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Avasimibe

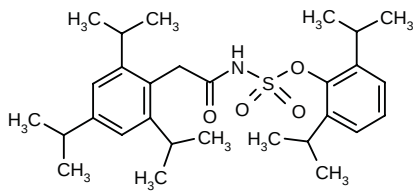
Prop INN

Treatment of Lipoprotein Disorders

ACAT Inhibitor

CI-1011

N-[2-(2,4,6-Triisopropylphenyl)acetyl]sulfamic acid 2,6-diisopropylphenyl ester



$C_{29}H_{43}NO_4S$ Mol wt: 501.7277

CAS: 166518-60-1
CAS: 166518-61-2 (as sodium salt)

EN: 217771

Synthesis

The synthesis of avasimibe has been performed by different related ways: Scheme 1.

1) The reduction of 2,4,6-triisopropylbenzoyl chloride (I) with $LiAlH_4$ in ethyl ether gives 2,4,6-triisopropylbenzyl alcohol (II) (1-4), which by reaction with $SOCl_2$ in toluene is converted into 2,4,6-triisopropylbenzyl chloride (III). The reaction of (III) with NaCN or KCN in DMSO affords 2,4,6-triisopropylphenylacetonitrile (IV) (1), which is hydrolized with aqueous H_2SO_4 or KOH in diethyleneglycol/water, yielding the phenylacetic acid (V). The reaction of (V) with $SOCl_2$ or $(COCl)_2$ in DMF affords the expected acyl chloride (VI), which is finally condensed with 2,6-diisopropylphenyl sulfamate (VII) by means of triethylamine in hot toluene (1-3).

2) The sulfamate (VII) can be obtained by condensation of 2,6-diisopropylphenol (VIII) with chlorosulfonyl isocyanate (IX) in refluxing toluene to give the isocyanate (X), which is hydrolyzed with water to the sulfamate (VII) (1, 3).

3) The intermediate benzyl chloride (III) can also be obtained by direct chloromethylation of 1,3,5-triisopropylbenzene (XI) with paraformaldehyde/HCl in acetic acid (1).

4) Phenylacetic acid (V) can also be obtained by condensation of 1,3,5-triisopropylbenzene (XI) with glyoxylic acid (XIV) by means of H_2SO_4 in refluxing acetic acid, yielding a mixture of acetoxyacetic acid (XV) and hydroxyacetic acid (XVI). This mixture is finally reduced with HI in acetic acid to the phenylacetic acid (V) (1).

5) The acetonitrile (IV) can also be obtained by reaction of benzyl bromide (XII) with KCN in DMSO (1-3)

6) Avasimibe can also be obtained by reaction of benzyl alcohol (II) with PBr_3 in ether to give the benzyl bromide (XII) (1-4), which is treated with Mg in THF to yield the corresponding Grignard reagent (XIII). Finally, this compound is condensed with the already described isocyanate (X) in refluxing THF (4).

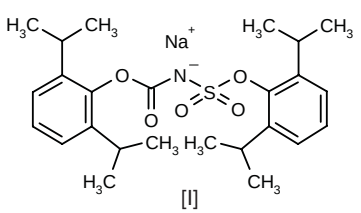
Description

White powder, m.p. 169.5-70.4 °C (1); white solid, m.p. 178-80 °C (2).

Introduction

In recent years, the intensive research efforts of many companies have focused on the design and synthesis of acyl-CoA:cholesterol *O*-acyltransferase (ACAT, EC 2.3.1.26) inhibitors. However, the hypocholesterolemic effects observed in human trials and adrenal toxicity evident from experimental studies have been disappointing (5). Nevertheless, current advances in the molecular biology of ACAT inhibitors and success in identifying highly bioavailable potent inhibitors free from adrenotoxic effects, has provided new hope that ACAT inhibitors will be potential therapy for treating atherosclerotic disease, possibly independently of lowering LDL-cholesterol.

Parke Davis has identified a series of oxysulfonyl carbamate ACAT inhibitors, including the water soluble CI-999 [I] with high bioavailability (6). However, despite



[I]

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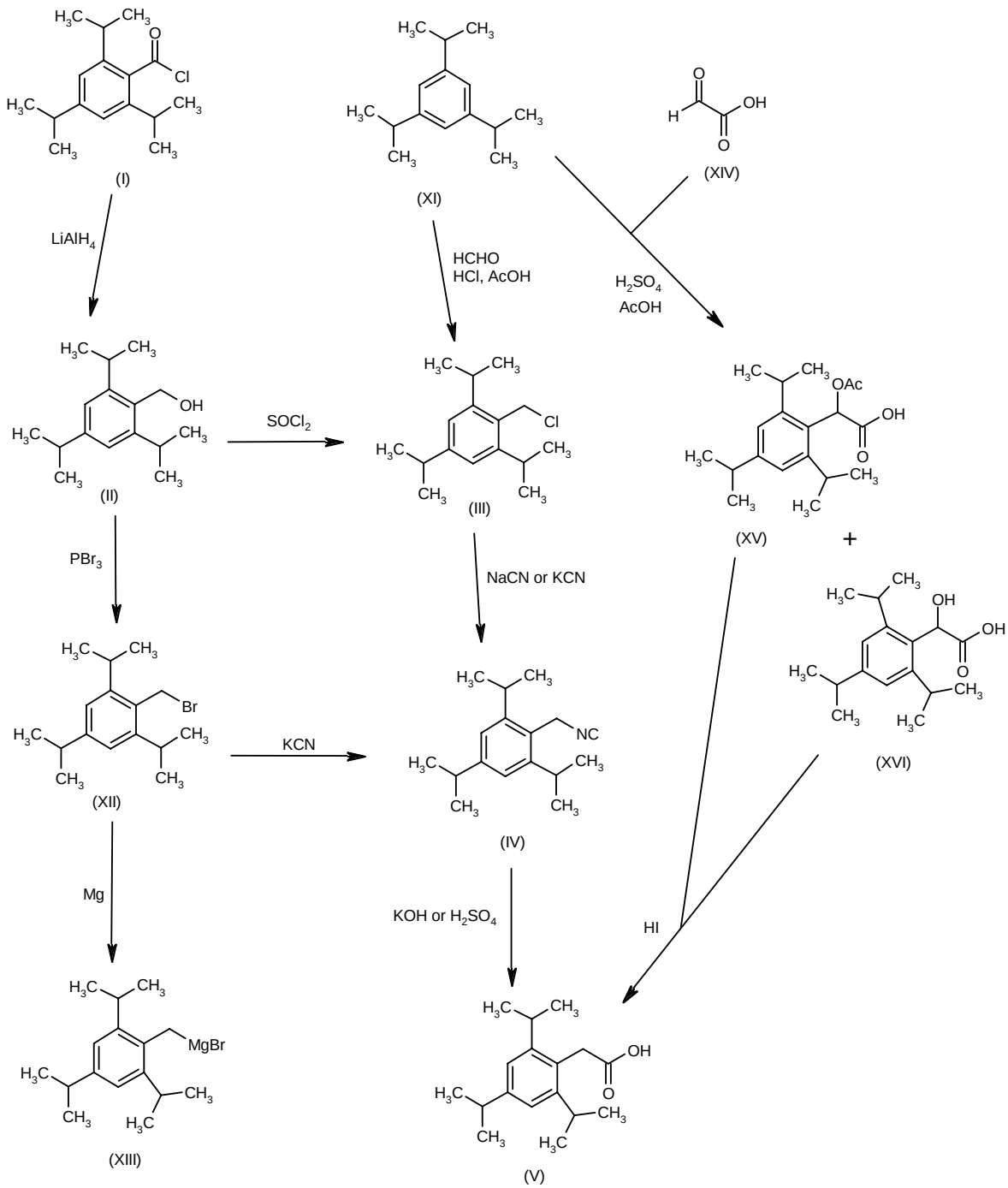
Scheme 1: Synthesis of Avasimibe



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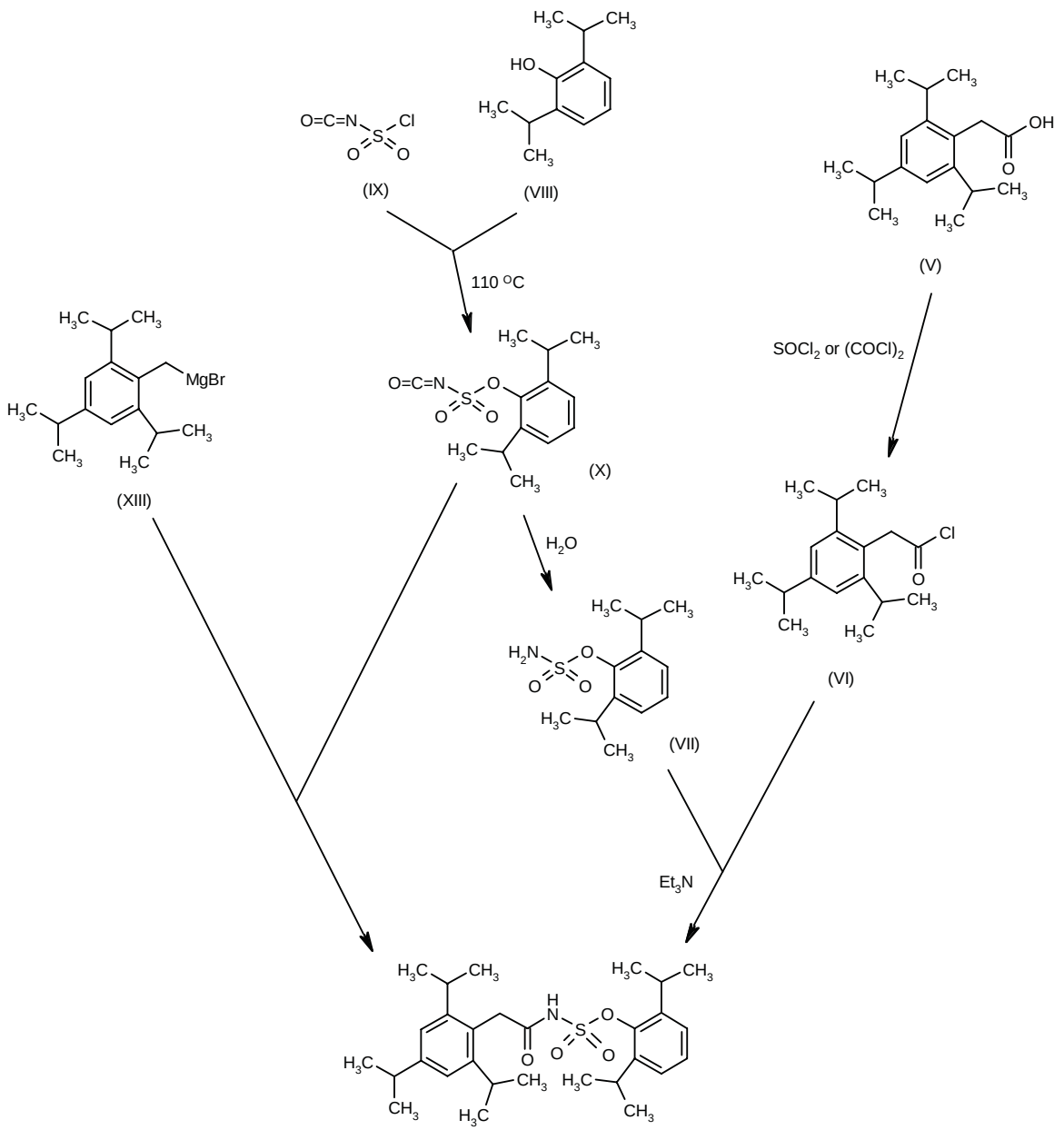
potent hypolipidemic effects, CI-999 was found to degrade into two products in acidic aqueous media in addition to exhibiting five different physical polymorphs which undergo humidity-dependent interconversion before preparation of a stable crystalline form. Moreover, the agent displayed an instability to pharmaceutical excipients and induced various cytochrome P450 isozymes (7). To overcome the problem of solution

Scheme 1: Continued



instability in acid aqueous media and to identify other agents with equivalent or improved *in vitro* and *in vivo* activities, an isosteric replacement strategy was employed, resulting in CI-1011 (avasimibe) (2). Parke Davis has recently synthesized another series of closely related amides which are novel acylphosphonamide and acylphosphoramidate analogs of CI-999 and CI-1011. Sulfoacetic acid and phosphorous containing bioisoteric substitutions made in CI-1011 resulted in agents more potent than CI-999 and CI-1011 *in vitro*, while maintaining equivalent potency *in vivo* when tested in cholesterol-fed rats (8).

Results obtained from clinical trials with agents such as avasimibe and other novel agents will provide further information towards the understanding of the role of ACAT in lipoprotein and arterial wall metabolism. The chemical structure and biological activity of ACAT inhibitors have been described previously in this journal (5).

Pharmacological Actions

Avasimibe is a potent hypocholesterolemic and antiatherosclerotic with no significant toxic effects. The agent was found to be completely stable over a broad range of pH values (4.2-12) and temperatures (25-60 °C) for up to 72 h. When the ACAT inhibitory ability of avasimibe was examined *in vitro*, an IC_{50} value of 0.7 μM was obtained with 0.2 mg/ml of microsomes from livers of cholesterol-fed rats (7), while in rat hepatocytes, it dose-dependently decreased ACAT activity, with a maximum suppression of 75% observed with 10 μM (9).

A reduction in storage of cholesteryl esters was also observed in rat hepatocytes with avasimibe exposure. The avasimibe-induced reduction in ACAT activity was potentiated when cells were incubated with βLDL (93% reduction). In addition, incubation of cells with 3 μM avasimibe increased bile acid synthesis 2.9-fold and cholesterol 7α-hydroxylase activity was increased 2.6- and 1.7- fold in the absence and presence of βLDL, respectively. These results suggest that avasimibe treatment of hepatocytes produces a shift from cholesteryl ester storage and secretion to conversion of cholesterol into bile acids (9).

Other *in vitro* studies have demonstrated that avasimibe inhibited apoB secretion from HepG2 cells with significant reductions of 25, 27 and 43% observed after incubation with 0.01, 1.0 and 10 μM avasimibe, respectively. The compound (10 μM) significantly inhibited ACAT activity by 79% and cellular hepatic cholesteryl ester mass by 32%. Further kinetic analysis of the ACAT inhibitory properties of avasimibe was performed using a multicompartmental model. Results demonstrated that although avasimibe did not affect synthesis of apoB, intracellular apoB degradation increased significantly and proportionately with the observed 38% decrease in secretion. Avasimibe was suggested to decrease apoB secretion posttranslationally since its effect on apoB degradation was found to be confined to a rapidly turning over degrading compartment. Furthermore, a significant (26%) decrease in microsomal triglyceride transfer protein (MTP) mRNA abundance was observed after 24 h incubation, as well as a reduction in MTP protein levels after 5 days of treatment with the agent (10).

The effects of avasimibe in combination with atorvastatin and progesterone on cholesterol storage and secretion were assessed *in vitro* using 14-day-old human monocyte-derived macrophages. In noncholesterol-loaded cells, avasimibe and atorvastatin alone had no effect on free cholesterol, cholesteryl ester or cholesterol efflux, while progesterone increased free cholesterol by 25%. However, in cholesterol-loaded cells, each agent alone induced a reduction in cholesteryl ester accompanied by an increase in the secretion of free cholesterol; these effects were potentiated when cholesterol-loaded cells were exposed to combinations of the agents (11).

The results of several *in vivo* studies have demonstrated the efficacy of avasimibe in standard cholesterol-fed rat models. Avasimibe (0.1-10 mg/kg) dose-dependently prevented the overnight increase in dietary cholesterol observed after a single high-fat, high-cholesterol meal by 32-72%, with an ED_{50} value of 0.4 mg/kg (7). Avasimibe-treated rats fed a high-cholesterol diet exhibited a decrease in the accumulation of liver cholesteryl ester without alterations in free liver cholesterol levels. Although cholesterol 7α-hydroxylase activity and mRNA were not affected, LDL-receptor mRNA was downregulated by 22-39% with avasimibe treatment (9).

Similarly, in the rat model of preestablished hypercholesterolemia, administration of 0.03 and 0.1 mg/kg avasimibe for 7 days resulted in 38 and 45% reductions, respectively, in total cholesterol (ED_{50} = 0.9 mg/kg). An elevation in HDL was also observed and found to be 600% in females as compared to 100% in males (12).

Results from further *in vivo* experiments in rats demonstrated that a single dose of avasimibe (30 mg/kg) lowered plasma triglycerides by enhancing VLDL catabolism. If normal and sucrose-fed animals were administered avasimibe followed by an injection of Triton WR-1339 (600 mg/kg i.v.) 4 h after dosing to block VLDL clearance and then given a second dose of avasimibe 4 h later, plasma triglycerides increased and VLDL-cholesteryl ester efflux was reduced by 40%. Animals treated for 4 weeks with avasimibe (10 mg/kg i.v.) and then administered Triton WR-1339 (600 mg/kg) displayed reductions in plasma cholesterol and VLDL-cholesteryl esters of 72 and 83%, respectively (13).

Avasimibe also lowered plasma triglycerides by 48, 47 and 42% in hamsters fed a high-cholesterol diet and treated with 3, 10 or 30 mg/kg/day avasimibe, respectively, for 10 weeks. Total cholesterol, VLDL-cholesterol and LDL-cholesterol were also lowered with a 30 mg/kg dose resulting in 34, 71 and 47% reductions, respectively. Avasimibe treatment significantly decreased the aortic fatty streak area by 68, 86 and 93% for the respective doses (14). Moreover, avasimibe-treated (30 mg/kg) hamsters fed a lithogenic diet exhibited a > 95% reduction in gallbladder cholesterol content, and gallstone formation was prevented in all treated animals as compared to the control group in which gallstones were observed in 14/20 animals (15).

The efficacy of avasimibe was also demonstrated in rabbit, minipig and cynomolgus monkey animal models. Endogenously hypercholesterolemic rabbits fed a casein-rich diet for 6 weeks and than placed on a diet containing 12.5 mg/kg avasimibe for 8 weeks, displayed 70% reductions in plasma cholesterol. ApoB levels were also reduced while direct secretion of LDL was decreased (16). Two studies using New Zealand white rabbits fed a high-cholesterol diet and coadministered the HMG-CoA reductase inhibitors simvastatin (2.5 mg/kg) or atorvastatin (5 mg/kg) alone or in combination with avasimibe (10 mg/kg) for 8 weeks have shown that coadministration of the drugs results in a potentiation of the hypolipidemic effects observed with each agent alone, in addition to blunting of progression of atherosclerotic lesion and regression of preestablished lesions (17, 18). Furthermore, the abnormal vascular function including

responses to acetylcholine and nitroglycerin and oxygen production associated with hypercholesterolemia in rabbits fed high-cholesterol diets were normalized in avasimibe-treated animals (19).

Avasimibe (25 mg/kg/day) administered to minipigs fed high-cholesterol diets reduced plasma cholesterol, VLDL-cholesterol, LDL-cholesterol, triglyceride and VLDL-triglycerides by 20, 34, 28, 38 and 49%, respectively; hepatic VLDL- and LDL-apoB production were also decreased in treated animals (20).

When avasimibe (30 mg/kg/day p.o.) was administered to healthy cynomolgus monkeys fed a normal diet, total cholesterol and lipoprotein A levels were significantly decreased after 1 week of treatment, with a 30% reduction in LDL:HDL ratio observed; triglyceride levels were not affected by treatment. Although treatment lowered apoB-100 levels by 80%, the decreases in lipoprotein A were found to be associated with a reduction (47%) in apoA and not apoB-100 (21).

The efficacy of avasimibe (100 and 500 mg/kg/day for 21 days) to reduce lipoprotein A levels was examined in double transgenic mice expressing human lipoprotein A fed a normal diet. Lipoprotein A levels were significantly decreased by 20 and 44% in mice administered 100 and 500 mg/kg/day avasimibe, respectively, for 21 days. The high dose of avasimibe was also found to significantly inhibit lipoprotein A assembly by 18%, further indicating that avasimibe is a potential lipoprotein A reducing agent (22).

Pharmacokinetics and Metabolism

A liquid chromatographic/mass spectrometric method to quantitate avasimibe concentrations in rat and human plasma has been described and found to be suitable for routine measurements of concentrations ranging from 0.5-500 ng/ml for rat plasma and 0.1-100 ng/ml for human plasma (23, 24).

The bioavailability and efficacy of avasimibe in a hydroxypropyl cellulose nanoparticle suspension (10 and 750 mg/kg) were compared to conventional carboxymethyl-cellulose/Tween 80 (CMC/T; 10 mg/kg avasimibe) and methyl-cellulose/Tween 80 (MC/T; 750 mg/kg avasimibe) suspensions in rats and dogs. Although the bioavailability for a low dose of 10 mg/kg was similar, the high dose (750 mg/kg) was 2.6- to 8.6-fold higher when administered in the nanoparticle suspension as compared to MC/T. Similar efficacy was observed with regard to reductions (10-30%) in total cholesterol measured in rats treated with either suspension, while a slightly improved efficacy was observed with the nanoparticle suspension of 750 mg/kg in dogs (25).

The pharmacokinetics of single and multiple doses of avasimibe were evaluated in rats administered the compound by gavage or in the diet at doses of 750, 1500 or 3000 mg/kg for 14 days or 50, 250 and 1500 mg/kg for 13 or 15 weeks. Results showed that C_{max} and AUC values were 1.5- to 3.5-fold lower in males as compared to females, with similar or higher values obtained following

Box 1: Safety and efficacy of avasimibe in patients with hypertriglyceridemia (30) [from Prous Science CSLine database].

Study Design	Multicenter, randomized, double-blind, placebo-controlled clinical trial
Study Population	Patients with combined hyperlipidemia (n = 130)
Intervention Groups	Avasimibe (A) 50 mg/day p.o. x 8 weeks (n = 25) A125 mg/day p.o. x 8 weeks (n = 26) A250 mg/day p.o. x 8 weeks (n = 26) A500 mg/day p.o. x 8 weeks (n = 25) Placebo (P) (n = 25)
Adverse Events	Occurred at similar rates in drug and placebo-treated patients; 0 deaths or serious adverse events; only minimal laboratory changes
Results	Avasimibe treatment resulted in significant ($p<0.05$) reductions compared with placebo only in levels of VLDL-cholesterol and triglycerides. Efficacy measured as mean (SE) % change from baseline: VLDL = -5 (4) (P), -27 (4) (A50), -25 (4) (A125), -23 (4) (A250), -32 (4) (A500) TG = 0 (4) (P), -22 (4) (A50), -17 (4) (A125), -16 (4) (A250), -23 (4) (A500) LDL = -3 (5) (P), -3 (5) (A50), 14 (5) (A125), 1 (5) (A250), 6 (5) (A500) TC = 0 (2) (P), -5 (2) (A50), -1 (2) (A125), -3 (2) (A250), -5 (2) (A500) HDL = 3 (2) (P), 2 (2) (A50), 2 (2) (A125), 1 (2) (A250), 2 (2) (A500) ApoB = 2 (2) (P), -3 (2) (A50), 5 (2) (A125), 1 (2) (A250), -1 (2) (A500) ApoAI = 2 (2) (P), -3 (2) (A50), -1 (2) (A125), -2 (2) (A250), -5 (2) (A500)
Conclusions	Avasimibe is capable of reducing levels of VLDL-cholesterol and triglycerides in humans and is safe over a wide dose range during 8 weeks of treatment

2-week diet administration as compared to gavage. C_{max} and AUC values increased less than proportionally with increasing dose and t_{max} was found to be independent of dose. After 2 and 13 weeks, increases in hepatic cytochrome P450 concentration and erythromycin-*N*-demethylase activity were noted, with activity peaking on day 14; autoinduction of hepatic enzymes was reversible since values returned to normal 4 weeks after washout (26, 27). Similar pharmacokinetics were obtained for dogs when avasimibe was administered at doses of 10, 100 and 1000 mg/kg p.o. in gelatin capsules for 12 weeks, although no gender differences were observed (28).

The clinical pharmacokinetics of avasimibe have also been evaluated in two phase I, placebo-controlled trials. In a single-dose study, healthy subjects in the fasted or fed state received either 12.5, 50 or 125 mg avasimibe with a high-fat breakfast or 250 or 500 mg avasimibe with a Step 1 American Heart Association (AHA) breakfast. In a multiple-dose trial, healthy subjects were administered avasimibe (50, 125, 250 or 500 mg) with the Step 1 AHA breakfast on days 1, 8 and 22. C_{max} and AUC values were increased when avasimibe was administered with food, with greater increases noted in subjects fed the high-fat diet. While C_{max} values were similar in subjects receiving single or multiple doses, AUC values were reduced by 46-58.2% in subjects administered multiple doses on day 22 as compared to day 1 values of subjects given a single dose; these results indicate possible autoinduction of avasimibe metabolism in the multidose trial. In fasted or fed states, the elimination $t_{1/2}$ for avasimibe ranged from 15.3-24.1 h in both the single- and multiple-dose trials (29).

Clinical Studies

In a randomized, double-blind, placebo-controlled clinical trial, 130 patients with hypertriglyceridemia received either avasimibe (50, 125, 250 or 500 mg) or a placebo once daily for 8 weeks. Significant reductions in VLDL-cholesterol and triglycerides were observed in all treated patients with no effects on total-cholesterol, LDL-cholesterol, HDL-cholesterol, apoB or apoAI. Avasimibe treatment was concluded to be effective and safe with the incidence of side effects similar in both untreated and treated patients (30) (Box 1).

Manufacturer

Warner-Lambert Company (US).

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