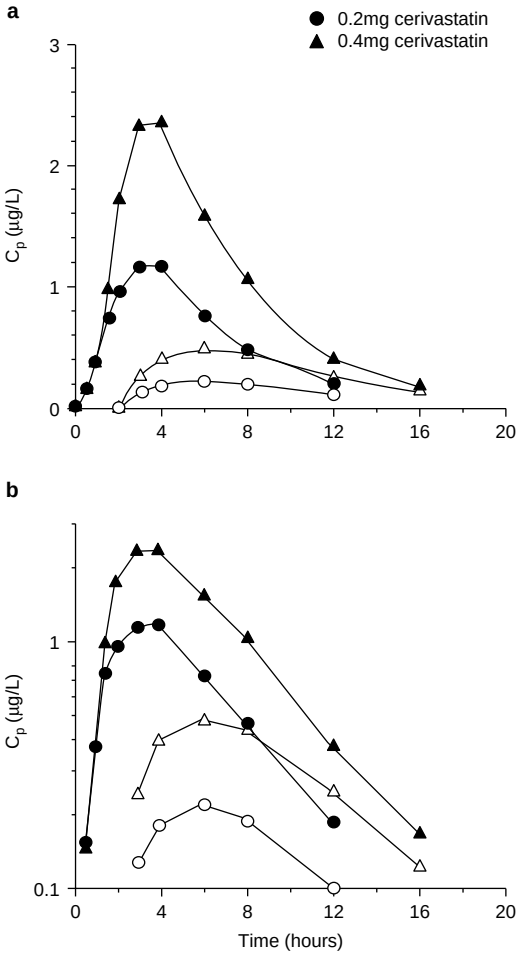

Fig. 2. Plasma concentration (C_p) *vs* time profiles of cerivastatin and its major metabolite, M-23, following administration of cerivastatin sodium 0.2mg and 0.4mg to healthy young male individuals [n = 25; geometric mean values, shown on (**a**) a linear and (**b**) a semi-logarithmic scale].

2. Cerivastatin Drug Interaction Study Programme: Rationale and Results

The detailed drug-drug interaction programme for cerivastatin (table I) examined all the major areas of concern in relation to the target population, on the basis of the pharmacokinetic profile of the drug (section 1) and information available regarding the interaction profile of other HMG-CoA reductase inhibitors.

With respect to pharmacokinetic drug-drug interactions, the properties of cerivastatin are as follows:

- *Absorption*: cerivastatin possesses a carboxylic acid functional group
- *Distribution*: cerivastatin is highly bound to plasma proteins, mainly albumin (99.1 to 99.5%)
- *Metabolism/elimination*: cerivastatin undergoes moderate first-pass metabolism (approximately 40%), and clearance is exclusively via CYP-mediated (CYP 2C8 and CYP 3A4) bio-

Table I. Overview of the interaction study programme performed for cerivastatin

Comedication	Result	Reference no.
Antacid, based on aluminium-magnesium hydroxide (Maalox®)	No interaction[a]	12
H_2 receptor antagonist: cimetidine	No interaction	12
Gastric acid secretion inhibitor: omeprazole	No interaction	30
Bile acid sequestering agent: cholestyramine	Loss in cerivastatin bioavailability: by 21% with concurrent administration, and by 8% with 5-hour interval between administrations	31
Oral anticoagulant: warfarin	No interaction	32
Cardiac glycoside: digoxin	No interaction	33
Macrolide antibacterial: erythromycin	Increase in cerivastatin AUC: by 21% in healthy individuals, and by 51% in hypercholesterolaemic patients	34; data on file, Bayer AG
Azole antifungal: itraconazole	Moderate increase in cerivastatin AUC: by 38% in hypercholesterolaemic patients	Data on file, Bayer AG
Calcium antagonist: nifedipine	No interaction	35
T-type calcium antagonist: mibefradil	No interaction	Data on file, Bayer AG
Immunosuppressive agent: cyclosporin	3- to 5-fold increase in cerivastatin, M-1 and M-23 exposure (AUC, C_{max})	36

a No interaction confirmed by statistical evaluation (ANOVA with bioequivalence criteria).[37]

AUC = area under the concentration-time curve; **C_{max}** = maximum plasma concentration.

transformation, with biliary/renal excretion of the metabolites.

In addition, important and clinically relevant interactions have been reported for other HMG-CoA reductase inhibitors when coadministered with the following agents: cyclosporin, fibric acid derivatives, niacin, erythromycin, bile acid sequestrants, warfarin, digoxin, cimetidine, itraconazole and antacids.[4-6] Therefore, a series of pharmacological studies was performed to evaluate the interaction potential of cerivastatin with these agents.[38]

2.1 Absorption

Because cerivastatin has a carboxylic acid functional group, it was important to investigate whether changes in gastric pH influenced the extent and rate of cerivastatin absorption.

No significant differences in the key pharmacokinetic parameters [AUC, C_{max}, time to C_{max} (t_{max}) and $t_{½}$] were observed when single doses of cerivastatin 0.2mg were administered alone or concomitantly with 10ml Maalox® 70 suspension.[12] Similarly, the single-dose pharmacokinetic parameters of cerivastatin 0.2mg were not altered when the drug was administered after 4 days' therapy with an H_2 receptor antagonist (cimetidine 400mg twice daily)[12] or 5 days' treatment with a proton-pump inhibitor (omeprazole 20 mg/day).[30]

The bile acid sequestrant cholestyramine has a mode of action that is complementary to cerivastatin, and these agents may be used concomitantly. Importantly, cholestyramine has a strong adsorption capacity and has been reported to influence the absorption of coadministered drugs, including HMG-CoA reductase inhibitors.[4,5]

Cholestyramine 12g significantly reduced the bioavailability of cerivastatin 0.2mg (21% decrease in AUC). This reduction is similar to findings reported for other HMG-CoA reductase inhibitors.[31] However, when cerivastatin was taken at least 1 hour after cholestyramine, the AUC for cerivastatin decreased by only 8 to 16% and the C_{max} by 32%.[31] These changes are unlikely to be of clinical significance when the drugs are taken as recommended (i.e. at least one hour apart: the resin before a meal and cerivastatin after an evening meal or at bedtime).

2.2 Distribution

Cerivastatin is highly protein bound in plasma (>99%, primarily to albumin), and thus there is a potential for drug-drug interactions by mutual displacement from plasma protein binding sites.

However, neither free fatty acids nor drugs well known for their high plasma protein binding [warfarin, phenylbutazone, clofibrate, ibuprofen, propranolol, imipramine, gemfibrozil, nifedipine, salicylic acid, nicotinic acid, furosemide, phenytoin, digitoxin and glibenclamide (glyburide)] showed any interaction at therapeutic concentrations *in vitro*.[25] In addition, concomitant administration of cerivastatin 0.3 mg/day and warfarin did not affect the pharmacokinetics of either the *R* or the *S* enantiomer of warfarin or the pharmacokinetics of cerivastatin, nor were any pharmacodynamic effects observed (section 2.4).[32]

2.3 Metabolism

2.3.1 Nonspecific CYP Inhibition

Cimetidine is a nonspecific inhibitor of CYP and, as reviewed in section 2.1, concomitant administration of cerivastatin with cimetidine had no effect on the bioavailability and pharmacokinetics of cerivastatin, or the sum of cerivastatin and immunoactive metabolite concentrations as determined by radioimmunoassay.[12] This cimetidine/cerivastatin interaction study illustrated that the metabolic pathways of cerivastatin involved in its first-pass metabolism and elimination are rather insensitive to nonspecific CYP enzyme inhibition.

In addition, no pharmacokinetic drug-drug interactions could be demonstrated between cerivastatin and warfarin, a drug mainly cleared via CYP 2C9-mediated biotransformation,[32] or omeprazole, a drug with known CYP 2C19 inhibitory potential.[30]

2.3.2 Studies with CYP 3A4 Inhibitors

Mechanistic interaction studies have been conducted with cerivastatin and a variety of CYP 3A4 inhibitors. The rationale for these studies was, first, that *in vitro* studies have shown that cerivastatin is metabolised by CYP 3A4,[27,28] and, second, that prominent interactions have been observed with other HMG-CoA reductase inhibitors (e.g. lovastatin and simvastatin[39-43]) metabolised by this class of enzymes.[44,45]

Erythromycin is a specific and potent CYP 3A4 inhibitor.[46] Therefore, a study was carried out to assess the effect of erythromycin on the pharmacokinetics (particularly first-pass metabolism) of cerivastatin.[34]

In this randomised, nonblinded crossover study, 12 healthy young men received single oral doses of cerivastatin 0.3mg alone or on the fourth day of 4 days' treatment with erythromycin 500mg 3 times daily.[34] The erythromycin regimen was chosen to ensure maximum inhibition of CYP 3A4 during cerivastatin exposure. Plasma and urine samples were analysed for cerivastatin and its major metabolites by validated specific high performance liquid chromatography assays.[47] Cerivastatin was safe and well tolerated, and no clinically relevant treatment-emergent changes in laboratory parameters were observed. Pre- and concomitant treatment with erythromycin had a moderate influence on cerivastatin clearance, leading to a mean 13% increase in C_{max} and a slightly increased terminal half-life ($t_{½\beta}$) [by approximately 10%], with a consequent mean 21% elevation in AUC. Values for t_{max} remained unchanged.[34]

A detailed mechanistic explanation of these results is provided in figure 3. The dual metabolic pathway of cerivastatin, which involves more than one CYP isozyme, allowed attenuation of the CYP 3A4 inhibition on the M-1 pathway (60% decrease in M-1 AUC), mainly by a shift to the CYP 2C8-mediated M-23 pathway (60% increase in M-23 AUC), resulting in a 21% increase (90% confidence intervals: 11 to 31%) in the AUC of the parent drug. The need for a dosage adjustment could not be derived from these data. The small increase in the cerivastatin $t_{½\beta}$ does not predict accumulation of cerivastatin above the known steady-state concentrations with a once-daily dosage regimen.[34]

The moderate changes in the pharmacokinetics of cerivastatin in healthy volunteers observed in

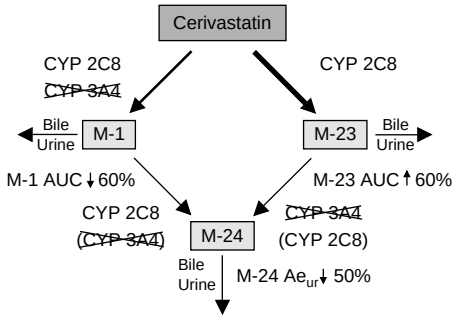

Fig. 3. Mechanistic explanation of interaction results for cerivastatin with the cytochrome P450 (CYP) 3A4 inhibitor erythromycin.[34] **Ae$_{ur}$** = urinary excretion; **AUC** = area under the concentration-time curve.

this study were confirmed in a multiple-dose study under therapeutic conditions: 16 patients receiving cerivastatin 0.3 mg/day for hypercholesterolaemia received 10 days' treatment with erythromycin 500mg twice daily. A 51% increase in the cerivastatin AUC was observed (90% confidence interval: 29 to 76%, n = 16), with no observable effects on safety and tolerability (data on file, Bayer AG).

These results were very similar to those detected during concomitant administration of cerivastatin and itraconazole, another potent CYP 3A4 inhibitor. In this multiple-dose study, 16 patients receiving cerivastatin 0.3 mg/day also received itraconazole 200 mg/day for 10 days. The observed increase in the cerivastatin AUC was 38% (90% confidence interval: 25 to 54%), again without any attributable clinical effects on safety and tolerability (data on file, Bayer AG).

Because both erythromycin and itraconazole inhibited cerivastatin metabolism by about 50% at maximum doses, it can be predicted that the interaction between cerivastatin and mibefradil, another potent CYP 3A4 inhibitor, will not be clinically relevant. Indeed, in 12 healthy young individuals receiving mibefradil 100 mg/day, neither the pharmacokinetics of cerivastatin nor the steady-state mibefradil trough plasma concentrations were influenced by single- and multiple-dose administration of cerivastatin 0.3mg (data on file, Bayer AG).

Thus, the high predictive value of the *in vitro* elucidation of cerivastatin's metabolic pathway and CYP isoform profile in combination with mechanism-based *in vivo* interaction studies was confirmed.

2.3.3 Substrate Studies

The evidence reviewed in sections 2.3.1 and 2.3.2 indicates that inhibitors of CYP do not significantly affect cerivastatin pharmacokinetics. A number of studies have been conducted to determine whether cerivastatin itself affects the metabolism of concomitantly administered drugs.

A series of investigations into the *in vitro* enzyme affinity of cerivastatin for common CYP subclasses showed that all inhibitory constants (K_i values) determined for cerivastatin were greater than those expected to be relevant *in vivo* (data on file, Bayer AG). For instance, K_i values published by Ikeda et al.[48] for cerivastatin and CYP 3A4 were approximately 200 μmol/L,[48] corresponding to plasma concentrations approximately 10 000-fold higher than the therapeutic concentrations achieved with cerivastatin, even at the highest dose currently under clinical evaluation (0.8mg). Even in the liver, where cerivastatin concentrations may be 100-fold higher than in plasma,[25] cerivastatin would not achieve sufficient concentrations to inhibit the metabolism of other CYP 3A4 substrates.

These *in vitro* findings and assumptions were confirmed in an *in vivo* study that investigated the potential interaction of cerivastatin and the dihydropyridine calcium antagonist nifedipine. Nifedipine was used as a CYP 3A4 'probe drug', since its metabolism is primarily mediated via CYP 3A4. The pharmacokinetics of both drugs remained completely unaffected with concomitant administration of nifedipine 60mg GITS (gastrointestinal therapeutic system – a once-daily modified release tablet) and cerivastatin 0.3mg.[35]

2.4 Studies with Other Agents

Drug interactions have been reported with other HMG-CoA reductase inhibitors and both digoxin and warfarin. As these 2 potential comedications have narrow therapeutic indices, interaction studies with cerivastatin were conducted.

The steady-state plasma and urinary digoxin concentrations and renal clearance of digoxin were not affected by concomitant administration of cerivastatin 0.2mg.[33] Similarly, there was no evidence of any change in the pharmacokinetics of either warfarin or cerivastatin when the 2 agents were administered together, and the effects of warfarin on prothrombin time and factor VII were unaltered.[32]

Cyclosporin is another agent known to interact with HMG-CoA reductase inhibitors. To evaluate the drug-drug interaction potential of cerivastatin and cyclosporin, cerivastatin 0.2 mg/day was administered to 12 kidney transplant patients already receiving cyclosporin and other immunosuppressive agents.[36] Plasma levels of cerivastatin and metabolites were increased 3- to 5-fold compared with a control group receiving cerivastatin alone. However, cerivastatin elimination was unaffected, and no significant accumulation occurred during multiple-dose administration of cerivastatin.[36] Nevertheless, in patients receiving cyclosporin, cerivastatin therapy should be initiated at the lower end of the dosage range and titrated carefully.

Cerivastatin had no influence on the steady-state blood concentration *vs* time profiles of either cyclosporin or cyclosporin plus metabolites. The mechanism of the interaction is still under investigation, but is not attributable to CYP 3A4 inhibition. Similar interaction findings have been reported for other HMG-CoA reductase inhibitors.[49]

3. Conclusion

A thorough assessment of a drug's interaction profile, i.e. its potential for interaction with relevant coadministered drugs in the target population, is mandatory when establishing safe therapeutic use of a new drug. The formal *in vivo* drug-drug interaction programme for cerivastatin investigated all major areas of concern in relation to the target population, and was based on the pharmacokinetic profile and a complete elucidation of metabolic pathways, the CYP isoform profile, and investigations of CYP enzyme affinity.

In summary, the favourable interaction profile of cerivastatin is based on 3 key features:

- Cerivastatin is an uncomplicated drug with respect to bioavailability and biopharmaceutics.
- Cerivastatin is eliminated via a dual metabolic pathway as known metabolites. Because more than one CYP isozyme is involved (CYP 2C8 and CYP 3A4), cerivastatin evades accumulation when one or the other of these pathways is inhibited by coadministered drugs. Furthermore, cerivastatin possesses no CYP enzyme inhibitory or inducing activity.
- The lack of any apparent clinically relevant interaction between cerivastatin and many common drugs (including digoxin, warfarin, antacids, cimetidine, nifedipine, omeprazole, erythromycin and itraconazole) renders cerivastatin a logical choice when an HMG-CoA reductase inhibitor is required for the treatment of patients with hypercholesterolaemia, and particularly those taking multiple comedications.

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