

**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 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

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.

### **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 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.

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 colestesvelam 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 Cholestagel and glyburide (also known as glibenclamide) caused a decrease in the AUC<sub>0-inf</sub> and C<sub>max</sub> 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<sub>max</sub> 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 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.

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

#### **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 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- $\alpha$ -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 3.75mmol/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.

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**

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**

23 March 2010

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