EZETROL® Tablet

Ezetimibe

COMPOSITION

Each tablet of EZETROL for oral administration contains 10 mg ezetimibe.

THERAPEUTIC CLASS

EZETROL is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols.

MECHANISM OF ACTIONS

Ezetimibe 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. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe does not increase bile acid excretion (like bile acid sequestrants) and does not inhibit cholesterol synthesis in the liver (like statins).

In a 2-week clinical study in 18 hypercholesterolemic patients, EZETROL inhibited intestinal cholesterol absorption by 54 %, compared with placebo. By inhibiting the absorption of intestinal cholesterol, ezetimibe reduces the delivery of cholesterol to the liver. Statins reduce cholesterol synthesis in the liver. Together these distinct mechanisms provide complementary cholesterol reduction. EZETROL, administered with a statin, reduces total-C, LDL-C, Apo B, and TG and increases HDL-C in patients with hypercholesterolemia, beyond either treatment alone. Administration of EZETROL with fenofibrate is effective in improving serum total-C, LDL-C, Apo B, TG, HDL-C, and

non-HDL-C in patients with mixed hyperlipidemia. The effects of Ezetimibe given either alone or in addition to an HMG-CoA reductase inhibitor or fenofibrate on cardiovascular morbidity and mortality have not been established.

Clinical studies demonstrate that elevated levels of total-C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [^{14}C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat soluble vitamins A and D.

PHARMACOKINETICS

ABSORPTION

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 EZETROL 10-mg tablets. EZETROL can be administered with or without food.

DISTRIBUTION

Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

METABOLISM

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.

ELIMINATION

Following oral administration of ^{14}C-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.

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.

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 EZETROL. Therefore, no dosage adjustment is necessary in the elderly.

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 WARNING AND PRECAUTION).

Renal Insufficiency

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl $\leq$ 30 ml/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

An additional patient in this study (post-renal transplant and receiving multiple medications, including cyclosporine) had a 12-fold greater exposure to total ezetimibe.

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. Therefore, no dosage adjustment is necessary on the basis of gender.

Race

Based on a meta-analysis of pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians.

CLINICAL STUDIES

Primary Hypercholesterolemia

Monotherapy

In two, multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, EZETROL 10 mg significantly lowered total-C, LDL-C, Apo B, and TG and increased HDL-C compared to placebo (see Table 1). Reduction in LDL-C was consistent across age, sex, race, and baseline LDL-C. In addition, EZETROL 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.

Table 1: Mean Response to EZETROL in Patients with Primary Hypercholesterolemia (Mean % Change from Baseline)

	Treatment group	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Study 1	Placebo	205	+1	+1	-1	-1	-1
	EZETROL	622	-12	-18	-15	-7	+1
Study 2	Placebo	226	+1	+1	-1	+2	-2
	EZETROL	666	-12	-18	-16	-9	+1
Pooled Data (Studies 1 & 2)	Placebo	431	0	+1	-2	0	-2
	EZETROL	1288	-13	-18	-16	-8	+1

[a] Median % change from baseline

Co-Administration with a Statin

EZETROL Initiated Concurrently with a Statin

In four, multicenter, double-blind, placebo-controlled, 12-week trials, in 2382 patients with hypercholesterolemia, EZETROL 10 mg or placebo was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin. In general, the incremental effect on LDL-C reduction was independent of the dose or specific statin

used. In addition, LDL-C reduction for EZETROL co-administered with the lowest tested dose (10 mg) of any of the statins was similar to or greater than the LDL-C reduction of the highest tested dose of the corresponding statin administered alone (Table 2).

Table 2: Mean % Change from Baseline in Plasma Concentration of Calculated LDL-C for EZETROL Administered with Statins

	Atorvastatin Study	Simvastatin Study	Pravastatin Study	Lovastatin Study
Placebo	+4	-1	-1	0
EZETROL	-20	-19	-20	-19
10 mg statin	-37	-27	-21	-20
EZETROL **+ 10 mg statin**	-53	-46	-34	-34
20 mg statin	-42	-36	-23	-26
EZETROL **+ 20 mg statin**	-54	-46	-40	-41
40 mg statin	-45	-38	-31	-30
EZETROL **+ 40 mg statin**	-56	-56	-42	-46
80 mg statin	-54	-45	-	-
EZETROL **+ 80 mg statin**	-61	-58	-	-
Pooled data: All statin doses	-44	-36	-25	-25
Pooled data: All EZETROL **+ statin doses**	-56	-51	-39	-40

In a pooled analysis of all EZETROL + statin doses, EZETROL had a beneficial effect on total-C, Apo B, TG, and HDL-C (Table 3).

Table 3: Pooled Analysis of the Mean % Change from Baseline in Total-C, ApoB, TG, and HDL-C

	Total-C	Apo B	TG[a]	HDL-C
EZETROL **+ Atorvastatin**	-41	-45	-33	+7
Atorvastatin alone	-32	-36	-24	+4
EZETROL **+ Simvastatin**	-37	-41	-29	+9

Simvastatin alone	-26	-30	-20	+7
EZETROL **+ Pravastatin**	-27	-30	-21	+8
Pravastatin alone	-17	-20	-14	+7
EZETROL **+ Lovastatin**	-29	-33	-25	+9
Lovastatin alone	-18	-21	-12	+4

[a] median % change

EZETROL ***Added to On-going Statin Therapy***

In a multicenter, double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (100 to 160 mg/dl, depending on baseline characteristics) were randomized to receive either EZETROL 10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82 %), LDL-C goal at study endpoint was achieved by 72 % and 19 % of patients randomized to EZETROL and placebo, respectively.

EZETROL, added to on-going statin therapy, significantly lowered total-C, LDL-C, Apo B, and TG and increased HDL-C, compared with placebo (Table 4). LDL-C reductions were consistent across all statins.

Table 4: Mean Response to Addition of EZETROL to On-going Statin Therapy[a] in Patients with Hypercholesterolemia (Mean % Change from Baseline)

Treatment (Daily Dose)	**N**	**Total-C**	**LDL-C**	**Apo B**	**TG[b]**	**HDL-C**
On-going Statin +Placebo	390	-2	-4 (-6 mg/dl [c])	-3	-3	+1
On-going Statin + EZETROL	379	-17	-25 (-36 mg/dl[c])	-19	-14	+3

[a] Percentages of patients receiving each statin: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)

[b] Median % change from baseline

[c] Change in LDL-C from baseline LDL-C (138 mg/dl and 139 mg/dl for statin + EZETROL and statin + placebo, respectively)

EZETROL or placebo added to statin therapy reduced median C-reactive protein by 10 % or 0 % from baseline, respectively.

In a multicenter, double-blind, 14 week study, 621 patients with hypercholesterolemia receiving atorvastatin 10 mg daily with an LDL-C > 130 mg/dl were randomized to receive atorvastatin 20 mg or EZETROL 10 mg added to atorvastatin 10 mg therapy. The atorvastatin dose could be titrated up to 80 mg in the atorvastatin arm and up to 40 mg in the EZETROL plus atorvastatin co-administration arm, based on patients not attaining LDL-C goal (< 100 mg/dl). The mean baseline LDL-C was 187 mg/dl and approximately 60 % of the patients had heterozygous familial hypercholesterolemia (HeFH). At study end, there was a significant difference in attainment of LDL-C goal between patients in the EZETROL co-administration arm (22 %) and patients on atorvastatin monotherapy (7 %). At week 4, there was a significant difference in LDL-C reductions between co-administration patients (24 %; EZETROL + atorvastatin 10 mg) and monotherapy patients (9 %; atorvastatin 20 mg). In the sub-group of patients with HeFH, similar results for LDL-C goal attainment and LDL-C reductions were achieved.

In a similarly designed study in 100 patients with hypercholesterolemia receiving simvastatin 20 mg and not at LDL-C goal, the addition of EZETROL 10 mg to simvastatin titration compared to titration of simvastatin alone produced similar advantages to those observed in the atorvastatin study described above. For example, significant differences in LDL-C goal attainment (27 % for EZETROL + simvastatin vs. 3 % for simvastatin alone) and LDL-C reductions (24 % for EZETROL+ simvastatin vs. 11 % for simvastatin alone) were achieved.

Co-administration with Fenofibrate

In a multicenter, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidemia, 625 patients were treated for up to 12 weeks and 576 for up to 1 year. Patients were randomized to receive placebo, EZETROL alone, 160 mg fenofibrate alone, or EZETROL and 160 mg fenofibrate.

EZETROL co-administered with fenofibrate significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to fenofibrate administered alone. The percent decrease in TG and percent increase in HDL-C for EZETROL co-administered with fenofibrate were comparable to those for fenofibrate administered alone (see Table 5).

Table 5: Response to EZETROL and Fenofibrate Initiated Concurrently in Patients with Mixed Hyperlipidemia (Mean[a] % Change from Untreated Baseline[b] at 12 weeks)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C	Non-HDL-C
Placebo	63	0	0	-1	-9	+3	0
EZETROL	185	-12	-13	-11	-11	+4	-15
Fenofibrate 160 mg	188	-11	-6	-15	-43	+19	-16
EZETROL + Fenofibrate 160 mg	183	-22	-20	-26	-44	+19	-30

[a] For triglycerides, median % change from baseline

[b] Baseline - on no lipid-lowering drug

Improvements in lipid endpoints after 1 year of treatment were consistent with the 12-week data displayed above.

Homozygous Familial Hypercholesterolemia (HoFH)

A study was conducted to assess the efficacy of EZETROL in the treatment of HoFH. This double-blind, randomized, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40 mg). Patients were randomized to one of three treatment groups, atorvastatin or simvastatin (80 mg), EZETROL 10 mg administered with atorvastatin or simvastatin (40 mg), or EZETROL 10 mg administered with atorvastatin or simvastatin (80 mg). Results are shown in Table 6. EZETROL, administered with atorvastatin (40 or 80 mg) or simvastatin (40 or 80 mg), significantly

reduced LDL-C compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg.

Table 6: Mean Response to EZETROL in Patients with HoFH (Mean % Change from Baseline)

Treatment (Daily Dose)	N	LDL-C
Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-7
EZETROL + Atorvastatin (40, 80 mg) or Simvastatin (40, 80 mg)	33	-21
Sub-group analysis: EZETROL *+ Atorvastatin (80 mg) or Simvastatin (80 mg)*	17	-27

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies of the effects on the ability to drive and use of machines have been performed. However, certain side effects that have been reported with EZETROL may affect some patient's ability to drive or operate machinery. Individual responses to EZETROL may vary (See SIDE EFFECTS).

ANIMAL PHARMACOLOGY

The hypocholesterolemic effect of ezetimibe was evaluated in Rhesus monkeys, a model for the human metabolism of cholesterol, as well as in dogs. Rhesus monkeys were fed a cholesterol-containing diet that mimics a human Western diet. Ezetimibe was found to have an ED_{50} of 0.0005 mg/kg/day for inhibiting the rise in plasma cholesterol levels (ED_{100} = 0.003 mg/kg/day). The ED_{50} in dogs was found to be 0.007mg/kg/day. These results are consistent with EZETROL being an extremely potent cholesterol absorption inhibitor.

In dogs given ezetimibe ($\geq$0.03 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 3-fold. However, a dose of 300 mg/kg/day administered

to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In mice given ezetimibe (0.3 to 5 mg/kg/day) and fed a normal or cholesterol rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively. The relevance of these preclinical findings to humans is unknown.

ANIMAL TOXICOLOGY

Acute Toxicity

In animals, no toxicity was observed after single oral doses of 5000 mg/kg of ezetimibe in rats and mice and 3000 mg/kg in dogs.

Chronic Toxicity

Ezetimibe was well tolerated by mice, rats and dogs. No target organs of toxicity were identified in chronic studies at daily doses up to 1500 (males) and 500 mg/kg (females) in rats, up to 500 mg/kg in mice, or up to 300 mg/kg in dogs.

The safety of concomitant administration of ezetimibe and statins was assessed in rats and dogs. When ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin or lovastatin, for three months, toxicologic findings were consistent with those seen with statins administered alone.

Carcinogenicity

In two-year studies conducted in mice and rats, ezetimibe was not carcinogenic.

Mutagenesis

Ezetimibe was not genotoxic in a series of *in vivo* and *in vitro* tests.

Combinations of ezetimibe with atorvastatin, simvastatin, pravastatin, or lovastatin were not genotoxic in a series of *in vitro* and *in vivo* assays.

Reproduction

Ezetimibe did not affect the fertility of male or female rats.

Development

Ezetimibe was not teratogenic in rats or rabbits and had no effect on prenatal or postnatal development.

Concomitant administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits, a low incidence of skeletal malformations (fused sternebrae, fused caudal vertebrae, reduced number of caudal vertebrae) was observed when ezetimibe (1000 mg/kg; ≥146 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe) was administered with lovastatin (2.5 and 25 mg/kg), simvastatin (5 and 10 mg/kg), pravastatin (25 and 50 mg/kg), or atorvastatin (5, 25, and 50 mg/kg). Exposure to the pharmacologically active form of the statin ranged from 1.4 (atorvastatin) to 547 (lovastatin) times the human exposure at 10 mg daily (simvastatin or atorvastatin) or 20 mg daily (lovastatin and pravastatin) based on AUC_{0-24hr}.

INDICATIONS:

Primary Hypercholesterolemia

EZETROL, administered with an HMG-CoA reductase inhibitor (statin) or alone, 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), and triglycerides (TG) and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

EZETROL, administered in combination with fenofibrate, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia.

Homozygous Familial Hypercholesterolemia (HoFH)

EZETROL, administered with a statin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

DOSAGE AND ADMINISTRATION:

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with EZETROL.

The recommended dose of EZETROL is 10 mg once daily, used alone, with a statin or with fenofibrate. EZETROL can be administered at any time of the day, with or without food.

Use in the Elderly

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

Use in Pediatric Patients

Children and adolescents ≥ 10 years: No dosage adjustment is required (see *Characteristics in Patients [Special Populations]*).

Children < 10 years: treatment with EZETROL is not recommended.

Use in Hepatic Impairment

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

Use in Renal Impairment

No dosage adjustment is required for renally impaired patients (see. *Characteristics in Patients [Special Populations]*).

Co-administration with bile acid sequestrants

Dosing of EZETROL should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

WARNING AND PRECAUTION

When EZETROL is to be administered with a statin or with fenofibrate, which are contraindicated during pregnancy and lactation, please refer to the Package Insert for that particular medication.

Liver Enzymes

In controlled co-administration trials in patients receiving EZETROL with a statin, consecutive transaminase elevations (≥3 X the upper limit of normal [ULN]) have been observed. When EZETROL is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin. (see SIDE EFFECTS.)

Skeletal Muscle

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with EZETROL compared with the relevant control arm (placebo or statin alone). However, myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 X ULN was 0.2% for EZETROL vs 0.1% for placebo, and 0.1% for EZETROL co-administered with a statin vs 0.4% for statins alone.

In post-marketing experience with EZETROL, cases of myopathy and rhabdomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolysis were taking a statin prior to initiating EZETROL. However, rhabdomyolysis has been reported very rarely with EZETROL monotherapy and very rarely with the addition of EZETROL to agents known to be associated with increased risk of rhabdomyolysis. All patients starting therapy with EZETROL should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. EZETROL and any statin that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected. The presence of these symptoms and a creatine phosphokinase (CPK) level >10 times the ULN indicates myopathy.

Hepatic Insufficiency

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

Fibrates

The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied. Therefore, co-administration of EZETROL and fibrates (other than fenofibrate) is not recommended (see DRUG INTERACTIONS).

Fenofibrate

If cholelithiasis is suspected in a patient receiving EZETROL and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered (see SIDE EFFECTS and the Package Insert for fenofibrate).

Cyclosporine

Caution should be exercised when initiating ezetimibe in the setting of cyclosporine. Cyclosporine concentrations should be monitored in patients receiving EZETROL and cyclosporine (see DRUG INTERACTIONS).

Anticoagulants

If EZETROL is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored (See DRUG INTERACTIONS).

Pregnancy

No clinical data on exposed pregnancies are available. Animal studies of ezetimibe administered alone do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. However, caution should be exercised when prescribing to pregnant women.

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

When ezetimibe is to be administered with a statin, which is contraindicated during pregnancy and lactation, please refer to the Package Insert for that particular statin.

Nursing mother

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether ezetimibe is excreted into human breast milk, therefore, EZETROL should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

Overdosage

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, was generally well tolerated.

A few cases of overdosage with EZETROL have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

SIDE EFFECTS

Clinical studies of up to 112 weeks duration in which EZETROL 10 mg daily was administered alone (n=2396), with a statin (n=11,308), or with fenofibrate in 3551 patients demonstrated: EZETROL was generally well tolerated, adverse reactions were usually mild and transient, the overall incidence of side effects reported with EZETROL was similar to that reported with placebo, and the discontinuation rate due to adverse experiences was comparable between EZETROL and placebo.

The following common (≥1/100, <1/10) or uncommon (≥1/1,000, <1/100); drug-related adverse experiences were reported in patients taking EZETROL alone (2396), and at a greater incidence than placebo (n=1159), or in patients taking EZETROL co-administered with a statin (n = 11,308) and at a greater incidence than statin administered alone (n=9361).

EZETROL administered alone:

Investigations:

Uncommon: ALT and/or AST increased; blood CPK increased; gamma glutamyltransferase increased; liver function test abnormal

Respiratory, Thoracic and Mediastinal Disorders:

Uncommon: cough

Gastrointestinal Disorders:

Common: abdominal pain; diarrhea; flatulence

Uncommon: dyspepsia; gastroesophageal reflux disease; nausea

Musculoskeletal and Connective Tissue Disorders

Uncommon: arthralgia; muscle spasms; neck pain

Metabolism and Nutrition Disorders:

Uncommon: decreased appetite

Vascular Disorders:

Uncommon: hot flush; hypertension

General Disorders and Administration Site Condition:

Common: fatigue

Uncommon: chest pain; pain

EZETROL co-administered with a statin:

Investigations:

Common: ALT and/or AST increased

Nervous System Disorders:

Common: headache

Uncommon: paresthesia

Gastrointestinal Disorders

Uncommon: dry mouth; gastritis

Skin and Subcutaneous Tissue Disorders

Uncommon: pruritus; rash; urticaria

Musculoskeletal and Connective Tissue Disorders

Common: myalgia

Uncommon: back pain; muscular weakness; pain in extremity

General Disorders and Administration Site Condition

Uncommon: asthenia; edema peripheral

EZETROL co-administered with fenofibrate:

Gastrointestinal Disorders

Common: abdominal pain

In a multicenter, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidemia, 625 patients were treated for up to 12 weeks and 576 for up to 1 year. This study was not designed to compare treatment groups for infrequent events. Incidence rates (95% CI) for clinically important elevations (> 3 X ULN, consecutive) in serum transaminases were 4.5% (1.9, 8.8) and 2.7% (1.2, 5.4) for fenofibrate monotherapy and EZETROL co-administered with fenofibrate, respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6% (0.0, 3.1) and 1.7% (0.6, 4.0) for fenofibrate monotherapy and EZETROL co-administered with fenofibrate, respectively (see WARNING AND PRECAUTION). There were no CPK elevations > 10 X ULN in either treatment group in this study.

Laboratory Values

In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was similar between EZETROL (0.5 %) and placebo (0.3 %). In co-administration trials, the incidence was 1.3% for patients treated with EZETROL co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. (See WARNING AND PRECAUTION.)

Clinically important elevations of CPK (≥10 X ULN) in patients treated with EZETROL administered alone or co-administered with a statin were similar to elevations seen with placebo or statin administered alone, respectively.

Post-marketing Experience

The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment:

Blood and lymphatic system disorders: thrombocytopaenia

Nervous system disorders: dizziness; paraesthesia

Gastrointestinal disorders: nausea; pancreatitis; constipation

Skin and subcutaneous tissue disorders: erythema multiforme

Musculoskeletal and connective tissue disorders: arthralgia; myalgia; myopathy/rhabdomyolysis (See PRECAUTIONS)
General disorders and administration site conditions: asthenia
Immune system disorders: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria
Hepatobiliary disorders: hepatitis; cholelithiasis; cholecystitis
Psychiatric disorders: depression

CONTRA INDICATIONS

Hypersensitivity to any component of this medication.
The combination of EZETROL with an HMG-CoA reductase inhibitor is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminase.
When EZETROL is to be administered with a statin or with fenofibrate, which are contraindicated during pregnancy and lactation, please refer to the Package Insert for that particular medication.

DRUG INTERACTIONS

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.

Ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide or midazolam during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

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.

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 to cholestyramine may be lessened by this interaction.

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 WARNING AND PRECAUTION).

Fibrates: The safety and effectiveness of ezetimibe co-administered with fenofibrate have been evaluated in a clinical study (see SIDE EFFECTS and CLINICAL STUDIES, *Co-administration with Fenofibrate*); co-administration of ezetimibe with other fibrates has 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 (see ANIMAL PHARMACOLOGY). Although the relevance of this preclinical finding to humans is unknown, co-administration of EZETROL with fibrates (other than fenofibrate) is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. This increase is not considered clinically significant.

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.

Statins: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, ~~or~~ fluvastatin, or rosuvastatin.

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 EZETROL added to warfarin or fluindione. Most of these patients were also on other medications (See WARNING AND PRECAUTION).

If there is any adverse events please inform to
PT Organon Pharma Indonesia Tbk, Jakarta. Telephone : (021) 31107001; Email : dpoc.indonesia@organon.com

STORAGE

Do not store above 30°C. Store in the original package.

PRESENTATION

EZETROL, box of 3 blisters @ 10 tablets; Reg. No.: DKI0387101010A1

HARUS DENGAN RESEP DOKTER
ON DOCTOR PRESCRIPTION ONLY

Manufactured by:
MSD International GmbH (Puerto Rico Branch) LLC, Puerto Rico
Packed by:
~~Schering-Plough Labo N.V., Belgium.~~ Organon Heist bv, Belgium
Registered by:

PT Organon Pharma Indonesia Tbk

Pasuruan, Jawa Timur

PI Version 2.2

WPC-EZE-T-102009

ORGANON