Acotral Ezetimibe

Tablets

Made in Argentina - Sale under prescription

FORMULA:
Each tablet of Acotral contains: Ezetimibe 10 mg
Excipients: lactose monohydrate, sodium lauryl sulfate, sodium croscarmellose, magnesium stearate, microcrystalline cellulose, povidone, q. s.

THERAPEUTIC ACTION:
Hypocholesterolemiant.

INDICATIONS:
ACOTRAL reduces total cholesterol, LDL-C, Apo B and TG values; and increases HDL-C in patients with hypercholesterolemia. In general, maximum to almost maximum responses are achieved within 2 weeks, and they are maintained during the chronic therapy.
ACOTRAL is effective in patients with hypercholesterolemia, in men and women, young people as well as old people, administered alone or with an HMG-CoA reductase inhibitor. The experience in pediatric and adolescent patients (ages 9 to 17) has been limited to patients with Homozygous Familial Hypercholesterolemia (HoFH) or sitosterolemia.

Primary Hypercholesterolemia:
Monotherapy
Ezetimibe, administered alone is indicated as a supporting therapy to a food regime aimed at reducing elevated values of total-C, LDL-C and Apo B to patients with primary hypercholesterolemia (homozygous familial and non-familial hypercholesterolemia).
Combination Therapy with HMG-CoA Reductase Inhibitors
Ezetimibe, administered in combination with HMG-CoA reductase inhibitors is indicated as a supporting therapy to a food regime aimed at reducing elevated values of total-C, LDL-C and Apo B to patients with primary hypercholesterolemia (homozygous familial and non-familial hypercholesterolemia).
Ezetimibe, together with an ongoing HMG-CoA reductase inhibitor therapy, significantly reduced total-C, LDL-C, Apo B and TG and increased HDL-C, compared to an HMG-CoA reductase inhibitor administered alone. In general, LDL-C reductions induced by Ezetimibe were consistent with all HMG-CoA reductase inhibitors.
When those patients who received ezetimibe concurrently with an HMG-CoA reductase inhibitor were compared to those receiving the corresponding HMG-CoA reductase inhibitor alone, ezetimibe significantly reduced total-C, LDL-C, Apo B and TG, and with the exception of pravastatin, it increased HDL-C compared to those HMG-CoA reductase inhibitors administered alone. In general, LDL-C reductions induced by ezetimibe were consistent for all HMG-CoA reductase inhibitors.

Homozygous Familial Hypercholesterolemia (HoFH)
The combination of ezetimibe with atorvastatin or simvastatin is indicated for the reduction of high levels of total-C, and LDL-C in patients with HoFH, as a supporting therapy to other lipid-reducing treatments (i.e., LDL apheresis) or whenever such treatments are unavailable.
In patients with a clinical and/or genotypical HoFH diagnosis, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40 mg), the addition of ezetimibe to the treatment with atorvastatin 40 mg or simvastatin 40 mg significantly reduced LDL-C (21%), compared to the increase in the dose of simvastatin or atorvastatin in 40-80 mg monotherapy (7%). In those patients treated with ezetimibe plus atorvastatin 80 mg or with ezetimibe plus simvastatin 80 mg, LDL-C was reduced by 27%.

Homozygous Sitosterolemia
Ezetimibe is indicated as a supporting therapy to a food regime aimed at reducing elevated values of sitosterol and campesterol patients with homozygous familial sitosterolemia.
In patients with homozygous sitosterolemia with elevated values of plasma sitosterol (> 5 mg/dl) under ongoing therapeutic regimen (diet, bile acid bound resins, HMG-CoA reductase inhibitors, ileum bypass surgery and/or LDL apheresis), ezetimibe significantly reduced plasma sitosterol and campesterol, by 21% and 24%, respectively, compared to baseline values. In contrast, those patients who received placebo showed 4% and 3% increases in baseline sitosterol and campesterol respectively. In those patients treated with ezetimibe, mean phytosterol plasma levels were gradually reduced throughout the study. The effects of plasma sitosterol and campesterol reduction on the cardiovascular disease and mortality risk reduction have not been established.
Sitosterol and campesterol reductions were consistent among patients taking ezetimibe concomitantly with bile acid sequestrants and patients who were not receiving a concomitant therapy with bile acid sequestrants.
The therapy with lipid-modifying agents should be included in multiple interventions on risk factors in individuals under an increased risk of arteriosclerotic vascular disease due to hypercholesterolemia. Lipid-modifying agents must be used in addition to an appropriate diet (including a restricted intake of saturated fats and cholesterol) and when the response to such diet and other non-pharmacological measures has been inadequate.
Before starting therapy with ezetimibe, secondary causes of dyslipidemia (i.e. diabetes, hypothyroidism, obstructive hepatic disease, chronic renal insufficiency, and LDL-C increasing / HDL-C reducing drugs [progestins, anabolic steroids, and corticosteroids]) shall have to be excluded, or treated, when appropriate. A lipid profile will have to be established to estimate total-C, LDL-C, HDL-C and TG values. For TG > 400 mg/dl (>4,5 mmol/l), LDL-C concentrations shall have to be determined by ultracentrifugate.
At the time of admission into hospital due to an acute coronary event, or 24 hours post admission, lipids shall have to be measured. These values may help the physician determine whether the LDL-C reducing therapy should be initiated before releasing the patient from hospital or at the time of release.

PHARMACOLOGICAL ACTION:
Clinical studies have shown that high levels of total cholesterol (total-C), low density lipoproteins (LDL-C) and apolipoprotein B (Apo-B), the main proteinic constituent of LDL, promote human arteriosclerosis. Moreover, reduced levels of cholesterol in high-density lipoproteins (HDL-C) are associated to the development of arteriosclerosis. Epidemiological studies have determined that cardiovascular disease and mortality are directly proportional to total-C and LDL-C values and indirectly proportional to HDL-C values. Just as LDL, lipoproteins rich in enriched-cholesterol triglycerides, including very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL) and their remains, may also promote arteriosclerosis. The independent effect of the increase in HDL-C or the reduction in triglycerides (TG) on coronary, cardiovascular disease, and mortality risk has not yet been established.
Ezetimibe reduces total-C, LDL-C, Apo-B and TG and increases HDL-C in patients with hypercholesterolemia. The administration of Ezetimibe with an HMG-CoA reductase inhibitor is effective to improve plasma levels of total-C, LDL-C, Apo-B, TG and HDL-C more significantly than under separate treatments. The effects of ezetimibe administered alone or in addition to an HMG-CoA reductase inhibitor on cardiovascular disease and mortality have not yet been established.

Mechanism of action
Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol through the small intestine. In a 2-week clinical trial performed on 18 hypercholesterolemic patients, ezetimibe inhibited the intestinal absorption of cholesterol by 54% compared to placebo. Ezetimibe did not have clinically significant effects on plasma liposoluble vitamins A, D and E concentrations, and it did not impair the production of adrenocortical steroid hormones.
The cholesterol contained in the liver derives from three main sources. The liver may synthesize cholesterol, absorb the cholesterol from the lipoproteins in the blood flow or absorbit it from the cholesterol previously absorbed by the small intestine. Intestinal cholesterol mainly derives from the cholesterol secreted in the bile and from the cholesterol contained in the food intake.
Ezetimibe has a mechanism of action different from that of other cholesterol-reducing agents (i.e., HMG-CoA reductase inhibitors, bile acid sequestrants [resins], fibrates and phytostanols).
Ezetimibe does not inhibit the synthesis of cholesterol in the liver, nor does it increase bile acid excretion. Instead, ezetimibe is localized and seems to act on the brush border of the small intestine by inhibiting the absorption of cholesterol, leading to a reduction in the delivery of intestinal cholesterol into the liver. This causes a reduction in the deposits of hepatic cholesterol and an increase in the plasma cholesterol clearance; this different mechanism is complementary to that of HMG-CoA reductase inhibitors.

FARMACOKINETICS:
Absorption
Following oral administration, ezetimibe is significantly absorbed and conjugated to a phenolic glucoronide pharmacologically active (ezetimibe-glucuronide). After one single dose of Ezetimibe 10 mg, 3.4 to 5.5 ng/mL ezetimibe mean peak plasma concentrations (Cmax) were attained within 4 to 12 hours (Tmax). Ezetimibe-glucoronide 45 to 71 ng/mL mean Cmax values were attained within 1 to 2 hours (Tmax). No substantial deviation was observed in the dose proportion between 5 and 20 mg. The total bioavailability of ezetimibe cannot be determined since the compound is practically insoluble in the aqueous medium adequate for injection. Ezetimibe shows a variable bioavailability; the coefficient of variation, based on the inter-subject variability, was 35 to 60% for AUC values.
Effect of foods on oral absorption
The concomitant administration of foods (fatty or non-fatty) had no effect on the significance of ezetimibe absorption administered in the form of 10 mg tablets. The Cmax value of ezetimibe increased by 38% with the intake of fat meals. Ezetimibe may be administered with or without food.
Distribution
Ezetimibe and ezetimibe-glucuronide are strongly bound (>80%) to plasma proteins.
Metabolism and excretion
Ezetimibe is primarily metabolized in the small intestine and the liver through conjugation with glucoronide derivatives (a phase II reaction) without subsequent bile or renal excretion. A minimum oxidative metabolism has been observed (a phase I reaction) in all the assessed species.
In humans, ezetimibe is rapidly metabolized into ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the main compounds detected in plasma derived from the drug, representing 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 an approximate 22-hour mean life both for ezetimibe as well as for ezetimibe-glucuronide. Plasma concentration profiles show multiple peaks, thus suggesting enterohepatic recycling.
Following oral administration of ^{14}C- ezetimibe (20 mg) in human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) represented approximately 93% of the total plasma radioactivity. 48 hours post ezetimibe administration, there were no detectable levels of plasma radioactivity.
Approximately 78% and 11% of the radioactivity administered was eliminated through the feces and urine throughout a 10-day collection period. Ezetimibe was the main component of feces and represented 69% of the administered dose, whereas ezetimibe-glucuronide was the main component in urine and represented 9% of the administered dose.
Special populations:
Geriatric Patients
Following multiple ezetimibe doses (10 mg once a day) during 10 days, total ezetimibe plasma concentrations were twice higher in elder healthy subjects (> 65 years) than in young subjects.
Pediatric Patients
Following multiple ezetimibe doses (10 mg once a day) during 7 days, ezetimibe absorption and metabolism were similar in adolescents (10 to 18 years of age) and adults. Based on total ezetimibe values, there are no pharmacokinetic differences between adolescents and adults. There are no reported pharmacokinetic data on the pediatric population < 10 years of age.
Genre
Following multiple ezetimibe doses (10 mg once a day) during 10 days, total ezetimibe plasma concentrations were slightly higher (< 20%) in women than in men.
Hepatic insufficiency
Following a single dose of ezetimibe 10 mg, the mean area under the curve (AUC) for total ezetimibe increased approximately 1.7-fold in patients with low hepatic insufficiency (score Child-Pugh 5 a 6), compared to healthy subjects. Mean AUC values for total ezetimibe and ezetimibe increased approximately 3-4 times and 5-6 times, respectively, in patients with moderate (score Child-Pugh 7 a 9) or severe (score Child-Pugh 10 a 15) hepatic insufficiency. In a 14-day multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, mean AUC values for total ezetimibe and ezetimibe increased approximately 4 times on day 1 and day 14 compared to healthy subjects. Due to unknown effects of the higher exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ezetimibe is not recommended in these patients.

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Renal insufficiency
Following a single dose of ezetimibe 10 mg in patients with severe renal disease (mean ClCr ≤ 30 ml/min/1.73 m^2), mean AUC values for total ezetimibe, ezetimibe-glucuronide and ezetimibe increased approximately 1.5-fold, compared to healthy subjects.
Drug interactions
Ezetimibe had no significant effect on a series of test drugs (caffeine, dextrometorphane, tolbutamide, and midazolam IV) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4, respectively). This indicates that ezetimibe does not inhibit or induce these cytochrome P450 isoenzymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.
Warfarin: The concomitant administration of ezetimibe had no significant effect on warfarin bioavailability and prothrombine time.
Digoxin: The concomitant administration of ezetimibe had no significant effect on digoxin bioavailability or ECG parameters (FC, PR, QT and QTc intervals) in healthy adults.
Gemfibrozil: The concomitant administration of gemfibrozil (600 mg twice daily) significantly increased the oral bioavailability of total ezetimibe by 1.7 times. Ezetimibe (10 mg/day) did not significantly affect gemfibrozil bioavailability.
Oral Contraceptives: The concomitant administration of ezetimibe with oral contraceptives had no significant effect on ethynil estradiol or levonorgestrel bioavailability in healthy female adults.
Cimetidine: Multiple doses of cimetidine (400 mg twice daily) had no significant effect on ezetimibe and total ezetimibe bioavailability.
Antacids: The administration of a single antacid dose had no significant effect on the oral bioavailability of total ezetimibe, ezetimibe-glucuronide or ezetimibe based on AUC values. The total ezetimibe Cmax value was reduced by 30%.
Glipizide: The amounts of ezetimibe at steady state had no significant effect on the pharmacokinetics or the pharmacodynamics of glipizide. A single dose of glipizide (10 mg) had no significant effect on the exposure to total ezetimibe or ezetimibe.
HMG-CoA reductase inhibitors: In studies performed on healthy hypercholesterolemic adult subjects (LDL-C ≥ 130 mg/dl), the concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of lovastatin, simvastatin, pravastatin, atorvastatin or fluvastatin. There was no significant effect on the bioavailability of total ezetimibe or ezetimibe with lovastatin (20 mg once daily), pravastatin (20 mg once daily), atorvastatin (10 mg once daily), or fluvastatin (20 mg once daily).
Fenofibrate: In healthy hypercholesterolemic adults (LDL-C > 130 mg/dl), the concomitant administration of fenofibrate (200 mg once a day) increased the mean total ezetimibe Cmax and AUC values in approximately 64% and 48%, respectively. Fenofibrate pharmacokinetics were not significantly affected by ezetimibe (10 mg once a day).
Cholestiramine: In a study performed in forty healthy hypercholesterolemic adult subjects (LDL-C > 130 mg/dl), the concomitant administration of cholestiramine (4 g twice daily) reduced mean total ezetimibe and ezetimibe AUC values by approximately 55% and 80%, respectively.

ADMINISTRATION:
The patient will have to go into a standard cholesterol-reducing diet before receiving ezetimibe, and he/she shall have to continue with the diet during therapy with ACOTRAL.
The recommended dose of ACOTRAL is 10 mg once daily. ACOTRAL may be administered with or without food.

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ACOTRAL may be administered with an HMG-CoA reductase inhibitor to strengthen the hypolipemiant effect. The daily dose of ACOTRAL may be taken simultaneously with the HMG-CoA reductase inhibitor, according to the dose recommendations for the HMG-CoA reductase inhibitor.
Patients with hepatic insufficiency
It is not necessary to adjust the dose in patients with low hepatic insufficiency.
Patients with renal insufficiency
It is not necessary to adjust the dose in patients with renal insufficiency.
Geriatric patients
It is not necessary to adjust the dose in geriatric patients.
Co-administration with bile acid sequestrants
ACOTRAL has to be administered ≥ 2 hours before or ≥ 4 hours after the administration of a bile acid sequestrant.

CONTRAINDICATIONS:
Hypersensitivity to any ingredient included in this medication.
The combination of ezetimibe with an HMG-CoA reductase inhibitor is contraindicated in patients with active hepatic disease or persistent inexplicable serum transaminase elevations.
All HMG-CoA reductase inhibitors are contraindicated in pregnant women or nursing mothers. If ezetimibe is administered with an HMG-CoA reductase inhibitor to a woman who may potentially become pregnant, refer to pregnancy and HMG-CoA reductase inhibitors.

PRECAUTIONS:
Hepatic enzymes
In controlled-monotherapy clinical trials, the incidence of consecutive elevations (≥ 3 x the upper normal limit [ULN]) of serum transaminase was similar between ezetimibe (0.5%) and placebo (0.3%).
In controlled clinical trials of ezetimibe administration initiated concurrently with an HMG-CoA reductase inhibitor, the incidence of consecutive elevations (> 3 x ULN) of serum transaminase was 1.3% for patients treated with ezetimibe administered with HMG-CoA reductase inhibitors and 0.4% for patients treated with HMG-CoA reductase inhibitors alone. These elevations in transaminase values were generally asymptomatic, not associated with cholestasis, and they returned to baseline values after the discontinuation of the therapy or either with its continuation. If ezetimibe is coadministered with an HMG-CoA reductase inhibitor, hepatic function tests will have to be performed at the beginning of treatment and in accordance with the recommendations related to the HMG-CoA reductase inhibitor.
Skeletal muscle
No excess of myopathy or rabdomyolisis associated with ezetimibe has been observed, compared to the relevant control (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rabdomyolisis are acknowledged adverse reactions caused by HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CPK > 10 X ULN was 0.2% for ezetimibe vs 0.1% for placebo and 0.1% for ezetimibe coadministered with an HMG-CoA reductase inhibitor vs 0.4% for the HMG-CoA reductase inhibitor administered alone.
Hepatic insufficiency
Due to the unknown effects of the higher exposure to ezetimibe in patients with moderate to severe hepatic insufficiency, ezetimibe is not recommended in these patients.

Drug interactions
Cholestiramine: The concomitant administration of cholestiramine reduced ezetimibe mean AUC values by approximately 55%. The increased reduction of LDL-C due to the addition of ezetimibe to cholestiramine may be reduced through this interaction.
Fibrates: The efficacy and safety of ezetimibe administered with fibrates has not yet been established. The coadministration of ezetimibe with fibrates is not recommended until the use in patients has been studied.
Fenofibrate: The concomitant administration of fenofibrate caused an increase in total ezetimibe concentrations by approximately 1.5 times.
Gemfibrozil: The concomitant administration of gemfibrozil increased total ezetimibe concentrations by approximately 1.7 times.
HMG-CoA reductase inhibitors: No clinically significant pharmacokinetic interactions were observed when ezetimibe was coadministered with atorvastatin, simvastatin, pravastatin, lovastatin or fluvastatin.
Ciclosporine: A 12-fold ezetimibe increase was observed in a renal transplant patient who received multiple medications, including ciclosporine. Those patients receiving ezetimibe and ciclosporine together must be carefully monitored.

Pregnancy
Category C pregnancy
There are no adequate or well-controlled studies of ezetimibe in pregnant women. ACOTRAL should only be used during pregnancy if the potential benefit justifies the risk of the fetus.
All HMG-CoA reductase inhibitors are contraindicated in pregnant women or nursing mothers. If ezetimibe is administered with an HMG-CoA reductase inhibitor to a woman who may potentially become pregnant, refer to pregnancy and to the indications included in the HMG-CoA reductase inhibitor insert.
Labor and birth
The effects of ezetimibe during labor and birth remain unknown.
Nursing mothers
It is not known whether ezetimibe is excreted in human milk, therefore ACOTRAL shall not be used in nursing mothers, unless the potential benefit justifies the risk to the fetus.
Pediatric use
Ezetimibe pharmacokinetics in adolescents (ages 10 to 18) has been similar to the pharmacokinetics in adults. The treatment experience with ezetimibe in the pediatric population is limited to 4 patients (ages 9 to 17) in the sitosterolemia study and 5 patients (ages 11 to 17) in the HoFH study. It is not recommended to treat children (< 10 years of age) with ACOTRAL.
Geriatric Use
Of the patients who received ezetimibe in clinical trials, 948 were ≥ 65 (including 206 who were ≥ 75). The efficacy and safety of ezetimibe were similar between these patients and younger subjects. We cannot eliminate the possibility of a higher sensitivity experienced by older subjects.

ADVERSE REACTIONS:
The safety of ezetimibe has been evaluated in over 4700 patients in clinical trials. Clinical trials on ezetimibe (administered alone or with an HMG-CoA reductase inhibitor) have shown that ezetimibe was generally well tolerated. The overall incidence of adverse events reported with ezetimibe was similar to that reported with placebo, and the discontinuation percentage due to adverse events was also similar between ezetimibe and placebo.
Monotherapy
Adverse experiences reported in ≥ 2% of the patients treated with ezetimibe and with a higher incidence than that of placebo in placebo-controlled studies on ezetimibe, regardless of the etiology assessment were: fatigue, abdominal pain, diarrhea, viral infection, faryngitis, sinusitis, arthralgia, back pain and cough.
The frequency of less common adverse events was comparable between ezetimibe and placebo.
Combination with an HMG-CoA reductase inhibitor
The safety of ezetimibe has been assessed in combination studies in over 2000 patients.
In general, adverse experiences were similar between ezetimibe administered with HMG-CoA reductase inhibitors and HMG-CoA reductase inhibitors administered alone. However, the frequency in transaminase elevations was slightly higher in patients who received ezetimibe with an HMG-CoA reductase inhibitor than in patients treated with an HMG-CoA reductase inhibitor alone.
Adverse clinical experiences reported in ≥ 2% of patients and with a higher incidence than in placebo, regardless of the cause, in studies of ezetimibe combined with HMG-CoA reductase inhibitors were:
Chest pain, vertigo, fatigue, headache, abdominal pain, diarrhea, faryngitis, sinusitis, higher respiratory tract infection, arthralgia and back pain.
Post-marketing experience
The following adverse reactions have been reported post marketing of ezetimibe: hypersensitivity reactions, including angioedema and rash.

OVERDOSE:
No overdose cases have been reported with ezetimibe. The administration of ezetimibe 50 mg/day to 15 subjects during 14 days was generally well-tolerated. In case of an overdose, it is recommended to apply symptomatic and support measures.
In case of an overdose, please refer to the closest hospital or toxicology center.

PACKAGING:
Packs containing 20 tablets.

KEEP IN THE ORIGINAL PACKAGE IN A COLD AND DRY ENVIRONMENT, AWAY FROM LIGHT.
DO NOT EXPOSE TO TEMPERATURES OVER 30° C.
KEEP THIS AND ALL DRUGS AWAY FROM CHILDREN.

PHOENIX
Compromiso por la Salud

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Recyclable Material

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