VALCORE TABLET

I. THERAPEUTIC CLASS
VALCORE TABLET is a lipid-lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol.

II. ACTIVE INGREDIENTS
VALCORE TABLET is available for oral use as tablets containing 10 mg of ezetimibe, and 10 mg of simvastatin (VALCORE TABLET 10 MG/10 MG) or 20 mg of simvastatin (VALCORE TABLET 10 MG/20 MG).

III. INDICATIONS
Primary Hypercholesterolemia
VALCORE TABLET is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.
Homozygous Familial Hypercholesterolemia (HoFH)
VALCORE TABLET is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

IV. CLINICAL PHARMACOLOGY
IV a. Mechanism of Action
EZETIMIBE-SIMVASTATIN TABLET
Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. Ezetimibe-Simvastatin Tablet contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. Ezetimibe-Simvastatin Tablet reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C through dual inhibition of cholesterol absorption and synthesis.
Ezetimibe
Ezetimibe inhibits the intestinal absorption of cholesterol. Ezetimibe is orally active and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.
Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction.
In a 2-week clinical study in 18 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.
A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [14C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat-soluble vitamins A and D.
Simvastatin
After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active β-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy - 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.
Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes, the ratios of total- to HDL-C and LDL- to HDL-C are reduced.
IV b. Pharmacokinetics
IV b-1. Absorption
Ezetimibe
After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.
Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10 mg tablets.
Simvastatin
The availability of the β-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose, consistent with extensive hepatic first-pass extraction. The major metabolites of simvastatin present in human plasma are the β-hydroxyacid and four additional active metabolites.
Relative to the fasting state, the plasma profiles of both active and total inhibitors were not affected when simvastatin was administered immediately before a test meal.
IV b-2. Distribution
Ezetimibe
Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.
Simvastatin
Both simvastatin and the β-hydroxyacid are bound to human plasma proteins (95%).
The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of drug occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1.3 to 2.4 hours post-dose.
IV b-3. Metabolism
Ezetimibe
Ezetimibe is metabolized primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.
Simvastatin
Simvastatin is an inactive lactone which is readily hydrolyzed in vivo to the corresponding β- hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.
In man simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is its primary site of action, with subsequent excretion of drug equivalents in the bile. Consequently, availability of active drug to the systemic circulation is low.
Following an intravenous injection of the β-hydroxyacid metabolite, its half-life averaged 1.9 hours.
IV b-4. Elimination
Ezetimibe
Following oral administration of 14C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.
Simvastatin
Following an oral dose of radioactive simvastatin to man, 13% of the radioactivity was excreted in the urine and 60% in the feces within 96 hours. The amount recovered in the feces represents absorbed drug equivalents excreted in bile as well as unabsorbed drug. Following an intravenous injection of the β-hydroxyacid metabolite an average of only 0.3% of the IV dose was excreted in urine as inhibitors.
IV b-5. Characteristics in Patients (Special Populations)
Pediatric Patients
The absorption and metabolism of ezetimibe are similar between children and adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available. Clinical experience in pediatric and adolescent patients (ages 9 to 17) has been limited to patients with HoFH or homozygous sitosterolemia.
Geriatric Patients
Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe.
Hepatic Insufficiency
After a single 10 mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score >9) hepatic insufficiency, ezetimibe is not recommended in these patients (see VII. PRECAUTIONS).
Renal Insufficiency
Ezetimibe
After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 mL/min/1.73m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9).
An additional patient in this study (post-renal transplant and receiving multiple medications including cyclosporine) had a 12-fold greater exposure to total ezetimibe.
Simvastatin
In a study of patients with severe renal insufficiency (creatinine clearance <30 mL/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately two-fold higher than those in healthy volunteers.
Gender
Plasma concentrations for total ezetimibe are slightly higher (<20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe.
Race
Based on a meta-analysis of pharmacokinetic studies with ezetimibe, there were no pharmacokinetic differences between Blacks and Caucasians. There were too few patients in other racial or ethnic groups to permit further pharmacokinetic comparisons.

IVc. CLINICAL STUDIES
In controlled clinical studies, Ezetimibe-Simvastatin Tablet significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolemia.
Primary Hypercholesterolemia
Ezetimibe-Simvastatin Tablet
Five multicenter, double-blind studies conducted with Ezetimibe-Simvastatin Tablet in patients with primary hypercholesterolemia are reported: two were comparisons with simvastatin, two were comparisons with atorvastatin, and one was a comparison with rosuvastatin.
In a multicenter, double-blind, placebo-controlled, 12-week trial, 887 hypercholesterolemic patients were randomized to one of ten treatment groups: placebo, ezetimibe (10 mg), simvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or coadministered ezetimibe and simvastatin equivalent to Ezetimibe-Simvastatin Tablet (10/10, 10/20, 10/40, and 10/80). When patients receiving Ezetimibe-Simvastatin Tablet were compared to those receiving all doses of simvastatin, Ezetimibe-Simvastatin Tablet significantly lowered total-C, LDL-C, Apo B, TG, non- HDL-C, and C-reactive protein. The effects of Ezetimibe-Simvastatin Tablet on HDL-C were similar to the effects seen with simvastatin. Further analysis showed Ezetimibe-Simvastatin Tablet significantly increased HDL-C compared with placebo. (See Table 1)

Table 1
Response to Ezetimibe-Simvastatin Tablet in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total -C	LDL -C	Apo B	HDL -C	TG[a]	Non-HDL-C
Pooled data (All EzetimibeSimvastatin Tablet doses)[c]	353	-38	-53	-42	+8	-28	-49
Pooled data (All simvastatin doses)[c]	349	-26	-38	-29	+8	-15	-34
Ezetimibe10 mg	92	-14	-20	-15	+7	-13	-19
Placebo	93	+2	+3	+3	+2	-2	+2
Ezetimibe-Simvastatin tablet by dose							
10/10	87	-32	-46	-36	+9	-21	-41
10/20	86	-37	-51	-41	+8	-31	-47
10/40	89	-39	-55	-44	+9	-32	-51
10/80	91	-43	-61	-47	+6	-28	-55
Simvastatin by dose							
10 mg	81	-21	-31	-23	+5	-4	-27
20 mg	90	-24	-35	-25	+6	-14	-31
40 mg	91	-29	-42	-33	+8	-19	-37
80 mg	87	-32	-46	-35	+11	-26	-41

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] Ezetimibe-Simvastatin Tablet doses pooled (10/10-10/80) significantly reduced total -C, LDL-C, Apo B, TG, and non-HDL-C compared to simvastatin, and significantly increased HDL-C compared to placebo.

In a similarly designed study, results for all lipid parameters were generally consistent. In a pooled analysis of these two studies, the lipid response to Ezetimibe-Simvastatin Tablet was similar in patients with TG levels greater than or less than 200 mg/dL.
In a multicenter, double-blind, controlled, 23-week study, 710 patients with known CHD or CHD risk equivalents, as defined by the NCEP ATP III guidelines, and an LDL-C ≥ 130 mg/dL were randomized to one of four treatment groups: co-administered ezetimibe and simvastatin equivalent to Ezetimibe-Simvastatin Tablet (10/10, 10/20, and 10/40), or simvastatin 20 mg. Patients not reaching an LDL-C <100 mg/dL had their simvastatin dose titrated at 6-week intervals to a maximal dose of 80 mg. At Week 5, the LDL-C reductions with Ezetimibe-Simvastatin Tablet 10/10, 10/20, or 10/40 were significantly larger than with simvastatin 20 mg. In addition, at Week 5, significantly more patients receiving Ezetimibe-Simvastatin Tablet 10/10, 10/20, or 10/40 attained LDL-C target compared to those receiving simvastatin 20 mg (see Table 2). Week 5 results for LDL-C reduction and percentage attaining LDL-C target were consistent with the end of study results (Week 23).

Table 2
Response to Ezetimibe-Simvastatin Tablet after 5 weeks in Patients with CHD or CHD Risk Equivalents and an LDC-C≥ 130 mg/dL

	Simvastatin 20 mg	Ezetimibe-Simvastatin Tablet 10/10	Ezetimibe-Simvastatin Tablet 10/20	Ezetimibe-Simvastatin Tablet 10/40
N	253	251	109	97
Percent change LDL-C	-38	47	-53	-59
Percent attaining LDL-C goal	46	75	83	88

In a multicenter, double-blind, 6-week study, 1902 patients with primary hypercholesterolemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of eight treatment groups: Ezetimibe-Simvastatin Tablet (10/10, 10/20, 10/40, or 10/80) or atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg). When patients receiving all doses of Ezetimibe-Simvastatin Tablet were compared to those receiving all doses of atorvastatin, Ezetimibe-Simvastatin Tablet lowered total-C, LDL-C, Apo B, and non-HDL-C, and increased HDL-C significantly more than atorvastatin. The effects of Ezetimibe-Simvastatin Tablet on TG were similar to the effects seen with atorvastatin. (See Table 3)

Table 3
Response to Ezetimibe-Simvastatin Tablet and Atorvastatin Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated baseline [b])

Treatment (daily dose)	N	Total -C	LDL -C	Apo B	HDL -C	TG[a]	Non-HDL-C
Pooled data (All Ezetimibe-Simvastatin Tablet doses)	951	-38[c]	-53[c]	-43[c]	+8[c]	-27	-49[c]
Pooled data (All Atorvastatin doses)	951	-34	-45	-38	+4	-26	-42
Ezetimibe-Simvastatin Tablet by dose							
10/10	238	-34[d]	-47[d]	-37[d]	+8	-26	-43[d]
10/20	238	-37[d]	-51[d]	-40[d]	+7	-25	-46[d]
10/40	238	-41[d]	-57[d]	-46[d]	+9[d]	-27	-52[d]
10/80	237	-43[d]	-59[d]	-48[d]	+8[d]	-31	-54[d]
Atorvastatin by dose							
10 mg	238	-27	-36	-31	+7	-21	-34
20 mg	237	-32	-44	-37	+5	-25	-41
40 mg	237	-36	-48	-40	+4	-24	-45
80 mg	239	-40	-53	-44	+1	-32	-50

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] p<0.05 for difference with atorvastatin
[d] p<0.05 for difference with atorvastatin at equal mg doses of the simvastatin component

In a multicenter, double-blind, 24-week, forced titration study, 788 patients with primary hypercholesterolemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to receive co-administered ezetimibe and simvastatin equivalent to Ezetimibe-Simvastatin Tablet (10/10 and 10/20) or atorvastatin 10 mg. For all three treatment groups, the dose of the statin was titrated at 6-week intervals to 80 mg. At each pre-specified dose comparison, Ezetimibe-Simvastatin Tablet lowered LDL-C to a greater degree than atorvastatin (see Table 4).

Table 4
Response to Ezetimibe-Simvastatin Tablet and Atorvastatin in Patients with Primary Hypercholesterolemia (Mean [a]% change from untreated baseline[b])

Treatment	N	Total- C	LDL- C	Apo B	HDL- C	TG[a]	Non-HDL- C
Week 6							
Atorvastatin 10 mg[c]	262	- 28	-37	-32	+5	-23	-35
Ezetimibe-Simvastatin Tablet 10/10[d]	263	- 34[f]	-46[f]	-38[f]	+8[f]	-26	-43[f]
Ezetimibe-Simvastatin Tablet 10/20[e]	263	-36[f]	-50[f]	-41[f]	+10[f]	-25	-46[f]
Week 12							
Atorvastatin 20 mg	246	-33	-44	-38	+7	-28	-42
Ezetimibe-Simvastatin Tablet 10/20	250	-37[f]	-50[f]	-41[f]	+9	-28	-46[f]
Ezetimibe-Simvastatin Tablet 10/40	252	-39[f]	-54[f]	-45[f]	+12[f]	-31	-50[f]
Week 18							
Atorvastatin 40 mg	237	-37	-49	-42	+8	-31	-47
Ezetimibe-Simvastatin Tablet 10/40g	482	-40[f]	-56[f]	-45[f]	+11[f]	-32	-52[f]
Week 24							
Atorvastatin 80 mg	228	-40	-53	-45	+6	-35	-50
Ezetimibe-Simvastatin Tablet 10/80g	459	-43[f]	-59[f]	-49[f]	+12[f]	-35	-55[f]

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] Atorvastatin: 10 mg start dose titrated to 20 mg, 40 mg, and 80 mg through Weeks 6, 12, 18, and 24
[d] Ezetimibe-Simvastatin Tablet: 10/10 start dose titrated to 10/20, 10/40, and 10/80 through Weeks 6, 12, 18, and 24
[e] Ezetimibe-Simvastatin Tablet: 10/20 start dose titrated to 10/40, 10/40, and 10/80 through Weeks 6, 12, 18, and 24
[f] p ≤ 0.05 for difference with atorvastatin i n the specified week
[g] Data pooled for common doses of Ezetimibe-Simvastatin Tablet at Weeks 18 and 24.

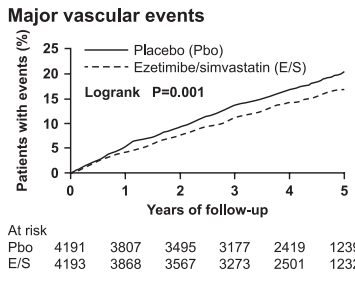
In a multicenter, double-blind, 6-week study, 2959 patients with primary hypercholesterolemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of six treatment groups: Ezetimibe-Simvastatin Tablet (10/20, 10/40, or 10/80) or rosuvastatin (10 mg, 20 mg, or 40 mg). When patients receiving all doses of Ezetimibe-Simvastatin Tablet were compared to those receiving all doses of rosuvastatin, Ezetimibe-Simvastatin Tablet lowered total-C, LDL-C, Apo B, TG, and non-HDL-C significantly more than rosuvastatin. The effects of Ezetimibe-Simvastatin Tablet on HDL-C were similar to the effects seen with rosuvastatin. (See Table 5).

Table 5
Response to Ezetimibe-Simvastatin and Rosuvastatin in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (daily dose)	N	Total- C	LDL- C	Apo B	HDL- C	TG[a]	Non-HDL- C
Pooled data (All Ezetimibe-Simvastatin Tablet doses)	1478	-40[c]	-56[c]	-45[c]	+8	-26[c]	-51[c]
Pooled data (All rosuvastatin doses)	1481	-37	-52	-42	+8	-25	-47
Ezetimibe-Simvastatin Tablet by dose							
10/20	492	-37[d]	-52[d]	-42[d]	+7	-23[d]	-47[d]
10/40	493	-39[e]	-55[e]	-44[e]	+8	-27	-50[e]
10/80	493	-44[f]	-61[f]	-50[f]	+8	-30[f]	-56[f]
Rosuvastatin by dose							
10 mg	492	-32	-46	-37	+7	-20	-42
20 mg	495	-37	-52	-43	+8	-26	-48
40 mg	494	-41	-57	-47	+8	-28	-52

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] p<0.05 for difference with rosuvastatin
[d] p<0.05 vs. rosuvastatin 10 mg
[e] p<0.05 vs. rosuvastatin 20 mg
[f] p<0.05 vs. rosuvastatin 40 mg

In a double-blind, placebo-controlled, 8-week study, 240 patients with hypercholesterolemia already receiving simvastatin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.6 to 4.1 mmol/L [100 to 160 mg/dL], depending on baseline characteristics) were randomized to receive either ezetimibe 10 mg or placebo in addition to their on-going simvastatin therapy. Among simvastatin-treated patients not at LDL-C goal at baseline (~80%), significantly more patients randomized to ezetimibe co-administered with simvastatin achieved their LDL-C goal at study endpoint compared to patients randomized to placebo co-administered with simvastatin, 76% and 21.5%, respectively. The corresponding LDL-C reductions for ezetimibe or placebo co-administered with simvastatin were also significantly different (27% or 3%, respectively). In addition, ezetimibe co-administered with simvastatin significantly decreased total-C, Apo B, and TG compared with placebo co-administered with simvastatin.
In a multicenter, double-blind, 24-week trial, 214 patients with type 2 diabetes mellitus treated with thiazolidinediones (rosiglitazone or pioglitazone) for a minimum of 3 months and simvastatin 20 mg for a minimum of 6 weeks with a mean LDL-C of 93 mg/dL, were randomized to receive either simvastatin 40 mg or the co-administered active ingredients equivalent to Ezetimibe-Simvastatin Tablet 10/20.
Ezetimibe-Simvastatin Tablet 10/20 was significantly more effective than doubling the dose of simvastatin to 40 mg in further reducing LDL-C (-21% and 0%, respectively), total-C (-14% and -1%, respectively), Apo B (-14% and -2%, respectively), and non-HDL-C (-20% and -2%, respectively) beyond the reductions observed with simvastatin 20 mg. Results for HDL-C and TG between the two treatment groups were not significantly different. Results were not affected by type of thiazolidinedione treatment.
Ezetimibe
In two, multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ezetimibe significantly lowered total-C (13%), LDL-C (19%), Apo B (14%), and TG (8%) and increased HDL-C (3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, race, and baseline LDL-C. In addition, ezetimibe had no effect on the plasma concentrations of the fat-soluble vitamins A, D, and E, had no effect on prothrombin time, and did not impair adrenocortical steroid hormone production.
Simvastatin
Ezetimibe-Simvastatin Tablet contains simvastatin. In two large, placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study (N=4,444 patients) and the Heart Protection Study (N=20,536 patients), the effects of treatment with simvastatin were assessed in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Simvastatin was proven to reduce: the risk of total mortality by reducing CHD deaths, the risk of non-fatal myocardial infarction and stroke, and the need for coronary and non-coronary revascularization procedures. The incremental benefit of Ezetimibe-Simvastatin Tablet on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has not been established.
Homozygous Familial Hypercholesterolemia (HoFH)
A double-blind, randomized, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analyzed from a subgroup of patients (n=14) receiving simvastatin 40 mg at baseline. Increasing the dose of simvastatin from 40 to 80 mg (n=5) produced a reduction of LDL-C of 13% from baseline on simvastatin 40 mg. Co-administered ezetimibe and simvastatin equivalent to Ezetimibe-Simvastatin Tablet (10/40 and 10/80 pooled, n=9), produced a reduction of LDL-C of 23% from baseline on simvastatin 40 mg. In those patients co-administered ezetimibe and simvastatin equivalent to Ezetimibe-Simvastatin Tablet (10/80, n=5), a reduction of LDL-C of 29% from baseline on simvastatin 40 mg was produced.
Prevention of Major Vascular Events in Chronic kidney Disease (CKD)
The Study of Heart and Renal Protection (SHARP) was a multinational, randomized, placebo- controlled, double-blind study conducted in 9438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. For the first year, patients were randomized in a ratio of 4:4:1, respectively, to Ezetimibe-Simvastatin Tablet 10/20, placebo, or simvastatin 20 mg daily. The 1-year simvastatin arm was included to enable the comparison of Ezetimibe-Simvastatin Tablet to simvastatin alone with regard to safety and lipids. At 1 year the simvastatin-only arm was re-randomized 1:1 to Ezetimibe-Simvastatin Tablet 10/20 or placebo. A total of 4650 patients were allocated to Ezetimibe-Simvastatin Tablet 10/20 and 4620 to placebo, and followed for a median of 4.9 years. Patients had a mean age of 62, and 63% were male, 72% Caucasian, 23% diabetic and, for those not on dialysis, the mean estimated glomerular filtration rate (eGFR) was 26.5 mL/min/1.73 m^2. There were no lipid entry criteria. Mean LDL-C at baseline was 108 mg/dL. As of the 1-year measurement, LDL-C was reduced 26% relative to placebo by simvastatin 20 mg alone and 38% for Ezetimibe-Simvastatin Tablet 10/20. At the midpoint of the study (2.5 years) mean LDL-C reduction for Ezetimibe-Simvastatin Tablet relative to placebo was 32%. All lipid measurements included patients no longer taking study medication.
The SHARP protocol-specified primary comparison was an intention-to-treat analysis of "major vascular events" (MVE; defined as nonfatal MI or cardiac death, stroke, or any revascularization procedure) in only those patients initially randomized to the Ezetimibe-Simvastatin Tablet (n=4193) or placebo (n=4191) groups. Secondary analyses included the same composite analyzed for the full cohort randomized (at study baseline or at year 1) to Ezetimibe-Simvastatin Tablet (n=4650) or placebo (n=4620), as well as the components of this composite.
The primary endpoint analysis showed that Ezetimibe-Simvastatin Tablet significantly reduced the risk of major vascular events (749 patients with events in the placebo group vs. 639 in the Ezetimibe-Simvastatin Tablet group) with a relative risk reduction of 16% (p=0.001) (see Figure 1).
Figure 1: Effect of Ezetimibe Combined with Simvastatin on the Primary Endpoint of Risk of Major Vascular Events.



The individual components of MVE in all randomized patients are presented in Table 6. Ezetimibe-Simvastatin Tablet significantly reduced the risk of stroke and any revascularization, with non-significant numerical differences favoring Ezetimibe-Simvastatin Tablet for nonfatal MI and cardiac death.

Table 6
Major Vascular Events by Treatment Group in All Randomized Patients in SHARP[a]

Outcome	Ezetimibe/Simvastatin 10/20 (N=4650)	Placebo (N=4620)	Risk Ratio (95% CI)	P-value
Major Vascular Events	701 (15.1%)	814 (17.6%)	0.85 (0.77-0.94)	0.001
Nonfatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	0.12
Cardiac Death	253 (5.4%)	272 (5.9%)	0.93 (0.78-1.10)	0.38
Any Stroke	171 (3.7%)	210 (4.5%)	0.81 (0.66-0.99)	0.038
Non-hemorrhagic Stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011
Hemorrhagic Stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any Revascularization	284 (6.1%)	352 (7.6%)	0.79 (0.68-0.93)	0.004
Major Atherosclerotic Events (MAE)[b]	526 (11.3%)	619 (13.4%)	0.83 (0.74-0.94)	0.002

[a] Intention-to-treat analysis on all SHARP patients randomized to Ezetimibe-Simvastatin tablets or placebo either at baseline or year 1.
[b] MAE; defined as the composite of nonfatal myocardial infarction, coronary death, non-hemorrhagic stroke, or any revascularization.

Nevertheless, this study design did not allow for a separate contribution of the ezetimibe or simvastatin to efficacy to significantly reduce the risk of major vascular events in patients with CKD.
The absolute reduction on LDL cholesterol achieved with Ezetimibe-Simvastatin Tablet was lower among patients with a lower baseline LDL-C (<2.5mmol/l) and patients on dialysis at baseline than the other patients, and the corresponding risk reductions in these two groups were attenuated.

V. DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Ezetimibe-Simvastatin Tablet and should continue on this diet during treatment with Ezetimibe-Simvastatin Tablet. The dosage should be individualized according to the baseline LDL-C level, the recommended goal of therapy, and the patient' s response. Ezetimibe-Simvastatin Tablet should be taken as a single daily dose in the evening, with or without food.

The dosage range is 10/10 mg/day through 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55%) may be started at 10/40 mg/day. After initiation or titration of Ezetimibe-Simvastatin Tablet, lipid levels may be analyzed after 2 or more weeks and dosage adjusted, if needed. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 10/80-mg dose of Ezetimibe-Simvastatin Tablet should be restricted to patients who have been taking Ezetimibe-Simvastatin Tablet 10/80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. (See VII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Dosage in Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage for patients with homozygous familial hypercholesterolemia is Ezetimibe-Simvastatin Tablet 10/40 mg/day or 10/80 mg/day in the evening. The 10/80 mg dose is only recommended when the benefits are expected to outweigh the potential risks (see above, VI. CONTRAINDICATIONS and VII. PRECAUTIONS, Myopathy/Rhabdomyolysis). Ezetimibe-Simvastatin Tablet should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable. In patients taking lomitapide concomitantly with Ezetimibe-Simvastatin Tablet, the dose of Ezetimibe-Simvastatin Tablet should not exceed 10/40 mg/day (see VI. PRECAUTIONS, Myopathy/Rhabdomyolysis and XI. DRUG INTERACTIONS).

Patients with Renal Impairment

In patients with mild renal insufficiency (estimated GFR ≥ 60 ml/min/1.73 m^2) no dosage adjustment is necessary. In patients with chronic kidney disease and estimated glomerular filtration rate <60 mL/min/1.73 m^2, the dose of Ezetimibe-Simvastatin Tablet is 10/20 mg once a day in the evening. In such patients, the use of higher doses should be closely monitored. (See VII. PRECAUTIONS, IVb-5. Characteristics in Patients (Special Populations) and IVc. CLINICAL STUDIES.)

Use in the Elderly

No dosage adjustment is required for elderly patients (see IVb-5. Characteristics in Patients [Special Populations]).

Use in Pediatric Patients

Treatment with Ezetimibe-Simvastatin Tablet is not recommended.

Use in Hepatic Impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6). Treatment with Ezetimibe-Simvastatin Tablet is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score > 9) liver dysfunction. (See VII. PRECAUTIONS and IVb-5. Characteristics in Patients [Special Populations].)

Co-administration with other medicines

Dosing of Ezetimibe-Simvastatin Tablet should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

In patients taking amiodarone, verapamil or diltiazem, or products containing elbasvir or grazoprevir concomitantly with Ezetimibe-Simvastatin Tablet, the dose of Ezetimibe-Simvastatin Tablet should not exceed 10/20 mg/day (see VII. PRECAUTIONS, Myopathy/Rhabdomyolysis and XI. DRUG INTERACTIONS).

In patients taking amlodipine concomitantly with Ezetimibe-Simvastatin Tablet, the dose of Ezetimibe-Simvastatin Tablet should not exceed 10/40 mg/day (see VII. PRECAUTIONS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS).

The safety and effectiveness of Ezetimibe-Simvastatin Tablet administered with fibrates have not been studied. Therefore, the combination of Ezetimibe-Simvastatin Tablet and fibrates should be avoided (see VI. CONTRAINDICATIONS, VII. PRECAUTIONS, Myopathy/Rhabdomyolysis and XI. DRUG INTERACTIONS).

VI. CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and nursing (see VIII. PREGNANCY and IX. NURSING MOTHERS).
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, erythromycin, boceprevir, telaprevir, clarithromycin, telithromycin, nefazodone, and drugs containing cobicistat) (see VII. PRECAUTIONS, Myopathy/Rhabdomyolysis and XI. DRUG INTERACTIONS).
- Concomitant administration of gemfibrozil, cyclosporine, or danazol (see VII. PRECAUTIONS, Myopathy/Rhabdomyolysis and XI. DRUG INTERACTIONS).

VII. PRECAUTIONS

Myopathy / Rhabdomyolysis

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of Rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma (i.e., elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting drugs that interfere with simvastatin metabolism and/or transporter pathways (see XI. DRUG INTERACTIONS). Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

In a clinical trial in which over 9000 patients with chronic kidney disease were randomized to receive Ezetimibe-Simvastatin Tablet 10/20 mg daily (n=4650) or placebo (n=4620) (median follow-up 4.9 years), the incidence of myopathy/rhabdomyolysis was 0.2% for Ezetimibe-Simvastatin Tablet and 0.1% for placebo. (See XII. SIDE EFFECTS.)

As with other HMG CoA reductase inhibitors, the risk of myopathy / Rhabdomyolysis is dose related for simvastatin.

In a clinical trial database in which 41,413 patients were treated with simvastatin, 24,747 (approximately 60%) of whom were enrolled in studies with a median follow- up of at least 4 years, the incidence of myopathy was approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which patients with a history of myocardial infarction were treated with simvastatin 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%.

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C-lowering efficacy. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 10/80-mg dose of Ezetimibe-Simvastatin Tablet should be restricted to patients who have been taking Ezetimibe-Simvastatin Tablet 10/80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. Patients unable to achieve their LDL-C goal utilizing the 10/40-mg dose of Ezetimibe-Simvastatin Tablet should not be titrated to the 10/80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering. In patients taking Ezetimibe-Simvastatin Tablet 10/80 mg for whom an interacting agent is needed, a lower dose of Ezetimibe-Simvastatin Tablet or an alternative statin-ezetimibe regimen with less potential for drug-drug interactions should be used (see below, IV. DOSAGE AND ADMINISTRATION, and V. CONTRAINDICATIONS).

All patients starting therapy with Ezetimibe-Simvastatin Tablet, or whose dose of Ezetimibe-Simvastatin Tablet is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness . Ezetimibe-Simvastatin Tablet therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and a CK level >10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from simvastatin treatment, muscle symptoms and CK increases resolved (see XII. SIDE EFFECTS). Periodic CK determinations may be considered in patients starting therapy with Ezetimibe-Simvastatin Tablet or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 10/80 mg dose. There is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long- standing diabetes mellitus. Such patients taking Ezetimibe-Simvastatin Tablet merit closer monitoring. Therapy with Ezetimibe-Simvastatin Tablet should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

In a clinical trial in which over 9000 patients with chronic kidney disease were randomized to receive Ezetimibe-Simvastatin Tablet 10/20 mg daily (n=4650) or placebo (n=4620). (median follow-up 4.9 years), the incidence of myopathy/rhabdomyolysis was 0.2% for Ezetimibe-Simvastatin Tablet and 0.1% for placebo. (See XII. SIDE EFFECTS.)

In a clinical trial in which patients at high risk of cardiovascular disease were treated with simvastatin 40 mg/day (median follow-up 3.9 years), the incidence of myopathy was approximately 0.05% for non-Chinese patients (n=7367) compared with 0.24% for Chinese patients (n=5468). While the only Asian population assessed in this clinical trial was Chinese, caution should be used when prescribing Ezetimibe-Simvastatin Tablet to Asian patients and the lowest dose necessary should be employed.

Drug Interactions

• Because Ezetimibe-Simvastatin Tablet contains simvastatin, the risk of myopathy/ rhabdomyolysisis increased by concomitant use of Ezetimibe-Simvastatin Tablet with the following drugs:

Contraindicated Drugs

• Potent inhibitors of CYP3A4: Concomitant use with medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses **(e. g. itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors , boceprevir, telaprevir, nefazodone or drugs containing cobicistat)** is contraindicated. If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with Ezetimibe-Simvastatin Tablet should be suspended during the course of treatment. (See VI. CONTRAINDICATIONS, XI. DRUG INTERACTIONS; and IVb. CLINICAL PHARMACOLOGY, Pharmacokinetics.)

• Gemfibrozil , cyclosporine, or danazol : Concomitant use of these drugs with VALCORE TABLET is contraindicated (see VI. CONTRAINDICATIONS, XI. DRUG INTERACTIONS, IVb. CLINICAL PHARMACOLOGY, Pharmacokinetics).

Other Drugs

• **Fusidic acid:** Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy/ rhabdomyolysis (see XI. DRUG INTERACTIONS, Other drug interactions). Co-administration with fusidic acid is not recommended. In patients where the use of systemic fusidic acid is considered essential, Ezetimibe-Simvastatin Tablet should be discontinued throughout the duration of fusidic acid treatment. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of Ezetimibe-Simvastatin Tablet and fusidic acid should only be considered on a case-by-case basis under close medical supervision.

• **Amiodarone**: In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. The dose of Ezetimibe-Simvastatin Tablet should not exceed 10/ 20 mg daily in patients receiving concomitant medication with amiodarone. (See XI. DRUG INTERACTIONS.)

Calcium channel blockers

• **Verapamil or diltiazem**: Patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. **The dose of Ezetimibe-Simvastatin Tablet should not exceed 10/ 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem.** (See XI DRUG INTERACTIONS, Other drug interactions.)

• **Amlodipine**: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. (see XI. DRUG INTERACTIONS) **The dose of Ezetimibe-Simvastatin Tablet should not exceed 10/ 40 mg daily in patients receiving concomitant medication with amlodipine.**

• **Lomitapide:** The dose of Ezetimibe-Simvastatin Tablet should not exceed 10/40 mg daily in patients with HoFH receiving concomitant medication with lomitapide (see XI. DRUG INTERACTIONS).

• **Moderate inhibitors of CYP3A4:** Patients taking other medicines labeled as having a moderate inhibitory effect on CYP3A4 concomitantly with Ezetimibe-Simvastatin Tablet, particularly higher Ezetimibe-Simvastatin Tablet doses, may have an increased risk of myopathy. When co-administering Ezetimibe-Simvastatin Tablet with a moderate inhibitor of CYP3A4, a dose adjustment of Ezetimibe-Simvastatin Tablet may be necessary.

• **Fibrates:** The safety and effectiveness of Ezetimibe-Simvastatin Tablet administered with fibrates have not been studied. Therefore, the concomitant use of Ezetimibe-Simvastatin Tablet and fibrates should be avoided. Concomitant use of gemfibrozil is contraindicated (see VI. CONTRAINDICATIONS).

• **Niacin (≥ 1 g/ day):** Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin. In a clinical trial (median follow-up 3.9 years) involving patients at high risk of cardiovascular disease and with well-controlled LDL-C levels on simvastatin 40 mg/day with or without ezetimibe 10 mg, there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses (≥ 1 g/day) of niacin. Therefore, the benefit of the combined use of simvastatin with niacin should be carefully weighed against the potential risks of the combination. In addition, in this trial, the incidence of myopathy was approximately 0.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 1.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg co-administered with extended-release niacin/laropiprant 2 g/40 mg. While the only Asian population assessed in this clinical trial was Chinese, because the incidence of myopathy is higher in Chinese than in non-Chinese patients, co-administration of Ezetimibe-Simvastatin Tablet with lipid modifying doses (≥ 1 g/day) of niacin is not recommended in Asian patients. (See XI. DRUG INTERACTIONS)

• **Inhibitors of Breast Cancer Resistant Protein (BCRP)**: Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of Ezetimibe-Simvastatin tablet may be necessary. Coadministration of elbasvir and grazoprevir with simvastatin has not been studied; however, the dose of Ezetimibe-Simvastatin tablet should not exceed 10/20 mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir (see XI. DRUG INTERACTIONS, Other drug interactions).

Liver Enzymes

In controlled co-administration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (≥ 3 X ULN) have been observed. (See XII. SIDE EFFECTS)

In a controlled clinical study in which over 9000 patients with chronic kidney disease were randomized to receive Ezetimibe-Simvastatin Tablet 10/20 mg daily (n=4650) or placebo (n=4620) (median follow-up period of 4.9 years), the incidence of consecutive elevations of transaminases (>3 X ULN) was 0.7% for Ezetimibe-Simvastatin Tablet and 0.6% for placebo. (See XII. SIDE EFFECTS)

It is recommended that LFTs be performed before treatment with Ezetimibe-Simvastatin Tablet begins and thereafter when clinically indicated. Patients titrated to the 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 X ULN and are persistent, the drug should be discontinued. Note that ALT may emanate from muscle; therefore ALT rising with CK may indicate myopathy (see VII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

There has been rare post marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with Ezetimibe-Simvastatin Tablet, promptly interrupt therapy. If an alternate etiology is not found do not restart Ezetimibe-Simvastatin Tablet. Ezetimibe-Simvastatin Tablet should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of Ezetimibe-Simvastatin Tablet.

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, Ezetimibe-Simvastatin Tablet is not recommended in these patients (see IVb-5. Characteristics in Patients [Special Populations]).

Anticoagulants

If Ezetimibe-Simvastatin Tablet is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored (see XI. DRUG INTERACTIONS).

VIII. PREGNANCY

Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolemia.

Ezetimibe-Simvastatin Tablet

Ezetimibe-Simvastatin Tablet is contraindicated during pregnancy.

Simvastatin

The safety of simvastatin in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. For this reason, Ezetimibe-Simvastatin Tablet should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Ezetimibe-Simvastatin Tablet should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see VI. CONTRAINDICATIONS).

Ezetimibe

No clinical data on exposed pregnancies are available for ezetimibe.

When ezetimibe was given with simvastatin, no teratogenic effects were observed in embryo-fetal development studies in pregnant rats. In pregnant rabbits, a low incidence of skeletal malformations was observed.

IX . NURSING MOTHERS

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether the active components of Ezetimibe-Simvastatin Tablet are excreted into human breast milk; therefore, women who are nursing should not take Ezetimibe-Simvastatin Tablet.

X. USE IN THE ELDERLY

Because advanced age (≥ 65 years) is a predisposing factor for myopathy, Ezetimibe-Simvastatin Tablet should be prescribed with caution in the elderly. In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥ 65 years of age had an increased risk of myopathy compared to patients <65 years of age.

XI. DRUG INTERACTIONS

Ezetimibe-Simvastatin Tablet

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with Simvastatin.

Ezetimibe-Simvastatin Tablet is bioequivalent to co-administered ezetimibe and simvastatin.

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors. Drugs or herbal products that inhibit certain enzymes (e.g. CYP3A4) and/or transporter (e.g. OATP1B) pathways may increase simvastatin and simvastatin acid plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

Consult the prescribing information of all concomitantly used drugs to obtain further information about their potential interactions with simvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

Contraindicated drugs

Concomitant use of the following drugs is contraindicated:

Potent Inhibitors of CYP3A4

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolizing enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase. Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of the simvastatin component of Ezetimibe-Simvastatin Tablet: Concomitant use of drugs labeled as having a potent inhibitory effect on CYP3A4 (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, drugs containing cobicistat) is contraindicated. (See VI. CONTRAINDICATIONS, VII. PRECAUTIONS, Myopathy/Rhabdomyolysis, and IVb. CLINICAL PHARMACOLOGY, Pharmacokinetics.).

Gemfibrozil, Cyclosporine, or Danazol (see VI. CONTRAINDICATIONS and VII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. This increase is not considered clinically significant. No clinical data are available. (See VI. CONTRAINDICATIONS and VII. PRECAUTIONS, Myopathy/Rhabdomyolysis.)

Cyclosporine: In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/min on a stable dose of cyclosporine, a single 10-mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100 mg dose of cyclosporine alone (see VI. CONTRAINDICATIONS and VII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Other drug interactions

Fibrates: Concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold; however, this increase is not considered clinically significant. The safety and effectiveness of Ezetimibe-Simvastatin Tablet administered with fibrates have not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of Ezetimibe-Simvastatin Tablet with fibrates is not recommended until use in patients is studied.

Fusidic Acid: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of fusidic acid (see VII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Amiodarone: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with higher doses of Ezetimibe-Simvastatin Tablet (see V. DOSAGE AND ADMINISTRATION and VII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental LDL-C reduction due to adding Ezetimibe-Simvastatin Tablet to cholestyramine may be lessened by this interaction.

Calcium Channel Blockers: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine (see V. DOSAGE AND ADMINISTRATION and VII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Lomitapide: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide (see IV. DOSAGE AND ADMINISTRATION and VI. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Moderate Inhibitors of CYP3A4: Patients taking other medicines labeled as having a moderate inhibitory effect on CYP3A4 concomitantly with Ezetimibe-Simvastatin Tablet, particularly higher Ezetimibe-Simvastatin Tablet doses, may have an increased risk of myopathy.

Inhibitors of the Transport Protein OATP1B1: Simvastatin acid is a substrate of the transport protein OATP1B1. Concomitant administration of medicinal products that are inhibitors of the transport protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and an increased risk of myopathy. (see V. CONTRAINDICATIONS; VI. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Niacin: In a study of 15 healthy adults, concomitant Ezetimibe-Simvastatin Tablet (10/20 mg daily for 7 days) caused a small increase in the mean AUCs of niacin (22%) and nicotinuric acid (19%) administered as NIASPAN extended-release tablets (1000 mg for 2 days and 2000 mg for 5 days following a low-fat breakfast). In the same study, concomitant NIASPAN slightly increased the mean AUCs of ezetimibe (9%), total ezetimibe (26%), simvastatin (20%) and simvastatin acid (35%).

Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid modifying doses (≥ 1 g/day) of niacin (see VI. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Colchicine: There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and Ezetimibe-Simvastatin Tablet in patients with renal insufficiency. Close clinical monitoring of such patients taking this combination is advised.

Inhibitors of Breast Cancer Resistant Protein (BCRP): Simvastatin is a substrate of the efflux transporter BCRP. Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy. When coadministering simvastatin with an inhibitor of BCRP, a dose adjustment of Ezetimibe-Simvastatin tablet may be necessary (see V. DOSAGE AND ADMINISTRATION, VII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Other Interactions

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of drugs metabolized by CYP3A4. The effect of typical consumption (one 250-mL glass daily) is minimal (13% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the area under the concentration-time curve) and of no clinical relevance. However, because larger quantities significantly increase the plasma levels of HMG-CoA reductase inhibitory activity, grapefruit juice should be avoided during Ezetimibe-Simvastatin Tablet therapy (see VII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Anticoagulants

In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting Ezetimibe-Simvastatin Tablet and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of Ezetimibe-Simvastatin Tablet is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. There have been post-marketing reports of increased International Normalized Ratio in patients who had ezetimibe added to warfarin or fluindione. Most of these patients were also on other medications (see VII. PRECAUTIONS).

The effect of Ezetimibe-Simvastatin Tablet on the prothrombin time has not been studied.

Antacids: Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

XII. SIDE EFFECTS

Ezetimibe-Simvastatin Tablet (or co-administration of ezetimibe and simvastatin equivalent to Ezetimibe-Simvastatin Tablet) has been evaluated for safety in approximately 12,000 patients in clinical trials. Ezetimibe-Simvastatin Tablet was generally well tolerated.

The following common (≥ 1/100, <1/10) or uncommon (≥ 1/1000, <1/100); drug-related adverse experiences were reported in patients taking Ezetimibe-Simvastatin Tablet (n=2404) and at a greater incidence than placebo (N=1340):

Investigations:
Common: ALT and/or AST increased; blood CK increased
Uncommon: blood bilirubin increased; blood uric acid increased; gamma-glutamyltransferase increased; international normalized ratio increased; protein urine present; weight decreased
Nervous system disorders:
Uncommon: dizziness; headache
Gastrointestinal disorders:
Uncommon: abdominal pain; abdominal discomfort; abdominal pain upper; dyspepsia; flatulence; nausea; vomiting
Skin and subcutaneous tissue disorders:
Uncommon: pruritus; rash
Musculoskeletal and connective tissue disorders:
Uncommon: arthralgia; muscle spasms; muscular weakness; musculoskeletal discomfort; neck pain; pain in extremity
General disorders and administration site conditions:
Uncommon: asthenia; fatigue; malaise; edema peripheral
Psychiatric disorders:
Uncommon: sleep disorder

The following common (≥ 1/100, <1/10) or uncommon (≥ 1/1000, <1/100); drug-related adverse experiences were reported in patients taking Ezetimibe-Simvastatin Tablet (n=9595) and at a greater incidence than statins administered alone (N=8883):

Investigations:
Common: ALT and/or AST increased
Uncommon: blood bilirubin increased; blood CK increased; gamma-glutamyltransferase increased
Nervous system disorders:
Uncommon: headache; paresthesia
Gastrointestinal disorders:
Uncommon: abdominal distension; diarrhea; dry mouth; dyspepsia; flatulence; gastroesophageal reflux disease; vomiting
Skin and subcutaneous tissue disorders:
Uncommon: pruritus; rash; urticaria
Musculoskeletal and connective tissue disorders:
Common: myalgia
Uncommon: arthralgia; back pain; muscle spasms; muscular weakness; musculoskeletal pain; pain in extremity
General disorders and administration site conditions:
Uncommon: asthenia; chest pain; fatigue; edema peripheral
Psychiatric disorders:
Uncommon: insomnia

Patients with Chronic Kidney Disease

In the Study of Heart and Renal Protection (SHARP) (see IVc. CLINICAL STUDIES, Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)), involving over 9000 patients treated with Ezetimibe-Simvastatin Tablet 10/20 mg daily (n=4650) or placebo (n=4620), the safety profiles were comparable during a median follow-up period of 4.9 years. In this trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse events were comparable (10.4% in patients treated with Ezetimibe-Simvastatin Tablet, 9.8% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was 0.2% in patients treated with Ezetimibe-Simvastatin Tablet and 0.1% in patients treated with placebo. Consecutive elevations of transaminases (> 3X ULN) occurred in 0.7% of patients treated with Ezetimibe-Simvastatin Tablet compared with 0.6% of patients treated with placebo. In this trial, there were no statistically significant increases in the incidence of pre-specified adverse events, including cancer (9.4% for Ezetimibe-Simvastatin Tablet, 9.5% for placebo), hepatitis, cholecystectomy or complications of gallstones or pancreatitis.

Post-marketing Experience

The following additional adverse reactions have been reported in post-marketing use with Ezetimibe-Simvastatin Tablet or during clinical studies or post-marketing use with one of the individual components. The adverse reactions reported for Ezetimibe-Simvastatin Tablet are consistent with those previously reported with ezetimibe and/or simvastatin.

Investigations: liver function test abnormal
Blood and lymphatic system disorders: thrombocytopenia; anaemia
Nervous system disorders: peripheral neuropathy
Respiratory, thoracic and mediastinal disorders: cough; interstitial lung disease
Gastrointestinal disorders: constipation; pancreatitis; gastritis, nausea
Skin and subcutaneous tissue disorders: alopecia; hypersensitivity reactions, including rash, urticaria, anaphylaxis, angio-edema; erythema multiforme
Musculoskeletal and connective tissue disorders: muscle cramps; myopathy/rhabdomyolysis (see VII. PRECAUTIONS, Myopathy/Rhabdomyolysis)

There have been very rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents (see VII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Metabolism and nutrition disorders: decreased appetite
Vascular disorders: hot flush; hypertension
General disorders and administration site conditions: pain
Hepato-biliary disorders: hepatitis/jaundice; fatal and non-fatal hepatic failure; cholelithiasis; cholecystitis
Reproductive system and breast disorders: erectile dysfunction
Psychiatric disorders: depression

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnea and malaise.

There have been rare post marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Laboratory Values

In controlled clinical coadministration trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was 1.7% for patients treated with Ezetimibe-Simvastatin Tablet. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. (See VII. PRECAUTIONS)

Clinically important elevations of CK (≥ 10 X ULN) were seen in 0.2% of the patients treated with Ezetimibe-Simvastatin Tablet

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including simvastatin.

XIII. OVERDOSAGE

Ezetimibe-Simvastatin Tablet

No specific treatment of overdosage with Ezetimibe-Simvastatin Tablet can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed. Co-administration of ezetimibe (1000 mg/kg) and simvastatin (1000 mg/kg) was well-tolerated in acute, oral toxicity studies in mice and rats. No clinical signs of toxicity were observed in these animals. The estimated oral LD50 for both species was ezetimibe ≥ 1000 mg/kg/simvastatin ≥ 1000 mg/kg.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, and 40 mg/day to 27 patients with homozygous sitosterolemia for 26 weeks, was generally well tolerated.

A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Simvastatin

A few cases of overdosage have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

XIV. STORAGE

Please refer to Outer Carton for storage conditions.

XV. DESCRIPTION AND EXCIPIENTS

VALCORE TABLET (10/10): Light tan, mottled, round 6 mm, biconvex tablets. Marking 511 on one side.
VALCORE TABLET (10/20): Light tan, mottled, round 8 mm, biconvex tablets. Marking 512 on one side.
Lactose monohydrate, Hypromellose, Croscarmellose sodium, Cellulose microcrystalline, Ascorbic acid, Citric acid anhydrous, Butylhydroxyanisole, Propyl gallate, Magnesium stearate, Pigment blend PB-220001 Yellow [Lactose monohydrate, Iron oxide yellow (E172), Iron oxide red (E172), Iron oxide black (E172)]

XVI. AVAILABILITY

VALCORE TABLET (10/10), each containing 10 mg of ezetimibe and 10 mg of simvastatin, is supplied in OPA/Aluminium/PVC-Aluminium blister and PVC/Aclar-Aluminium blister packs of 30 tablets.
VALCORE TABLET (10/20), each containing 10mg of ezetimibe and 20mg of simvastatin, is supplied in OPA/Aluminium/PVC-Aluminium blister and PVC/Aclar-Aluminium blister packs of 30 tablets.
Not all presentations may be available locally.

Product Owner

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