

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cholestagel 625 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 625 mg colesevelam (as hydrochloride).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Off-white, capsule-shaped film-coated tablets imprinted with “Cholestagel” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cholestagel co-administered with a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) is indicated as adjunctive therapy to diet to provide an additive reduction in low-density lipoprotein cholesterol (LDL-C) levels in adult patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone.

Cholestagel as monotherapy is indicated as adjunctive therapy to diet for reduction of elevated total-cholesterol and LDL-C in adult patients with isolated primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well tolerated.

4.2 Posology and method of administration

Posology

Combination therapy

The recommended dose of Cholestagel is 4 to 6 tablets per day. The maximum recommended dose is 3 tablets taken twice per day with meals or 6 tablets taken once per day with a meal. Clinical trials have shown that Cholestagel and atorvastatin, lovastatin or simvastatin can be co-administered or dosed apart.

Monotherapy

The recommended starting dose of Cholestagel is 3 tablets taken twice per day with meals or 6 tablets once per day with a meal. The maximum recommended dose is 7 tablets per day.

During therapy, the cholesterol-lowering diet should be continued, and serum total-C, LDL-C and triglyceride levels should be determined periodically during treatment to confirm favourable initial and adequate long-term responses.

When a drug interaction cannot be excluded with a concomitant medicinal product, Cholestagel should be administered at least four hours after the concomitant medication in order to minimize the risk of reduced absorption of the concomitant medication (see section 4.5).

Elderly population

There is no need for dose adjustment when Cholestagel is administered to elderly patients.

Paediatric population

The safety and efficacy of Cholestagel have not been established in children and adolescent patients; therefore, the use of Cholestagel in these patient populations is not recommended.

Method of administration

Cholestagel tablets should be taken orally with a meal and liquid.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Bowel or biliary obstruction

4.4 Special warnings and special precautions for use

Prior to initiating therapy with Cholestagel, if secondary causes of hypercholesterolaemia (i.e., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease) are considered, these should be diagnosed and properly treated.

For patients on ciclosporin starting or stopping Cholestagel or patients on Cholestagel with a need to start ciclosporin: Cholestagel reduces the bioavailability of ciclosporin (see also section 4.5). Patients starting on ciclosporin already taking Cholestagel should have their ciclosporin blood concentrations monitored as normal and their dose adjusted as normal. Patients starting on Cholestagel already taking ciclosporin should have their blood concentrations monitored prior to combination therapy and frequently monitored immediately starting co-therapy with the ciclosporin dose adjusted accordingly. It should be noted that stopping Cholestagel therapy will result in increased ciclosporin blood concentrations. Therefore, patients taking both ciclosporin and Cholestagel should have their blood concentrations monitored prior to and frequently after when Cholestagel therapy is stopped with their ciclosporin dose adjusted accordingly.

Caution should be exercised when treating patients with triglyceride levels greater than 3.4 mmol/L due to the triglyceride increasing effect with Cholestagel. Safety and efficacy are not established for patients with triglyceride levels greater than 3.4 mmol/L, since such patients were excluded from the clinical studies.

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

Cholestagel can induce or worsen present constipation. The risk of constipation should especially be considered in patients with coronary heart disease and angina pectoris.

Anticoagulant therapy should be monitored closely in patients receiving warfarin or similar agents, since bile acid sequestrants, like Cholestagel, have been shown to reduce absorption of vitamin K and therefore interfere with warfarin's anticoagulant effect (see also section 4.5).

Cholestagel can affect the bioavailability of the oral contraceptive pill when administered simultaneously. It is important to ensure that Cholestagel is administered at least 4 hours after the oral contraceptive pill to minimise the risk of any interaction (see also section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

In general

Cholestagel may affect the bioavailability of other medicinal products. Therefore when a drug interaction cannot be excluded with a concomitant medicinal product, Cholestagel should be

administered at least four hours after the concomitant medication to minimize the risk of reduced absorption of the concomitant medication

When administering medicinal products for which alterations in blood levels could have a clinically significant effect on safety or efficacy, physicians should consider monitoring serum levels or effects.

Interaction studies have only been performed in adults.

In interaction studies in healthy volunteers, Cholestagel had no effect on the bioavailability of digoxin, metoprolol, quinidine, valproic acid, and warfarin. Cholestagel 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.

There have been very rare reports of reduced phenytoin levels in patients who have received Cholestagel administered with phenytoin.

Anticoagulant therapy

Anticoagulant therapy should be monitored closely in patients receiving warfarin or similar agents, since bile acid sequestrants have been shown to reduce absorption of vitamin K and therefore interfere with warfarin's anticoagulant effect. Specific clinical interaction studies with colesevelam and vitamin K have not been performed.

Levothyroxine

In an interaction study in healthy volunteers, Cholestagel reduced the AUC and C_{\max} of levothyroxine when administered either concomitantly or after 1 hour. No interaction was observed when Cholestagel was administered at least four hours after levothyroxine.

Oral contraceptive pill

In an interaction study in healthy volunteers, Cholestagel reduced the C_{\max} of norethindrone as well as the AUC and C_{\max} of ethinylestradiol when administered simultaneously with the oral contraceptive pill. This interaction was also observed when Cholestagel was administered one hour after the oral contraceptive pill. However no interaction was observed when Cholestagel was administered four hours after the oral contraceptive pill.

Ciclosporin

In an interaction study in healthy volunteers, co-administration of Cholestagel and ciclosporin significantly reduced the $AUC_{0-\infty}$ and C_{\max} of ciclosporin by 34% by 44%, respectively. Therefore advice is given to closely monitor ciclosporin blood concentrations (see also section 4.4). In addition, based on theoretical grounds Cholestagel should be administered at least 4 hours after ciclosporin in order to further minimise the risks related to the concomitant administration of ciclosporin and Cholestagel. Furthermore, Cholestagel should always be administered at the same times consistently since the timing of intake of Cholestagel and ciclosporin could theoretically influence the degree of reduced bioavailability of ciclosporin.

Statins

When Cholestagel was co-administered with statins in clinical studies, an expected add-on LDL-C lowering effect was observed, and no unexpected effects were observed. Interaction studies with colesevelam in combination with pravastatin, rosuvastatin, or high dose HMG-CoA reductase inhibitors have not been performed.

Antidiabetic agents

Co-administration of Cholestagel and glyburide (also known as glibenclamide) caused a decrease in the $AUC_{0-\infty}$ and C_{\max} of glyburide by 32% and 47%, respectively. No interaction was observed when Cholestagel was administered four hours after glyburide.

Co-administration of Cholestagel and repaglinide had no effect on the AUC and caused a 19% reduction in the C_{max} of repaglinide, the clinical significance of which is unknown. No interaction was observed when Cholestagel was administered one hour after repaglinide.

No interaction was observed when Cholestagel and pioglitazone were administered simultaneously in healthy volunteers

Other forms of interaction

Cholestagel did not induce any clinically significant reduction in the absorption of vitamins A, D, E or K during clinical studies of up to one year. However, caution should be exercised when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies, such as patients with malabsorption. In these patients, monitoring vitamin A, D and E levels and assessing vitamin K status through the measurement of coagulation parameters is recommended and the vitamins should be supplemented if necessary.

4.6 Pregnancy and lactation

Pregnancy

No clinical data are available on the use of Cholestagel in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Lactation

The safety of Cholestagel has not been established in breast-feeding women. Caution should be exercised when prescribing to breast-feeding women.

4.7 Effects on ability to drive and use machines

Cholestagel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In controlled clinical studies involving approximately 1400 patients, the following adverse reactions were reported in patients given Cholestagel. The reporting rate is classified as very common ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1,000, < 1/100$), rare ($\geq 1/10,000, < 1/1,000$), very rare ($< 1/10,000$), including isolated.

Investigations
<i>Common:</i> Serum triglycerides increased
<i>Uncommon :</i> Serum transaminase increased
Nervous system disorders
<i>Common:</i> Headache
Gastrointestinal disorders
<i>Very common:</i> Flatulence, constipation
<i>Common:</i> Vomiting, diarrhoea, dyspepsia, , abdominal pain, abnormal stools, nausea
Musculoskeletal and connective tissue disorders
<i>Uncommon:</i> Myalgia

The background incidence of flatulence and diarrhoea were higher in patients receiving placebo in the same controlled clinical studies. Only constipation and dyspepsia were reported by a higher percentage among those receiving Cholestagel, compared with placebo.

Adverse reactions were generally mild or moderate in intensity.

Cholestagel in combination with statins did not result in any frequent unexpected adverse reactions compared with statins alone.

4.9 Overdose

Since Cholestagel is not absorbed, the risk of systemic toxicity is low. Gastrointestinal symptoms could occur. Doses in excess of the maximum recommended dose (4.5 g per day (7 tablets)) have not been tested.

Should overdosage occur, however, the chief potential harm would be obstruction of the gastrointestinal tract. The location of such potential obstruction, the degree of obstruction and the presence or absence of normal gut motility would determine treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: bile acid sequestrants, ATC code: C10A C 04

The mechanism of action for the activity of colestevlam, the active substance in Cholestagel, has been evaluated in several *in vitro* and *in vivo* studies. These studies have demonstrated that colestevlam 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 is then absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation.

Colestevlam is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. The LDL-C lowering mechanism of bile acid sequestrants has been previously established as follows: 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 effects 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 receptors. A concomitant increase in very low density lipoprotein synthesis can occur. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels.

In a 6-month dose-response study in patients with primary hypercholesterolaemia receiving 3.8 or 4.5 g Cholestagel, a 15 to 18% decrease in LDL-C levels was observed, which was evident within 2 weeks of administration. In addition, total-C decreased 7 to 10%, HDL-C increased 3% and triglycerides increased 9 to 10%. Apo B decreased by 12%. In comparison, in patients given placebo, LDL-C, total-C, HDL-C and apo-B were unchanged, while triglycerides increased 5%. Studies examining administration of Cholestagel as a single dose with breakfast, a single dose with dinner, or as divided doses with breakfast and dinner did not show significant differences in LDL-C reduction for different dosing schedules. However, in one study triglycerides tended to increase more when Cholestagel was given as a single dose with breakfast. Multi-centre, randomised, double-blind, placebo-controlled studies in 487 patients demonstrated an additive reduction of 8 to 16% in LDL-C when 2.3 to 3.8 g Cholestagel and a statin (atorvastatin, lovastatin or simvastatin) were administered at the same time. Initiation of add-on treatment with Cholestagel subsequent to statin therapy has not been specifically studied. Cholestagel has not been compared directly to other bile acid sequestrants in clinical trials.

In a 6 week study 129 patients with mixed hyperlipidaemia were randomised to fenofibrate 160 mg plus 3.8 g Cholestagel or fenofibrate alone. The fenofibrate plus Cholestagel group (64 patients)

demonstrated a 10% reduction on LDL-C levels versus 2% increase for the fenofibrate group (65 patients). Reductions were also seen for non-HDL-C, Total-C and Apo B. A small 5%, non-significant increase in triglycerides was noted. The effects of combination of fenofibrate and Cholestagel on the risks of myopathy or hepatotoxicity are not known.

So far, no studies have been conducted that directly demonstrate whether treatment with Cholestagel as monotherapy or combination therapy has any effect on cardiovascular morbidity or mortality.

5.2 Pharmacokinetic properties

Cholestagel is not absorbed from the gastrointestinal tract.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose (E460), microcrystalline
Silica, colloidal anhydrous
Magnesium stearate
Water, purified

Film-coating:

Hypromellose (E464)
Diacetylated monoglycerides

Printing ink:

Iron oxide black (E172)
Hypromellose (E464)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene bottles with a polypropylene cap.
Package sizes are: 24 tablets (1 X 24)
100 tablets (2 X 50)
180 tablets (1 X 180)

High density polyethylene bottles with a polypropylene cap without outer carton.
Package sizes are: 180 tablets (1 X 180)

Not all pack sizes may be marketed.

6.6 Instructions precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V., Gooimeer 10, NL-1411 DD Naarden, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/268/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 March 2004/12 March 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>