WelChol® PACKAGE INSERT
WelChol® Tablets
(colesevelam hydrochloride)
[koe le sev´ e lam]

Rx only

DESCRIPTION

WelChol® contains colesevelam hydrochloride (hereafter referred to as colesevelam), a non-absorbed, polymeric, lipid-lowering agent intended for oral administration. Colesevelam is a high capacity bile acid binding molecule. Colesevelam is poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide. Colesevelam is hydrophilic, and insoluble in water.

WelChol is an off-white, film-coated, solid tablet containing 625 mg colesevelam. In addition, each tablet contains the following inactive ingredients: magnesium stearate, microcrystalline cellulose, silicon dioxide, HPMC (hydroxypropyl methylcellulose), and acetylated monoglyceride. The tablets are imprinted using a water-soluble black ink.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action for the lipid-lowering activity of colesevelam, the active pharmaceutical ingredient in WelChol, has been evaluated in various *in vitro* and *in vivo* studies. These studies have demonstrated that colesevelam binds bile acids, including glycocholic acid, the major bile acid in humans.

Cholesterol is the sole precursor of bile acids. During normal digestion, bile acids are secreted into the intestine. A major portion of bile acids are then absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation.

Colesevelam is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-α-hydroxylase, is upregulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effect of increasing transcription and activity of the cholesterol biosynthetic enzyme, hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase, and increasing the number of hepatic low-density lipoprotein (LDL) receptors. These compensatory effects result in increased clearance of LDL cholesterol (LDL-C) from the blood, resulting in decreased serum LDL-C levels.[1, 2] Serum triglyceride levels may increase or remain unchanged.

Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (Apo B, a protein associated with LDL-C) are associated with an increased risk of atherosclerosis in humans. Similarly,

decreased levels of high-density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis[1]. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the levels of total-C and LDL-C, and inversely with the level of HDL-C.

The combination of colesevelam and an HMG-CoA reductase inhibitor is effective in further lowering serum total-C and LDL-C levels beyond that achieved by either agent alone. The effects of colesevelam either alone or with an HMG-CoA reductase inhibitor or with a PPARα agonist on cardiovascular morbidity and mortality have not been determined.

Pharmacokinetics

Colesevelam is a hydrophilic, water-insoluble polymer that is not hydrolyzed by digestive enzymes and is not absorbed. In 16 healthy volunteers, an average of 0.05% of a single ^{14}C-labeled colesevelam dose was excreted in the urine when given following 28 days of chronic dosing of 1.9 g of colesevelam twice per day.

CLINICAL STUDIES

WelChol reduces total-C, LDL-C, Apo B and non-HDL-C, and increases HDL-C when administered either alone or in combination with an HMG-CoA reductase inhibitor in patients with primary hypercholesterolemia.

Approximately 1400 patients were studied in eight clinical trials with treatment durations ranging from 4 to 50 weeks. With the exception of one long-term study, all studies were multicenter, randomized, double-blind, and placebo-controlled. A maximum therapeutic response to WelChol was achieved within 2 weeks and was maintained during long-term therapy.

Monotherapy

In a study in patients with LDL-C between 130 and 220 mg/dL (mean 158 mg/dL), WelChol was given for 24 weeks in divided doses with the morning and evening meals. As shown in Table 1, the mean LDL-C reductions were 15% and 18% at the 3.8 g and 4.5 g doses. The respective mean total-C reductions were 7% and 10%. The mean Apo B reductions were 12% in both treatment groups. WelChol at both doses increased HDL-C by 3%. There were small increases in triglycerides (TG) at both WelChol doses that were not statistically different from placebo.

Table 1:
WelChol 24 Week Trial
% Change in Lipid Parameters From Baseline

GRAMS/DAY	N	TOTAL-C	LDL-C	APO B	HDL-C	NON-HDL-C	TG
Placebo	88	+1	0	0	–1	+1	+5
3.8 g (6 tablets)	95	–7*	–15*	–12*	+3*	–10*	+10
4.5 g (7 tablets)	94	–10*	–18*	–12*	+3	–13*	+9

*p<0.05 for lipid parameters compared to placebo, for Apo B compared to baseline
LDL-C, total-C, and Apo B are mean values; HDL-C and TG are median values.

In a study in 98 patients with LDL-C between 145 and 250 mg/dL (mean 169 mg/dL), WelChol 3.8 g was given for 6 weeks as a single dose with breakfast, a single dose with dinner, or as divided doses with breakfast and dinner. The mean LDL-C reductions were 18%, 15%, and 18% for the three dosing regimens, respectively. The reductions with these three regimens were not statistically different from one another.

Combination Therapy
Co-administration of WelChol and an HMG-CoA reductase inhibitor (atorvastatin, lovastatin or simvastatin) demonstrated an additive reduction of LDL-C in three clinical studies. As demonstrated in Table 2, WelChol doses of 2.3 g to 3.8 g resulted in additional 8% to 16% reductions in LDL-C above that seen with the HMG-CoA reductase inhibitor alone.

Table 2:
WelChol in Combination with Atorvastatin, Simvastatin, and Lovastatin
% Change in Lipid Parameters

DOSE/DAY	N	TOTAL-C	LDL-C	APO B	HDL-C	NON-HDL-C	TG
Atorvastatin Trial (4-week)							
Placebo	19	+4	+3	–3	+4	+4	+10
Atorvastatin 10 mg	18	–27*	–38*	–32*	+8	–35*	–24*
WelChol 3.8 g/ Atorvastatin 10 mg	18	–31*	–48*	–38*	+11	–40*	–1
Atorvastatin 80 mg	20	–39*	–53*	–46*	+6	–50*	–33*
Simvastatin Trial (6-week)							
Placebo	33	–2	–4	–4*	–3	–2	+6
Simvastatin 10 mg	35	–19*	–26*	–20*	+3*	–24*	–17*
WelChol 3.8 g/ Simvastatin 10 mg	34	–28*	–42*	–33*	+10*	–37*	–12*
Simvastatin 20 mg	39	–23*	–34*	–26*	+7*	–30*	–12*
WelChol 2.3 g/ Simvastatin 20 mg	37	–29*	–42*	–32*	+4*	–37*	–12*
Lovastatin Trial (4-week)							
Placebo	26	+1	0	0	+1	+1	+1
Lovastatin 10 mg	26	–14*	–22*	–16*	+5	–19*	0
WelChol 2.3 g/ Lovastatin 10 mg together	27	–21*	–34*	–24*	+4	–27*	–1
WelChol 2.3 g/ Lovastatin 10 mg apart	23	–21*	–32*	–24*	+2	–28*	–2

*$p<0.05$ for lipid parameters compared to placebo, for Apo B compared to baseline
LDL-C, total-C and Apo B are mean values; HDL-C and TG are median values.

In all three studies, the LDL-C reduction achieved with the combination of WelChol and any given dose of HMG-CoA reductase inhibitor therapy was statistically superior to that achieved with WelChol or that dose of the HMG-CoA reductase inhibitor alone.

The LDL-C reduction with atorvastatin 80 mg was not statistically significantly different from the combination of WelChol 3.8 g and atorvastatin 10 mg.

The effect of WelChol when added to fenofibrate was assessed in 122 patients with mixed hyperlipidemia (Fredrickson Type IIb). Inclusion in the study required LDL-C ≥115 mg/dL and TG 150 to 749 mg/dL. Patients were treated with 160 mg of fenofibrate during the 8-week open-label period and then randomly assigned to receive fenofibrate 160 mg plus either WelChol 3.8 g or placebo for 6 weeks of double-blind treatment. The overall mean LDL-C at the start of randomized treatment was 144 mg/dL. The results of the study are summarized in Table 3.

TABLE 3
Response to WelChol Added to Fenofibrate in Patients with Mixed Hyperlipidemia
(Mean % Change from Treated Baseline[b] at 6 weeks)

Treatment	N	Total-C	LDL-C	APO B	HDL-C	Non-HDL-C	TG[a]
Placebo + Fenofibrate 160 mg	61	+2	+2	+1	-1	+2	-3
WelChol + Fenofibrate 160 mg	61	-6*	-10*	-7*	0	-8*	+6

*p≤0.0002 compared to placebo
[a]For triglycerides, median % change from baseline
[b]Treated Baseline: following 8-week treatment with open-label fenofibrate 160 mg

INDICATIONS AND USAGE

WelChol, administered alone or in combination with an HMG-CoA reductase inhibitor is indicated as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia (Fredrickson Type IIa).

Therapy with lipid lowering agents should be a component of multiple risk-factor intervention in patients at significant increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid altering agents should be used in addition to a diet restricted in saturated fat and cholesterol and when the response to diet and other non-pharmacological means has been inadequate.

Prior to initiating therapy with WelChol, secondary causes of hypercholesterolemia (i.e., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile obtained to assess total-C, HDL-C, and TG. For

individuals with TG less than 400 mg/dL, LDL-C can be estimated using the following equation:[3]

LDL-C = Total-C – [(TG/5) + HDL-C]

Periodic determination of serum cholesterol levels in patients as outlined in the National Cholesterol Education Program (NCEP) guidelines should be done to confirm a favorable initial and long-term response. The NCEP treatment guidelines are presented in Table 4.

Table 4
NCEP Guidelines

RISK CATEGORY	LDL-C GOAL	LDL LEVEL AT WHICH TO INITIATE THERAPEUTIC LIFESTYLE CHANGES (TLC)	LDL LEVEL AT WHICH TO CONSIDER DRUG THERAPY
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL
			10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* Some authorities recommend use of LDL cholesterol-lowering drugs in the category if LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL cholesterol e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
† Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals*

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on anti-hypertensive medication)
- Low HDL cholesterol (<40 mg/dL) †
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)

* In ATP III, diabetes is regarded as a CHD risk equivalent.
† HDL cholesterol ≥60 mg/dL counts as a “negative” risk factor; its presence removes one risk factor from the total count.

After the LDL-C goal has been achieved, if the TG is still ≥200mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

WelChol is contraindicated in individuals with bowel obstruction and in individuals who have shown hypersensitivity to any of the components of WelChol.

PRECAUTIONS

General

Patients with TG levels greater than 300 mg/dL were excluded from most WelChol clinical trials. Caution should be exercised when treating patients with TG levels greater than 300 mg/dL as bile acid sequestrants can increase TG levels.

In non-clinical safety studies, rats administered colesevelam at doses greater than 30-fold the projected human clinical dose experienced hemorrhage from vitamin K deficiency. WelChol did not induce any clinically significant reduction in the absorption of vitamins A, D, E or K during clinical trials of up to one year. However, caution should be exercised when treating patients with a susceptibility to vitamin K or fat soluble vitamin deficiencies.

The safety and efficacy of WelChol in patients with dysphagia, swallowing disorders, severe gastrointestinal motility disorders or major gastrointestinal tract surgery have not been established. Consequently, caution should be exercised when WelChol is used in patients with these gastrointestinal disorders.

Information for Patients

WelChol may be taken once per day with a meal or taken twice per day in divided doses with meals. Patients should be directed to take WelChol with a liquid and a meal, and adhere to their NCEP-recommended diet. Patients should tell their physicians if they are pregnant, are intending to become pregnant or are breastfeeding.

Laboratory Tests

Serum total-C, LDL-C and TG levels should be determined periodically based on NCEP guidelines to confirm favorable initial and adequate long-term responses.

Drug Interactions

WelChol has been studied in several human drug interaction studies in which it was administered with a meal and the test drug. WelChol was found to have no significant effect on the bioavailability of digoxin, fenofibrate, lovastatin, metoprolol, quinidine, valproic acid, and warfarin. WelChol decreased the C_{max} and AUC of sustained-release verapamil by approximately 31% and 11%, respectively. Since there is a high degree of variability in the bioavailability of verapamil, the clinical significance of this finding is unclear. In clinical studies, co-administration of WelChol with atorvastatin, lovastatin or simvastatin did not interfere with the lipid-lowering activity of the HMG-CoA reductase inhibitor. Other drugs have not been studied. When administering a drug with a narrow therapeutic index or margin of safety that has not been evaluated in formal drug-drug interaction studies (see aforementioned list of drugs), the drug should be administered at least one hour

before or four hours after WelChol, or the physician should consider monitoring blood levels of the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
A 104-week carcinogenicity study with colesevelam (WelChol) was conducted in CD-1 mice, at oral dietary doses up to 3 g/kg/day. This dose was approximately 50 times the maximum recommended human dose of 4.5 g/day, based on body weight, mg/kg. There were no significant drug-induced tumor findings in male or female mice. In a 104-week carcinogenicity study with colesevelam (WelChol) in Harlan Sprague-Dawley rats, a statistically significant increase in the incidence of pancreatic acinar cell adenoma was seen in male rats at doses >1.2 g/kg/day (approximately 20 times the maximum human dose, based on body weight, mg/kg) (trend test only). A statistically significant increase in thyroid C-cell adenoma was seen in female rats at 2.4 g/kg/day (approximately 40 times the maximum human dose, based on body weight, mg/kg).

Mutagenesis
Colesevelam and four degradants present in the drug substance have been evaluated for mutagenicity in the Ames test and a mammalian chromosomal aberration test. The four degradants and an extract of the parent compound did not exhibit genetic toxicity in an *in vitro* bacterial mutagenesis assay in *S. typhimurium* and *E. coli* (Ames assay) with or without rat liver metabolic activation. An extract of the parent compound was positive in the Chinese Hamster Ovary (CHO) cell chromosomal aberration assay in the presence of metabolic activation and negative in the absence of metabolic activation. The results of the CHO cell chromosomal aberration assay with two of the four degradants, decylamine HCl and aminohexyltrimethyl ammonium chloride HCl, were equivocal in the absence of metabolic activation and negative in the presence of metabolic activation. The other two degradants, didecylamine HCl and 6-decylamino-hexyltrimethyl ammonium chloride HCl, were negative in the presence and absence of metabolic activation.

Impairment of Fertility
Colesevelam did not impair fertility in rats at doses of up to 3 g/kg/day (approximately 50 times the maximum human dose, based on body weight, mg/kg).

Pregnancy

Pregnancy: Category B
Reproduction studies have been performed in rats and rabbits at doses up to 3 g/kg/day and 1 g/kg/day, respectively (approximately 50 and 17 times the maximum human dose, based on body weight, mg/kg) and have revealed no evidence of harm to the fetus due to colesevelam. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Requirements for vitamins and other nutrients are increased

in pregnancy. The effect of WelChol on the absorption of vitamins has not been studied in pregnant women.

Pediatric Use
The safety and efficacy of colesevelam (WelChol) have not been established in pediatric patients.

Geriatric Use
There is no evidence for special considerations when colesevelam (WelChol) is administered to elderly patients.

ADVERSE REACTIONS

WelChol treatment-emergent adverse events that occurred in greater than 2% of patients in an integrated safety analysis are presented in Table 5.

Table 5:
Frequent (>2%) Treatment-Emergent Adverse Events
By Treatment Category

BODY SYSTEM/ ADVERSE EVENT	Placebo (N=258) %	WelChol only (N=807) %
Body as a Whole		
Infection	13	10
Headache	8	6
Pain	7	5
Back Pain	6	3
Abdominal Pain	5	5
Flu Syndrome	3	3
Accidental Injury	3	4
Asthenia	2	4
Digestive System		
Flatulence	14	12
Constipation	7	11
Diarrhea	7	5
Nausea	4	4
Dyspepsia	3	8
Respiratory System		
Sinusitis	4	2
Rhinitis	3	3
Cough Increased	2	2
Pharyngitis	2	3
Musculoskeletal System		
Myalgia	0	2

Post Marketing Adverse Events

There have been rare reports of elevated thyroid stimulating hormone (TSH) levels in patients who have received WelChol co-administered with thyroid hormone replacement therapy.

OVERDOSAGE

Because WelChol is not absorbed, the risk of systemic toxicity is low. Doses in excess of 4.5 g per day have not been tested.

DOSAGE AND ADMINISTRATION

Monotherapy

The recommended starting dose of WelChol is 3 tablets taken twice per day with meals or 6 tablets once per day with a meal. The WelChol dose can be increased to 7 tablets, depending upon the desired therapeutic effect. WelChol should be taken with a liquid.

Combination Therapy

WelChol, at doses of 4 to 6 tablets per day, has been shown to be safe and effective when dosed at the same time (i.e., co-administered) as an HMG-CoA reductase inhibitor or when the two drugs are dosed apart [(see CLINICAL PHARMACOLOGY, **CLINICAL STUDIES**)]. WelChol should be taken with a liquid. For maximal therapeutic effect in combination with an HMG-CoA reductase inhibitor, the recommended dose of WelChol is 3 tablets taken twice per day with meals or 6 tablets taken once per day with a meal.

HOW SUPPLIED

WelChol (colesevelam hydrochloride), 625 mg, is supplied as an off-white, solid tablet imprinted with the word “Sankyo” over “C01”.

WelChol Tablets are available as follows:

Bottles of 180—NDC 65597-701-18

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Brief exposure to 40°C does not adversely affect the product. Protect from moisture.

REFERENCES

1. Grundy SM, Ahrens EH, Salen G. Interruption of the enterohepatic circulation of bile acids in man: comparative effects of cholestyramine and ileal exclusion on cholesterol metabolism. J Lab Clin Med 1971; 78: 94-121.
2. Shepherd J, Packard CJ, Bicker S, Veitch LTD, Gemmell MH. Cholestyramine promotes receptor-mediated low-density-lipoprotein catabolism. N Engl J Med 1980; 302: 1219-22.

3. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of LDL cholesterol in plasma without use of a preparative ultracentrifuge. Clin. Chem. 1972; 18(6): 499.

Manufactured for: Daiichi Sankyo, Inc.
Parsippany, New Jersey 07054

by: Patheon Inc.
Toronto, Ontario M3B, 1Y5

Active Ingredient: Product of Austria

Licensed from: Genzyme Corporation

P180020X

Month/Year