

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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Off-white, capsule-shaped film-coated tablets imprinted with "C625" 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 primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well-tolerated.

Cholestagel can also be used in combination with ezetimibe, with or without a statin, in adult patients with primary hypercholesterolaemia, including patients with familial hypercholesterolaemia (see section 5.1).

4.2 Posology and method of administration

Posology

Combination therapy

The recommended dose of Cholestagel for combination with a statin with or without ezetimibe is 4 to 6 tablets per day. The maximum recommended dose is 6 tablets per day taken as 3 tablets twice per day with meals or 6 tablets taken once per day with a meal. Clinical trials have shown that Cholestagel and statins can be co-administered or dosed apart, and that Cholestagel and ezetimibe can be co-administered or dosed apart.

Monotherapy

The recommended starting dose of Cholestagel is 6 tablets per day taken as 3 tablets 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 for which minor variations in the therapeutic level would be clinically important, or where no clinical data are available on co-administration, Cholestagel should be administered at least four hours before or 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 in children aged 0 to 17 years have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

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

The tablets should be swallowed whole and not broken, crushed or chewed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Bowel or biliary obstruction

4.4 Special warnings and special precautions for use

Secondary causes of hypercholesterolaemia

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.

Interaction with ciclosporin

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.

Effects on triglyceride levels

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.

Constipation

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

Anticoagulants

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).

Oral contraceptives

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 for which minor variations in the therapeutic level would be clinically important, Cholestagel should be administered at least four hours before or at least four hours after the concomitant medication to minimize the risk of reduced absorption of the concomitant medication. For concomitant medications which require administration via divided doses, it should be noted that the required dose of Cholestagel can be taken once a day.

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.

Co-administration of colesevelam and olmesartan decreases the exposure of olmesartan. Olmesartan should be administered at least 4 hours prior to colesevelam.

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, like Cholestagel, 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-inf} 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. Cholestagel had no effect on the bioavailability of lovastatin in an interaction study.

Antidiabetic agents

Co-administration of colesevelam and metformin extended-release (ER) tablets increases the exposure of metformin. Patients receiving concomitant metformin ER and colesevelam should be monitored for clinical response as is usual for the use of anti-diabetes drugs.

Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastrointestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam. Therefore glimepiride should be administered at least 4 hours prior to colesevelam.

Co-administration of colesevelam and glipizide decreases the exposure of glipizide. Glipizide should be administered at least 4 hours prior to colesevelam.

Co-administration of Cholestagel and glyburide (also known as glibenclamide) caused a decrease in the AUC_{0-inf} 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

Ursodeoxycholic acid

Cholestagel predominantly binds hydrophobic bile acids. In a clinical study Cholestagel did not affect the faecal excretion of endogenous (hydrophilic) ursodeoxycholic acid. However, formal interaction studies with ursodeoxycholic acid have not been performed. As noted in general, when a drug interaction cannot be excluded with a concomitant medicinal product, Cholestagel should be administered at least four hours before or at least four hours after the concomitant medication to minimise the risk of reduced absorption of the concomitant medication. Monitoring of the clinical effects of treatment with ursodeoxycholic acid should be considered.

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 Fertility, 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.

Breast-feeding

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

Fertility

There are no data on the effect of Cholestagel on fertility in humans. A study conducted in rats did not result in any differences in reproductive parameters between the groups that might imply reproductive effects attributable to colesevelam.

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

Summary of the safety profile

The most frequently occurring adverse reactions are flatulence and constipation, found within the gastrointestinal disorders system organ class.

Tabulated list of adverse reactions

In controlled clinical studies involving approximately 1400 patients and during post-approval use, the following adverse reactions were reported in patients given Cholestagel.

The reporting rate is classified as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

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, abdominal distension
<i>Uncommon:</i> Dysphagia
<i>Very rare:</i> Pancreatitis
<i>Not known:</i> Intestinal obstruction*,**
Musculoskeletal and connective tissue disorders
<i>Uncommon:</i> Myalgia
Investigations
<i>Common:</i> Serum triglycerides increased
<i>Uncommon:</i> Serum transaminases increased

* see section below for further information

** adverse reactions from post-marketing experience

Description of selected adverse events

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.

The incidence of intestinal obstruction is likely to be increased among patients with a history of bowel obstruction or removal.

Cholestagel in combination with statins and in combination with ezetimibe was well tolerated and the adverse reactions observed were consistent with the known safety profile of statins or ezetimibe alone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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: Lipid modifying agent, bile acid sequestrants, ATC code: C10A C 04

Mechanism of action

The mechanism of action for the activity of colesevelam, the active substance in Cholestagel, has been evaluated in several *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 is 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. 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 daily, 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.

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.

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.

The effect of 3.8 g Cholestagel plus 10 mg ezetimibe versus 10 mg ezetimibe alone on LDL-C levels was assessed in a multicentre, randomised, double-blind, placebo-controlled, parallel-group study in 86 patients with primary hypercholesterolaemia over a 6-week treatment period. The combination of ezetimibe 10 mg and Cholestagel 3.8 g daily therapy in the absence of a statin resulted in a significant combined effect for LDL-C lowering by 32% demonstrating an additional effect of 11% LDL-C lowering with Cholestagel and ezetimibe compared to ezetimibe alone.

The addition of Cholestagel 3.8 g daily to maximally-tolerated statin and ezetimibe therapy was assessed in a multi-centre, randomised, double-blind, placebo-controlled study in 86 patients with familial hypercholesterolaemia. A total of 85% of the patients were on either atorvastatin (50% of whom received 80 mg dose) or rosuvastatin (72% of whom received 40 mg dose). Cholestagel resulted in a statistically significant LDL-C reduction of 11% and 11% at 6 and 12 weeks vs an increase of 7% and 1% in the placebo group; mean baseline levels were 3.75 mmol/L and 3.86 mmol/L, respectively. Triglycerides in the Cholestagel group increased by 19% and 13% at 6 and 12 weeks vs an increase of 6% and 13% in the placebo group, but the increases were not significantly different. HDL-C and hsCRP levels were also not significantly different compared to placebo at 12 weeks.

Paediatric population

In the paediatric population, the safety and efficacy of 1.9 or 3.8 g/day Cholestagel was assessed in an 8 week multi-centre, randomised, double-blind, placebo-controlled study in 194 boys and postmenarchal girls, aged 10-17 years, with heterozygous FH on a stable dose of statins (47 patients, 24%) or treatment-naïve to lipid-lowering therapy (147 patients, 76%). For all patients, Cholestagel resulted in a statistically significant LDL-C reduction of 11% at 3.8 g/day and 4% at 1.9 g/day, versus a 3% increase in the placebo group. For statin-naïve patients on monotherapy, Cholestagel resulted in a statistically significant LDL-C reduction of 12% at 3.8 g/day and 7% at 1.9 g/day, versus a 1% reduction in the placebo group (see section 4.2). There were no significant effects on growth, sexual maturation, fat-soluble vitamin levels or clotting factors, and the adverse reaction profile for Cholestagel was comparable to that seen with placebo.

Cholestagel has not been compared directly to other bile acid sequestrants in clinical trials.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Arzneimittel GmbH

Ziegelhof 24

17489 Greifswald

Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/268/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 March 2004

Date of latest renewal: 30 March 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Genzyme Ireland Ltd., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

B CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached..

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL (24, 100 AND 180 TABLETS) WITH CARTON BOTTLE LABEL (180 TABLETS) WITHOUT CARTON

1. NAME OF THE MEDICINAL PRODUCT

Cholestagel 625 mg film-coated tablets
Colesevelam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 625 mg of colesevelam (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

24 film-coated tablets
100 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Tablets should be taken with liquid and with a meal.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 24
17489 Greifswald
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/268/001	24 tablets
EU/1/03/268/002	100 tablets
EU/1/03/268/003	180 tablets with carton
EU/1/03/268/004	180 tablets without carton

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cholestagel
625 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Cholestagel 625 mg film-coated tablets Colesevelam

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Cholestagel is and what it is used for
2. What you need to know before you take Cholestagel
3. How to take Cholestagel
4. Possible side effects
5. How to store Cholestagel
6. Contents of the pack and other information

1. What Cholestagel is and what it is used for

Cholestagel contains the active substance colesevelam (as hydrochloride). Taking Cholestagel helps to lower the level of cholesterol in your blood. Your doctor should only give you Cholestagel if a diet low in fat and cholesterol did not work well enough on its own.

Cholestagel works in your intestinal system by binding bile acids produced by your liver and carrying the bile acids out of your body with your faeces. This prevents your body from recycling the bile acids from your intestines in the usual way. Without the recycling process, your liver has to make additional bile acids. Your liver uses cholesterol from your blood to do this, which lowers the level of cholesterol in your blood.

Cholestagel is prescribed to treat a condition known as primary hypercholesterolaemia (when cholesterol in the blood is elevated) in adults.

- Cholestagel may be prescribed on its own in addition to a diet low in fat and cholesterol when treatment with a statin (a class of cholesterol-lowering medicines that work in the liver) is inappropriate or not well tolerated.
- Cholestagel may be used together with a statin and the diet low in fat and cholesterol when patients are not appropriately controlled by the statin on its own.
- Cholestagel may also be used together with ezetimibe (a cholesterol-lowering medicine that works by reducing cholesterol absorption from the gut), with or without a statin.

2. What you need to know before you take Cholestagel

Do not take Cholestagel:

- if you are allergic to colesevelam or to any of the other ingredients of this medicine (listed in section 6)
- if you have a blockage in your intestines or bile ducts (tubes that carry bile)

If you are prescribed Cholestagel and any other medicine together you must also read the patient information leaflet that comes with that particular medicine before you start to take your medicine.

Warnings and precautions

Talk to your doctor or pharmacist before taking Cholestagel

- if your triglyceride levels (a blood fat) are greater than 3.4 mmol/L
- if you have difficulty in swallowing, or have a major stomach or intestinal disorder
- if you suffer from constipation, as Cholestagel may induce or worsen this condition. This is especially important for patients with coronary heart disease and angina pectoris.

If you think any of these apply to you, you should inform your doctor or pharmacist before taking Cholestagel.

Before starting therapy with Cholestagel, your physician should make sure that certain conditions do not contribute to your elevated cholesterol levels. These could include poorly controlled diabetes, untreated hypothyroidism (low levels of thyroid hormone for which no treatment is being given currently), proteins in urine (nephrotic syndrome), altered protein levels in the blood (dysproteinemias), and blockage of the bile transport to your gall bladder (obstructive liver disease).

Children and adolescents

The safety and efficacy in children (below the age of 18 years) has not been studied. Therefore, Cholestagel is not recommended for use in this population.

Other medicines and Cholestagel

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If your doctor suspects that Cholestagel may have an effect on the absorption of the other medication, you may be advised to take Cholestagel at least 4 hours before or at least 4 hours after taking the other medication. If you need to take other medicines more than once a day, remember that your Cholestagel tablets can be taken once a day.

Cholestagel may affect the way in which the following medicines work:

- Anticoagulant therapy (medicines, such as warfarin, used to thin blood). If you are taking anticoagulant therapy you should consult with your physician to closely monitor anticoagulation levels, as Cholestagel may affect the absorption of vitamin K and therefore interfere with the activity of warfarin.
- Thyroid replacement therapy (medicines, such as thyroxine or levothyroxine, used to treat low thyroid hormone levels)
- Oral contraceptives (medicines to prevent pregnancy)
It is important you take Cholestagel at least 4 hours after you take the oral contraceptive to ensure that the effectiveness of the contraceptive is not affected.
- Verapamil or olmesartan (medicines used to treat high blood pressure). It is important that you take olmesartan at least 4 hours before you take Cholestagel.
- Antidiabetic medications (medicines used to treat diabetes, such as metformin extended-release (ER) tablets, glimepiride, glipizide, pioglitazone, repaglinide or glyburide). If you are taking medicines for diabetes, you should consult with your physician so that you can be closely monitored. It is important that you take glimepiride and glipizide at least 4 hours before you take Cholestagel.
- Anti-epileptic medicines (medicines, such as phenytoin, used to treat epilepsy).
- Ciclosporin (a medicine used to suppress the immune system).
- Ursodeoxycholic acid (a medicine used to dissolve gallstones or treat specific chronic liver diseases).

If you are going to take Cholestagel and one of these medicines, your doctor may want to do tests to make sure that Cholestagel does not interfere with these medicines.

Additionally, if you have any condition that could cause you to have a deficiency of vitamins A, D, E or K, your doctor may want to check your vitamin levels periodically while you are taking Cholestagel. If necessary, your doctor may advise you to take vitamin supplements.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are prescribed Cholestagel and a statin together it is important that you tell your doctor if you are pregnant or if you are planning to become pregnant because statins must not be used during pregnancy; the patient information leaflet that comes with that particular statin should be consulted. Tell your doctor if you are breast-feeding. Your doctor may stop your medicine.

Driving and using machines

Your ability to drive or operate machines is not affected by taking Cholestagel tablets.

3. How to take Cholestagel

Before starting therapy with Cholestagel, you should be advised to follow a cholesterol-lowering diet and you should continue this diet during treatment.

Always take Cholestagel exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are unsure. As described in Section 2, if you will be taking Cholestagel along with another medicine it is possible that your doctor will advise you to take Cholestagel at least 4 hours before or at least 4 hours after taking the other medicine.

If you take a medicine called either Neoral[®] or ciclosporin, please ensure to take it with Cholestagel in a consistent pattern over the day; either always together or always separate for a set number of hours.

You should take your Cholestagel tablets with food and liquid. The tablets should be swallowed whole. Do not break, crush or chew the tablets.

Combination therapy:

The recommended dose for Cholestagel, when used with a statin or ezetimibe or both together, is 4 to 6 tablets a day by mouth. Your doctor may tell you to take the Cholestagel dose either once a day or twice a day; in either case Cholestagel should be taken with a meal. The dosing of the statin and the ezetimibe should follow the instructions for that particular medicine. The medicines may be taken at the same time or at separate times according to what your doctor has prescribed.

Monotherapy:

The recommended dose for Cholestagel is 3 tablets taken twice a day with meals or 6 tablets a day with a meal. Your doctor may increase your dose to 7 tablets per day.

If you take more Cholestagel than you should

Please contact your doctor. Constipation or bloating could occur.

If you forget to take Cholestagel

You may take your dose with a later meal, but never take in one day more than the total number of tablets that your doctor has prescribed to you in a single day.

If you stop taking Cholestagel

Your cholesterol may increase to the level it was before treatment was started.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported in patients taking Cholestagel:

Very common (may affect more than 1 in 10 people): flatulence (wind), constipation.

Common (may affect up to 1 in 10 people): vomiting, diarrhoea, indigestion, abdominal pain, abnormal stools, feeling sick, bloating, headache, raised levels of triglycerides (fats) in your blood.

Uncommon (may affect up to 1 in 100 people): muscle pain, raised levels of liver enzymes in your blood, difficulty in swallowing.

Very rare (may affect up to 1 in 10,000 people): inflammation of the pancreas.

Not known (frequency cannot be estimated from the available data): blockage of the intestines (which can increase among patients with a history of blockage of the intestines or intestinal removal).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cholestagel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle label after “EXP”

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Cholestagel contains

- The active substance is colesevelam (as hydrochloride). Each tablet contains 625 mg colesevelam.

- The other ingredients (excipients) are:

Tablet core:

Microcrystalline cellulose (E460)

Silica colloidal anhydrous

Magnesium stearate

Purified water

Film-coating:

Hypromellose (E464)

Diacetylated monoglycerides

Printing ink:

Iron oxide black (E172)

Hypromellose (E464)

Propylene glycol

What Cholestagel looks like and contents of the pack

Cholestagel tablets are off-white, capsule-shaped film-coated tablets and imprinted with 'C625' on one side. The tablets are packed in plastic bottles with child resistant closures. Pack sizes are 24 (1 x 24), 100 (2 x 50) and 180 (1 x 180) tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder
CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 24
17489 Greifswald
Germany

Manufacturer
Genzyme Ireland Ltd., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu/>