SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Cholestagel. For information on changes after approval please refer to module 8.

1. Introduction

Epidemiological data and intervention studies have shown that elevated total and LDL cholesterol are risk factors for coronary heart disease (CHD), and that pharmacological intervention to decrease low-density lipoprotein (LDL) cholesterol decreases risk. The relationship between serum cholesterol and CHD death is concentration-related and continuous over the entire distribution of cholesterol levels.
HMG-CoA reductase inhibitors (statins) are first-line agents for the treatment of hypercholesterolaemic patients on diet measures. Alternatives are bile acid sequestrants, nicotinic acid derivatives and fibric acid derivatives. A target LDL cholesterol of being <3mmol/L is recommended both in primary and secondary prevention.

Despite the efficacy of the HMG-CoA reductase inhibitors, many patients with severe hypercholesterolaemia may not respond sufficiently and will require combination therapy, using an add-on approach, to achieve target LDL cholesterol levels. The major drawback of currently available bile acid resins or sequestrants is their lack of tolerability. Side effects of bile acid binding resins (colestipol, colestyramine) are primarily related to gastrointestinal intolerance, which include symptoms of nausea, bloating, abdominal pain, and constipation. The resins must be taken in large quantities as a gritty powder mixed in water or as numerous large tablets.

Cholestagel contains the active substance colesevelam hydrochloride, a poly (allylamine hydrochloride), cross-linked with epichlorohydrin and alkylated with (6-bromohexyl)trimethylammonium bromide and 1-bromodecane.

Colesevelam is a novel non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. 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. 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 LDL receptors. A concomitant increase in very low-density lipoprotein (VLDL) synthesis can occur. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels. VLDL production may increase triglyceride levels. HDL cholesterol is generally unaffected or slightly increased.

Cholestagel is indicated for co-administration with an HMG-CoA reductase inhibitor (statin) as adjunctive therapy to diet to provide an additive reduction in LDL-cholesterol (LDL-C) levels in patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone, and as monotherapy as adjunctive therapy to diet for reduction of elevated total and LDL-cholesterol in patients with isolated primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well tolerated.
Current European guidelines should be consulted to establish treatment approaches and goals for individual patients. Prior to initiating therapy with Cholestagel as combination therapy or monotherapy, patients should be placed on a cholesterol-lowering diet and a lipid profile performed to assess total-cholesterol (total-C), HDL-cholesterol (HDL-C) and triglyceride levels. During therapy, this 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.
Cholestagel tablets should be taken orally with a meal and liquid. When a drug interaction cannot be excluded with a concomitant medicinal product, that medication should be administered at least one

hour before or four hours after Cholestagel to minimize the risk of reduced absorption of the concomitant medication.

Combination therapy: Therapy with Cholestagel may be initiated when standard doses of the HMG-CoA reductase inhibitor are inadequate or not well tolerated; the SPC for that particular HMG-CoA reductase inhibitor should be consulted. 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. Co-administration with atorvastatin, lovastatin or simvastatin in clinical trials shows that Cholestagel can be dosed at the same time as one of these HMG-CoA reductase inhibitors or the two medicinal products can be 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.

2. Quality aspects

Composition

Cholestagel is presented as film coated tablets containing 625 mg of colesevelam hydrochloride as active ingredient. Other ingredients include microcrystalline cellulose, magnesium stearate, silica colloidal anhydrous, hypromellose and diacetylated monoglycerides.
Cholestagel is packaged in high-density polyethylene (HDPE) bottles with caps and induction seal liners.

Active substance

Colesevelam hydrochloride is poly(allylamine hydrochloride), cross-linked with epichlorohydrin and alkylated with (6-bromohexyl)trimethylammonium bromide and 1-bromodecane.

It is a white to off-white, non-crystalline hydroscopic powder, that is insoluble in all tested solvents (water, HCl, ammonium hydroxide, methylenechloride, acetonitrile, octanol and methanol). The pH is approximately 4.2 and the pK is 9.3. Colesevelam hydrochloride is achiral and exhibits no potential for polymorphism since it is not crystalline

The main steps of the synthesis of the active substance are the crosslinking of poly(allylamine hydrochloride) and the alkylation of the crosslinked polymer. The route of synthesis has been sufficiently described and the major steps are adequately controlled with appropriate in process controls.
Residual starting materials as well as organic impurities present in the starting materials are a source of the organic impurities in the active substance and appropriate tests have been set in the active substance specifications. There are five potential degradation products whose limits have been qualified in toxicological studies according to ICH guidelines

Active substance specification
An inherent problem for cross-linked polymers like colesevelam hydrochloride is the difficulties associated with their characterisation, as NMR and IR spectra do not provide detailed information. Due to the complex structure of the active substanceno direct measurement of the assay can be performed in both the active substance and the finished product. This leads to wider release and shelf life specifications than those commonly applied The specification of the active substance includes tests for description, identification (IR), bile acid binding (HPLC), loss on drying, organic impurities (GC, IC, HPLC and UV), residual solvents (GC) and particle size and size distribution (a mean particle size of 15 to 50 μM). The limits for the impurities are justified by toxicological and stability studies.

Batch analysis data have been provided for eight batches of colesevelam hydrochloride. The analytical results for all these batches comply with the proposed specification.

In conclusion it has been proven that the tests and limits in the specification are appropriate for controlling the quality of the active substance.

Stability of the active substance
Stability studies have been performed according to the ICH guidelines at long term (25°C/60% RH) and at accelerated conditions (40 °C/75% RH).
The parameters tested are appearance, bile acid binding, loss on drying, related substances by gas and ion chromatography and microbial testing (at specified timepoints). The analytical procedures for stability testing were the same as those used for the release of colesevelam hydrochloride and were stability indicating.The stability of colesevelam hydrochloride was also examined under "stress" conditions. These included temperature cycling (freeze-thaw studies), elevated temperature (40 ± 2°C/ambient humidity) and photostability testing.
All parameters evaluated comply with the active substance specification. The stability data presented show that colesevelam hydrochloride is a very stable substance and support the proposed re-test period when stored under the specified conditions.

Other ingredients

Each tablet core contains colesevelam hydrochloride, purified water, microcrystalline cellulose as dry binder, magnesium stearate as lubricant and silica, colloidal anhydrous as glidant.
The coating is composed of hydroxypropyl methylcellulose as a film former and diacetylated monoglycerides as plasticiser. All materials used are of non-animal origin and comply with the Ph. Eur. requirements.

Product development and finished product

During preformulation studies, it was determined that colesevelam hydrochloride has poor flow properties and compressibility. For this reason dry granulation was employed to improve the flow properties and increase the compressibility characteristics of the granules.

The manufacturing process is a standard dry granulation process followed by tabletting and film coating of the tablets.

The critical process parameters were identified during development and are adequately controlled.
The process validation has been performed on three commercial batches having the same composition and method of manufacture as the proposed commercial formulation. The process validation criteria were met in all cases and all samples met the pre-defined acceptance criteria.
The product used for clinical trials has been shown to be equivalent in terms of bile salt binding kinetics and binding isotherms with the one intended for marketing.

Product specification
The product specifications include tests by validated methods for the description, identification (IR), bile acid binding (HPLC), loss on drying, disintegration, uniformity of mass, related substances and impurities (GC, IC).

The specification and control tests applied for the finished product at time of release and throughout the life of the product, are in compliance with Ph Eur standards and ICH guidelines. The limits for each specification test are supported by stability data.

Batch analysis data from 9 production and validation scale batches of the finished product have been provided. All batches met the test limits as set in the release specification of the finished product.

Stability of the product
Stability studies have been conducted according to ICH guidelines at long term (25°C/60% RH) and accelerated conditions (40°C/75% RH) for up to 36 months and 6 months respectively on 26 batches of the drug product.
The parameters studied were description, bile acid binding (IC), loss on drying, disintegration, uniformity of mass, related substances and impurities (GC, IC) and microbial limits.

Based on the results of the above-mentioned studies it has been concluded that the proposed shelf life, of 2 years and the storage condition "Keep the container tightly closed" is acceptable.

Discussion on chemical, pharmaceutical and biological aspects.

The quality of Cholestagel is adequately documented. There are no major deviations from EU and ICH requirements.

The active substance is a very stable cross-linked polymer. Due to its complex nature no direct measurement of the assay of the active substance can be obtained, however its quality is satisfactorily characterised and documented. Bile acid binding capacity is the most relevant characteristic to clinical use. The excipients and the packaging material chosen are commonly used in these types of formulations. The manufacturing process of the finished product is a standard dry granulation process followed by the application of film coating and has been adequately described. Stability tests indicate that the product is chemically stable for the proposed shelf life.

3. Non-clinical aspects

GLP
Except for the investigations of the effects of vitamin supplementation in rats and mice, all pivotal safety studies generally followed ICH, CPMP and other relevant guidelines and were GLP compliant.

Pharmacology

Primary pharmacodynamics

In vitro studies
From the *in vitro* studies it can be concluded that colesevelam, colestipol, and cholestyramine demonstrated similar overall bile acid binding capacity when evaluated in mixed bile acid solutions. Colestipol binds bile acids in a cooperative manner, as judged by sigmoidal plots of binding density versus free bile acid concentration. In contrast, the binding curves of bile acids to colesevelam and cholestyramine show no evidence of cooperativity.
At all free ligand concentrations, colesevelam binds glycocholic acid significantly more tightly than does cholestyramine, which in turn proves more effective than colestipol. In contrast to the clear distinction found for glycocholic acid, the bile acid binding behaviours of other common bile acids are very similar for colesevelam as for cholestyramine. Colestipol binding to all bile acids is significantly weaker, especially at higher binding densities.
Fatty acids compete with bile acids for binding to colesevelam and cholestyramine. The reduction of bile acid binding to cholestyramine by fatty acids is greater than that to colesevelam. In addition, the dissociation of bile acids from colesevelam is retarded by the presence of fatty acids.

In vivo studies
The purpose of a first *in vivo* study was to compare the effects of colesevelam and cholestyramine on faecal bile acid excretion in rats and hamsters. Colesevelam caused a dose-related increase in faecal bile acid excretion in rats. In this study, colesevelam was shown to be approximately twice as potent on a gram basis as was cholestyramine in increasing faecal excretion of bile acids.
In the hamster model, colesevelam caused a dose-dependent increase in faecal bile acid excretion. Colesevelam was at least twice as potent as cholestyramine in increasing faecal excretion of bile acids.
The purpose of a second *in vivo* study was to evaluate the effect of treatment with colesevelam alone or in combination with an HMG-CoA reductase inhibitor (lovastatin) on serum cholesterol levels in beagle dogs administered the test material orally via a gelatin capsule once daily for 14 days.
Thirty (30) male beagle dogs of approximately 12.6 months of age were screened for serum cholesterol levels and selected for study based upon a <10% variation between consecutive screens. Animals received colesevelam alone (300 or 1000 mg/kg/day), lovastatin (5 mg/kg) alone, or both drugs in combination once a day for a total of 15 days.
Colesevelam alone reduced serum cholesterol by 7 and 23% when administered at doses of 300 and 1000 mg/kg/day, respectively, for 15 days. Lovastatin (5 mg/kg/day) alone reduced serum cholesterol

by 19%. The combination reduced serum cholesterol by 34 and 58% at 300 and 1000 mg/kg/day, respectively. The effect of the combination was greater than the effect of either agent alone.

Secondary pharmacodynamics
No secondary pharmacodynamic studies were performed. The lack of absorption of colesevelam suggested that these studies would be of limited value.

Safety pharmacology
No specific safety pharmacology studies were conducted. The lack of absorption of colesevelam, its insolubility and the range of toxicology studies can justify this omission.

Pharmacodynamic drug interactions
No studies were carried out on pharmacological drug interactions. Since colesevelam hydrochloride is not absorbed, interactions are more likely to be associated with issues related to absorption and binding in the gastrointestinal tract (s*ee also Pharmacokinetic drug interactions).*

Pharmacokinetics

Absorption- Bioavailability
Colesevelam hydrochloride is a polymeric substance that is insoluble in aqueous solution. The size distribution is controlled to ensure that particles are of a size that is essentially not absorbed from the gastrointestinal tract. The particles themselves are cationic and face a significant barrier to absorption through the highly anionic mucus layer that lines the entire intestine. Therefore, absorption of intact particles of colesevelam hydrochloride is expected to be negligible. Traditional absorption, distribution, metabolism, and excretion studies were therefore not conducted with colesevelam hydrochloride.
Excretion balance studies with radiolabeled colesevelam hydrochloride were conducted to demonstrate the non-absorbed nature of the product in male rat and male dog.
For both groups, the plasma radioactivity levels were low. As total radioactivity was measured, it is not known what compound is detected in the plasma. The plasma radioactivity levels were very low indicating that systemic exposure of [^{14}C] - colesevelam HCl is very low.

Distribution
The distribution of [^{14}C]-colesevelam hydrochloride following oral administration to male rats and male dogs were evaluated. Animals were sacrificed at 72 hours (dogs) or at 96 hours (rats) after dosing of [^{14}C]-colesevelam hydrochloride. No detectable levels of compound other than a minor amount of radioactivity within the stomach were retained within the examined tissues of rats. In dogs, the levels of radioactivity in blood, plasma, and most tissues were below the lower limit of quantification. Only the liver and gastrointestinal tract contained minimal quantities of radioactivity. No important differences were noted between single or repeated oral dosing, indicating that a 1-month colesevelam hydrochloride pretreatment did not have impact on the distribution of [^{14}C]-colesevelam hydrochloride.
The retention of radioactivity in the tissues was measured without information on tissue clearance. However, in the toxicity studies no toxicity in the gastrointestinal tract or in the liver was observed, indicating that the presence of radioactive material does not seem to have adverse consequences.
Due to low recovery of radiolabel in the dog, a second distribution study was done in dogs. Since full recovery was achieved in these samples, no other samples were counted.

Metabolism
No metabolite profiling work was done because of the non-absorbable nature of the compound and no significantly absorbable metabolites seem to be produced.

Excretion
The excretion of [^{14}C]-colesevelam hydrochloride following oral administration to male rats and male dogs was evaluated.
In both species, the radiolabel was shown to be almost completely eliminated within 48 hours via the faeces with only traces of radioactivity in the urine (<0.2% of the applied dose). The excretion data

were characterised by a low inter-animal variability. No important differences were noted between single dosed or repeated dosed dogs, suggesting that a 1-month colesevelam hydrochloride pretreatment did not have any impact on the absorption and distribution of [^{14}C]-colesevelam hydrochloride.
Recovery of polymer over 72 hours was not 100% in the first dog study. However, it is unlikely that it was due to absorption of the drug. The bulk of excreted radioactivity appeared in the faeces within 48 hours and no radioactivity was recovered from any tissues or contents within the animal. Indeed, in the second dog study conducted following the same protocol and using newly synthesised radiolabeled compound (higher specific activity), total excretion balance was found to be complete. Faeces contained 100% of the ^{14}C-label. Bile, plasma and urine contained only 0.13 to 0.15% of the dose.

Pharmacokinetic drug interactions
Colesevelam hydrochloride is a bile acid binding polymer that acts by ion exchange of chloride for a negatively charged bile acid. Because colesevelam hydrochloride is anticipated not to be absorbed, it is likely that any drug interactions would be limited to an effect on absorption secondary to binding of the interacting drug by the polymer. Because of its ion exchange characteristics it is possible that colesevelam hydrochloride will bind negatively charged drugs and inhibit their absorption. In addition, because bile acids are required for absorption of several fat-soluble substances, colesevelam hydrochloride could interfere with drug absorption by an effect secondary to bile acid sequestration.
Seven drugs were chosen based upon their known interactions with cholestyramine (warfarin, valproic acid, verapamil, quinidine, tetracycline) or on the basis of their likelihood of being utilised concurrently with colesevelam hydrochloride (lisinopril and metoprolol). The relative bioavailability by comparing the rate and extent of absorption of the drugs was determined after oral administration of 100 mg/kg alone or in combination with colesevelam hydrochloride in male beagle dogs.
The results of this study indicate that colesevelam hydrochloride does not alter the pharmacokinetic properties of the seven drugs used in this study. However, inspite of the many similarities between the gastrointestinal physiology of dogs and humans, the composition of bile salts is markedly different between dog and man. Thus, in contrast to man, the bile acids in dog are exclusively conjugated with taurine. Furthermore, cholic acid was predominantly found in dog bile (~80%), whereas cholic acid contributed only for ~40% in man. As a consequence, the concentration of 100 mg/kg colesevelam hydrochloride in dog is probably not as effective as a bile sequestrant as the clinical dosing in man. This was supported by the observation that only at 300 mg/kg colesevelam hydrochloride or higher dosing plasma cholesterol lowering activity was observed in dogs.

Toxicology

Single dose toxicity

No single-dose toxicity studies were conducted. This omission was justified by the high doses used in the repeat-dose studies (in the region of 2 to 3 g/kg/day). Furthermore, the mouse micronucleus study included doses up to 5 g/kg/day administered on two successive days. In this study, non-specific clinical signs were noted, including distended abdomen, irregular breathing, lethargy, diarrhoea, and 3 of 30 mice died at that high dose. In mice, the LD50 is higher than 5 g/kg/day. The maximum therapeutic dose (MTD) is 73 mg colesevelam HCl/kg/day (based on a 60 kg human). Thus, the dose administered to mice is a 68-fold multiple of the human dose.

Repeat dose toxicity

The repeat-dose toxicity of colesevelam hydrochloride was evaluated by oral administration in rats (90 days and 6 months) and dogs (13 weeks and 1 year). The treatment related effects observed in the 90-day study were related to the pharmacodynamic properties of colesevelam. The NOAEL in this study is 0.3 g/kg/day and the LOAEL is 1.5 g/kg/day, which corresponds, respectively, to 4 and 21 times the maximum therapeutic dose (MTD).

For the 6-month rat study, no significant adverse treatment-related effects were observed on body weight (change), clinical signs or ophthalmologic findings. There were no treatment related macroscopic changes. The microscopic lesions observed were observed throughout all groups and were therefore not considered related to treatment. By lowering the maximum dose the lethal

hemorrhagic effects associated with vitamin depletion had been eliminated. The NOAEL and LOAEL of this study was 0.2 and 1.2 g/kg/day (i.e. 2.7 and 16 times the MTD).

For the 13-week dog study, there was a slight decrease in body weight gain and food intake. All effects reported can be considered as directly or indirectly related to treatment. In addition, only slight reductions in red blood cell parameters were observed in high dose animals. In contrast to rats, plasma cholesterol levels were reduced in dogs. The NOAEL and LOAEL in this study was 0.2 and 0.67 mg/kg/day, respectively (i.e. 2.7 and 9 times the MTD).
For the 1-year dog study, increases in urinary volume and chloride levels were seen mainly in high dose animals. All effects reported can be considered as directly or indirectly related to treatment. Decrease of vitamin D and E levels were dose-related both in females and males. In females, the decrease of vitamin A level was also dose-related, whereas in male dogs the vitamin A level was only lowered in the HD group. There was higher urinary excretion of calcium and chloride in all treated animals and the dose-related decrease of urinary phosphate excretion in HD animals. After a 4-week recovery period, RBC, Hb, Ht, MCHC and MCV slightly deviated from normal levels in HD animals. Vitamin A, D and E levels returned to sub-normal levels in HD recovery animals. The NOAEL was 0,2 g/kg/day (2.7x MTD) and the LOAEL was 0.6 g/kg/day (8x MTD).

Interspecies comparison

In rats, dogs, and humans given a single dose of [^{14}C]-colesevelam hydrocloride, the bulk of excreted radioactivity appeared in the faeces and no radioactivity beyond minimal quantities in any tissues, plasma or urine were measured after a 72 hour or 96 hour period in dog and rat, respectively. These data are consistent with the non-absorbable nature of the compound. The NOAEL in rats and dogs were 0.2-0.6 g/kg/day. The recommended human therapeutic dose is 50-70 mg/kg/day.

Genotoxicity *in vitro* and *in vivo*

The genotoxicity of colesevelam hydrochloride has been studied with respect to gene mutations in prokaryotic cells (Ames test) and chromosome aberrations in eukaryotic (CHO) cells and with respect to chromosomal aberrations *in vivo* (micronucleus test). Due to the insolubility of colesevelam in aqueous media the tests have been performed with an HCl extract of the active compound. No genotoxicity was observed in any of these studies.

Carcinogenicity

A dietary carcinogenicity study of colesevelam in the albino mouse:
Five groups of Swiss mice (Crl:CD-(ICR)BR,) received colesevelam mixed in diet at 0 (basal diet)-0 (vitamin-supplemented basal diet)-0.3-1.0-3.0 g/kg/day for 104 weeks. Vitamin D and E of all groups were determined every 6 months in 5 animals/group. Reduced body weights were noted in high-dose males. No treatment-related effects were noted at blood smear examination or in ophtalmology parameters. Serum vitamin E concentrations were not significantly different from the controls in the groups fed vitamin-supplemented plus test article-supplemented diets. Survival in some groups was as low as 30%, although there was no significant difference between test and control groups. There seemed to be no difference in the incidences of neoplasms between test and control groups. However, examinations for neoplastic lesions in some tissues were conducted on a very low number of samples.
A dietary carcinogenicity study of colesevelam in the albino rat:
Sprague-Dawley CD rats received colesevelam mixed in the diet at doses of 0-0.8-1.6-2.4 g/kg/day. Because the animals in the high-dose group did not tolerate 2.4 g/kg/day, the study was aborted after 6 weeks.
A dietary carcinogenicity study of colesevelam in the albino rat:
Swiss CD(Crl:CD(SD)BR rats received colesevelam mixed in the diet at 0 (basal diet only)-0 (vitamin-supplemented basal diet)-0.4-1.2-2.4 g/kg/day for 104 weeks. The test article had no influence on survival. However, in all groups the survival rate was lower for males (except for the high-dose group) than for females. Reduced body weights and body weight gains were noted in high-dose males. A statistically significant decrease in vitamin D levels was noted for high-dose males. In rats there was a slight increase in pancreatic acinar cell adenoma in males at the high and intermediate dose (doses >16 times the maximum human dose). This finding is not considered clinically relevant.

There was a slight increase in C-cell adenoma of the thyroid in high-dose males and females, otherwise there seemed to be no treatment-related increase in the incidence of neoplasms. The occurrence of thyroid adenomas is a common type of tumour in old rats, and the slight difference between test and control animals may be incidental

Reproductive and developmental studies

The reproductive toxicity of orally administered colesevelam hydrochloride was studied in a Segment I study in rats, a Segment II study in rats and rabbits, and in a Segment III study in rats.

Study Type/ Study ID / GLP	**Species; Number/ sex/group**	**Route & Dose (g/kg/day)**	**Study design**	**Major Findings**
Male and female fertility and general reproduction toxicity study (GT-02-TX-12) (GLP study)	Sprague Dawley (CD) rat; (25/sex /gp)	Oral (diet)[1]. 0 (gp1); 0 control article; (gp2); 0,2 (gp3); 1 (gp4) and 2 (gp5)	Dosing in males: from day 28 premating to sacrifice (after mating). Dosing in females: day 15 premating to day 7 of gestation. Caesarean section on day 20 of gestation.	No treatment-related adverse effects on reproductive parameters. Food consumption was slightly increased and body weight gain slightly reduced.
Embryofetal / developmental toxicity study (GT-02-TX-13) (GLP study)	Sprague Dawley (CD) rat (25 dams /gp)	Oral (diet)[2]. 0 (gp1); 0 control article; (gp2); 0,3 (gp3); 1 (gp4) and 3 (gp5)	Pregnant females were dosed from Day 7 through 17 of presumed gestation. Caesarean section on Day 20 of gestation. Histological examination of female reproductive organs and external visceral/skeletal examination of litters.	No treatment-related adverse effects. Food consumption was increased from Day 10 onwards and body weight gain was reduced in gp 5 from Day 15-18.
Embryofetal / developmental toxicity study (GT-02-TX-14) (GLP study)	Rabbit (20 dams /gp)	Oral (gavage). 0 (gp1). 0.1 (gp2), 0.5 (gp3) and 1 (gp4)	Pregnant females were dosed from Day 6 through 18 of presumed gestation. Caesarean section on Day 20 of gestation. Histological examination of female reproductive organs and external visceral/skeletal examination of litters.	No treatment-related adverse effects. Food consumption and body weight gain of dams was not affected. The maternal no adverse effect level (NOAEL) for colesevelam hydrochloride is 0.5 g/kg/day. The 1 g/kg/day dosage slightly reduced body weight gains and absolute (g/day) food consumption values. The developmental NOAEL for colesevelam hydrochloride was at least 1 g/kg/day (*i.e*. 13 times the MTD).
*Peri & postnatal study (GT-02-TX-30) (GLP-study)	Sprague Dawley (CD) rat (24 dams /gp)	Oral (gavage[3]) 0 (gp1); 0.1 (gp2); 0.3 (gp3) and 1 (gp4)	Dams were dosed from Day 6 of gestation to Day 20, 21, or 22 *post partum*, inclusive. One male and 1 female were randomly selected from each litter, to form the adult F_1 generation on Day 21 *post partum*.	No treatment-related adverse effects

			Those rats not selected were killed and pathologically examined. The F_1 generation was examined for physical development, sensory/ reflex development, behaviour, and reproductive performance.	

[1]) gp 1 received basal diet, gp2 received cellulose at 2 g/kg/day (cellulose control)
[2]) gp 1 received basal diet and gp 2 received cellulose at 3 g/kg/day (cellulose control)
[3]) dose depicted is the total daily dose. Dams were dosed twice a day with half of the total daily dose.

No treatment-related adverse effects were found in the reproductive toxicity studies. This is not surprising as colesevelam does not reach the plasma. The only effect observed is the known effect on food consumption and body weight gain when colesevelam was administered to the animals via the diet.

Local tolerance

No local tolerance studies have been performed by the applicant. By virtue of its route of administration, colesevelam might induce local adverse effects in the (gastro)intestinal tract. However, macroscopic and histopathological evaluation of the gastrointestinal tract of animals after repeated dosing with colesevelam revealed no evidence for these effects.

Impurities

The applicant has conducted toxicity studies on 4 impurities (degradants) of colesevelam hydrochloride, (decylamine HCL, didecylamine HCL, decylamino-6-hexytrimethyl ammonium chloride hydrochloride, and aminohexyltrimethylammonium chloride hydrochloride). Each impurity has been tested for up to 15 mg/kg/day. No treatment-related adverse effects have been observed in the repeated dose toxicity studies.
The submitted repeated dose studies with the impurities are, however, acceptable taking into account the absence of adverse effects of these impurities and because the tested impurities will most probably not be absorbed from the gastrointestinal tract. Further, in view of their molecular structure it is not likely that these compounds are genotoxic.

Discussion on the non-clinical aspects

Colesevelam hydrochloride, the active ingredient in Cholestagel, is a novel bile acid sequestrant.
In the pharmacodynamic *in vitro* study, colesevelam, colestipol and cholestyramine demonstrated similar overall bile acid binding capacity when evaluated in mixed bile acid solutions. At all free ligand concentrations, colesevelam was found to bind glycocholic acid (GC) significantly more tightly than did cholestyramine, which in turn was more effective than colestipol. This is an important finding since GC is the major bile acid in humans. In contrast to the clear distinction for GC, the bile acid binding capacity of taurodeoxycholic acid (TDC), taurocholicdeoxycholic acid (TCDC), glycodeoxycholic acid (GDC), glycocholicdeoxycholic acid (GCDC) and taurocholic acid (TC) were very similar for colesevelam and cholestyramine.

The *in vivo* studies in hamsters and rats confirmed that colesevelam is effective in enhancing the faecal excretion of bile acids. Both colesevelam hydrochloride and cholestyramine cause a dose-dependent increase in bile acid sequestration in these two rodent species. Colesevelam was at least 2-fold more potent and efficacious in increasing faecal bile acid excretion in both models than was cholestyramine.
The *in vivo* study in dogs confirms that colesevelam lowered plasma cholesterol levels. Colesevelam alone reduced serum cholesterol by 7 and 23% when administered at doses of 300 and 1000 mg/kg/day, respectively, for 15 days. It can be argued that in dogs taurocholic acid instead of

glycocholic acid is the major bile acid, however this may rather support than undermine the cholesterol lowering potency of colesevelam.
Lovastatin (5 mg/kg/day) alone reduced serum cholesterol by 19%. The combination reduced serum cholesterol by 34 and 58% at 300 and 1000 mg/kg/day, respectively. The effect of the combination was greater than the effect of either agent alone. These data provide a scientific rationale for the single use of colesevelam for lowering cholesterol as well as for the use in combination with statins.
It can be concluded that the data on *in vitro* bile acid binding, the *in vivo* bile acid excretion in rats and hamsters, and plasma cholesterol lowering in dogs, support the mechanism of action of colesevelam as a bile acid sequestering and cholesterol-lowering polymer. Both the *in vitro* and the *in vivo* studies were conducted in generally accepted and appropriate models.

Colesevelam hydrochloride is a polymer that is not likely to be absorbed from the gastrointestinal tract due its particle size. The absence of specific safety pharmacology studies and secondary pharmacodynamic studies is justified by the insolubility of colesevelam and by the observation that colesevelam is not absorbed.

Traditional absorption, distribution, metabolism, and excretion studies were not conducted with colesevelam hydrochloride, as absorption was expected to be negligible. The results of the excretion balance studies in rat and dog (and in human) showed that the bulk of radioactivity was excreted in the faeces and no radioactivity beyond minimal quantities in any tissues, plasma or urine after a 72-hour or 96-hour period in dog and rat, respectively, and were consistent with the non-absorbable nature of colesevelam hydrochloride.

Because colesevelam hydrochloride is not absorbed, it is likely that any drug interactions would be limited to an effect on absorption of the medicinal product. The dog was chosen as the animal model to study these interactions. Seven medicinal products were chosen based upon their known interactions with cholestyramine (warfarin, valproic acid, verapamil, quinidine, and tetracycline) or on the basis of their likelihood of being utilised concurrently with colesevelam hydrochloride (lisinopril and metoprolol). The dose of colesevelam hydrochloride utilised (100 mg/kg) is approximately 1.4-fold the maximum projected human dose of 4.5 grams per day (73 mg/kg). However, despite the many similarities between the gastrointestinal physiology of dogs and humans, the composition of bile salts is markedly different between dog and man.

As a result of the non-absorbable nature of colesevelam, any toxicity noted is thus likely to be secondary to effects within the gastrointestinal tract. The toxicology studies were conducted in male and female rats and dogs. In the rat studies, toxic effects included anaemia and elevated levels of enzymes indicating liver and possibly skeletal and heart muscle injury. This can be explained by the decreased levels of fat-soluble vitamins observed, particularly vitamins E and K. From the anaemia and haemorrhages observed, vitamin K levels are considered to be decreased as well, although the levels were not analysed. In the rat studies, females seemed to be more sensitive for toxic liver effects than males, whereas males seemed to be more sensitive than females in developing fatal haemorrhages. The Harlan rat strain seemed to be most sensitive in developing anaemia. NOAEL in rats was about 0.2 g/kg/day. No repeat dose toxicology beyond 6 months was conducted in rats.
In the dog, studies of 13 weeks and 1 year were conducted. Again, decreased levels of fat-soluble vitamins were measured (A, D and E), whereas vitamin K was probably not severely affected, since haemorrhages were not observed. NOAEL was suggested to be 2.0 g/kg/day, however from the findings of decreased vitamin levels, increased alkaline phosphatase levels, and decreased body weights in the high-dose groups; NOAEL should rather be set to 0.6 g/kg/day.
The maximum doses used in the toxicology studies were in the range of 2 to 3.6 g/kg/day. This is 27 to 50 times the maximum human therapeutic dose (MTD) of approximately 73 mg/kg/day for a 60 kg person. Compared to the NOAEL in rats and dogs, the safety factor in humans at daily doses of 50-70-mg/kg would be about 2-3, which is a very low margin of safety.

The contaminants decylamine HCl, aminohexyltrimethyl ammonium chloride HCl, didecylamine and decylamino-6-hexyltrimethyl ammonium chloride, have been sufficiently qualified. They were individually tested in the bacterial mutation test (*S typhymurium, E Coli*) and in CHO cells. No evidence for genotoxicity of these compounds was found. In addition, the above-mentioned impurities

have been tested in a 28 day repeated dose toxicity study in rats. No treatment-related adverse effects have been observed. The submitted repeated dose studies with the impurities are acceptable taking into account the absence of adverse effects of these impurities and because the tested impurities will most probably not be absorbed from the gastrointestinal tract.

Based on its molecular structure, no genotoxic properties are expected from the active compound.
The Ames test and CHO test revealed no evidence for genotoxic potential of components in the HCl extract of Colesevelam. The *in vivo* mouse micronucleus test with Colesevelam was negative, but can be considered meaningless due to its low to absent intestinal absorption. Possible (local) genotoxic effects are not to be expected. Due to its molecular size it is unlikely that it will gain access to the genetic material in the cellular tissue.

The interpretation of the mouse and rat carcinogenicity studies may be hampered by low survival throughout the study groups. In the mouse study, there are no treatment-related tumour findings in the mouse study up to 3 g/kg/day, which equals 40 times the MTD. In addition, there are no treatment-related tumour findings in the rat carcinogenicty study up to 2.4 g/kg/day, which equals roughly 30 times the MTD.
When tested in a complete panel of reproduction toxicity studies, colesevelam did not induce treatment-related effects on fertility, embryonic or postnatal development.

Colesevelam is a substance of low acute toxicity. However, the safety margin in humans on repeated dosing for long periods is rather low. It should be noted that secondary toxic effects may develop because of the ability of colesevelam to produce depletion of fat-soluble vitamins, particularly vitamins E and K. Vitamin E depletion results in tissue damage of the liver, the skeletal and heart muscles, and blood vessels in most mammalian species, as visualised by the increase in enzyme characteristics for liver in the preclinical studies. Vitamin K depletion results in serious imbalance in the coagulation system, as demonstrated in the preclinical studies. The animal studies demonstrated that whereas short-time exposure was well tolerated, chronic exposure required the supplementation of fat-soluble vitamins in order to avoid vitamin depletion.

4. Clinical aspects

GCP

All clinical studies were conducted according to current GCP guidelines.

CLINICAL PHARMACOLOGY

Overview of Clinical Pharmacology Programme

Study	**Objective(s) of the Study**	**Study Design; Type of Control; Duration of Treatment**	**Test Product(s); Dosage Regimen; Route of Administration**	**Healthy Subjects or Diagnosis of Patients; (*n*)**
GTC-48-803 (PK)	Determine the extent of ^{14}C-colesevelam HCl absorption	Open-label, single arm; 28 days + single radio-labelled dose	Capsules; 1.9 g BID x 28 days, orally then a single 2.4 g dose of ^{14}C-colesevelam HCl (480µCi), oral	Healthy Subjects; n=20

Study	Objective(s) of the Study	Study Design; Type of Control; Duration of Treatment	Test Product(s); Dosage Regimen; Route of Administration	Healthy Subjects or Diagnosis of Patients; (*n*)
GTC-37-801 (PK)	Assess interaction between lovastatin and Cholestagel	Open-label, randomised, 3-period, crossover; Single dose	Lovastatin tablet, 20 mg; Cholestagel capsules (2.3 g) + lovastatin (20 mg) taken together; Cholestagel capsules (2.3 g) + lovastatin (20 mg) taken apart. All given orally	Healthy Subjects; n=24
GTC-48-804 (PK)	Assess the effect of Cholestagel on quinidine PK	Open-label, sequential treatment; Single dose	Quinidine gluconate ER tablets, 324 mg; Cholestagel capsules 4.5 g + quinidine gluconate tablets 324 mg; all oral	Healthy Subjects; n=26
GTC-48-805 (PK)	Assess the effect of Cholestagel on valproic acid PK	Open-label, sequential treatment; Single dose	Valproic acid capsules, 250 mg; Cholestagel capsules 4.5 g + valproic acid 250 mg; all oral	Healthy Subjects; n=26
GTC-48-806 (PK)	Assess the effect of Cholestagel on digoxin PK	Open-label, sequential treatment; Single dose	Digoxin tablets, 0.25 mg; Cholestagel capsules 4.5 g + digoxin 0.25 mg; all oral	Healthy Subjects; n=26
GTC-48-807 (PK)	Assess the effect of Cholestagel on warfarin PK	Open-label, sequential treatment; Single dose	Warfarin sodium tablets, 10 mg; Cholestagel capsules 4.5 g + warfarin sodium 10 mg; all oral	Healthy Subjects; n=26
GTC-48-808 (PK)	Assess the effect of Cholestagel on verapamil PK	Open-label, sequential treatment; Single dose	Verapamil HCl tablets, 240 mg; Cholestagel capsules 4.5 g + verapamil HCl 240 mg; all oral	Healthy Subjects; n=32
GTC-48-809 (PK)	Assess the effect of Cholestagel on metoprolol PK	Open-label, sequential treatment; Single dose	Metoprolol, 100 mg, oral; Cholestagel capsules 4.5 g + metoprolol 100 mg; all oral	Healthy Subjects; n=36
GTC-48-802 (PD)	Investigate effects of Cholestagel on sterol metabolism	Randomised, open-label, parallel design; 28 days	Capsules, 2.3 g or 3.8 g per day as split doses, oral	Mild to moderate hypercholesterolemia; n=24

Pharmacokinetics

A total of 8 studies were submitted in which human pharmacokinetics of Cholestagel were evaluated: one absorption study with ^{14}C-colesevelam and seven interaction studies (*see table above*). ADME

studies in humans were limited to absorption, because colesevelam hydrochloride is an insoluble polymeric substance that was not anticipated to be absorbed.

Absorption – Bioavailability
The absorption of Colesevelam has been determined in study GTC-48-803 in healthy volunteers. The absence of pharmacokinetic data in patients was justified by the applicant because there is no reason to believe that the pharmacokinetic profile of Colesevelam in patients would differ from that in normal volunteers.
16 subjects received an oral administration of ^{14}C-colesevelam (2400 mg dose as 6 capsules 400 mg Cholestagel). Studies examining polymer absorption rely on radiolabelling the polymer to assess uptake by the gastrointestinal tract. The study demonstrated that colesevelam is almost completely eliminated through the gastrointestinal tract system with negligible absorption. However, incomplete recovery was reported and a large variability in individual excretion was observed. Discrepancies were explained by incomplete faecal collections. The relatively low levels of radioactivity in whole blood and urine were probably caused by the residual radioactivity not incorporated into the polymer.

Comparison of trial formulations with finished product
The majority of clinical trials were conducted with Cholestagel capsules, while the Marketing Authorisation Application is for Cholestagel tablets. The change in formulation from capsules to tablets was made to decrease the number of units administered (375 mg capsules vs. 625 mg tablets).
Three lots of Cholestagel tablets and three lots of Cholestagel capsules were tested for *in vitro* equivalency of their bile acid binding kinetics and binding isotherms. Both the amounts of the bile acid sodium salts, glycocholic acid (GC), glycochenodeoxycholic acid (GCDC), and taurodeoxycholic acid (TDC) bound by Cholestagel capsules and tablets at equilibrium and the kinetics for each dosage form were sufficiently comparable. These data support the conclusion that Cholestagel capsules and tablets are equivalent. Further, lipid values from a small open tolerability study including 20 healthy volunteers taking tablets suggest that the efficacy is similar for tablets and capsules.

Influence of food
To examine the influence of various beverages on *in vitro* bile acid binding of Cholestagel tablets, the binding of Cholestagel tablets after disintegration in various beverages to the bile acid salts glycocholic acid (GC), glycochenodeoxycholic acid (GCDC), and taurodeoxycholic acid (TDC) were investigated. Both the amounts of the bile acid sodium salts bound by colesevelam tablets at equilibrium and the kinetics were sufficiently comparable after pretreatment (equilibrium study) and in solution with (kinetics study) the different beverages tested. The binding of colesevelam to the bile acids, was shown not to be influenced by common beverages (water, carbonated water, carbonated sweetened beverages, grape juice, orange juice, tomato juice, sports drinks, or 1% milk).

Special populations
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.

Interaction studies
A known problem in the use of currently approved bile acid sequestrants is their tendency to interact with other substances in the gastro-intestinal tract, thereby producing alterations in the pharmacokinetics of these medicinal products. Seven studies addressed the influence of Cholestagel on pharmacokinetics of the following substances: lovastatin, an HMG-CoA reductase inhibitor likely to be co-administered with Cholestagel; digoxin and warfarin, agents with narrow therapeutic indices, both of which have been reported to interact with cholestyramine and colestipol, verapamil and metoprolol, commonly used drugs in patients with cardiovascular disease; quinidine, an anti-arrhythmic with a narrow therapeutic index; and valproic acid, an anti-seizure medication that has been reported to interact with cholestyramine. In six of the seven studies, Cholestagel was administered at the maximum proposed dose of 4.5 g/day, thus maximising the probability of observing an effect of Cholestagel on absorption of the co-administered drug. In the interaction study with lovastatin a dose of 2.3 g/day was administered. In all of the studies, Cholestagel was administered as a single dose with a meal.

Cholestagel had no influence on the bioavailability of lovastatin when administered simultaneously together with the evening meal. However, the doses of both colesevelam (2.3 g) and lovastatin (20 mg) were low and a study should have been performed with maximum recommended doses of both drugs. When lovastatin was administered 4 hours later than Cholestagel statistical significant differences were found in C_{max} (decrease of 63 %) and AUC_{0-t} decrease of 37 % of lovastatin and C_{max} (increase of 61 %) and AUC_{0-t} (increase of 50 %) of lovastatin hydroxyacid. These differences are explained by the applicant as most likely contributed to food interactions and time dependency of lovastatin.
Colesevelam administered together with quinidine, valproic acid, digoxin, warfarin, or metoprolol did not significantly reduce the bioavailability of these study drugs. However, colesevelam administered together with verapamil reduced bioavailability of verapamil and the metabolite norverapamil. The clinical significance of this finding is unclear. It should be noted that there is a great deal of inter-individual variability for verapamil in the absence of Cholestagel, with 11- to 26-fold differences in the minimum and maximum values of C_{max}, AUC_{0-t} and AUC_{0-inf} in the subjects treated with verapamil alone. This variability is recognised by treating physicians who, therefore, alter their prescribed verapamil dosages according to the desired effect for each patient.
The repertoire of medicinal products in the drug-drug-interaction studies with colesevelam is limited. Bile acid sequestrants bind bile acids by ionic linkages and hydrophobic interactions. It is not clear why colesevelam should be more potent in binding bile acids, and less potent in interaction with drugs and other molecules (i.e. hormones, vitamins) compared to other bile acid sequestrant (i.e. cholestyramine, colestipol).
The Applicant has committed to perform further interaction studies post-marketing with Cholestagel.

Pharmacodynamics

Mechanism of action
Cholesterol homeostasis is largely controlled by the liver. Cholesterol can only be excreted from the body by hepatic secretion into bile. Net contributions to the hepatic cholesterol pool come from cholesterol synthesis via the rate-limiting enzyme HMG-CoA reductase and cholesterol derived from dietary absorption. Net excretion of cholesterol is accomplished either by direct secretion of cholesterol into bile, or by transformation of cholesterol to bile acids followed by secretion into bile. Although >95% of intestinal bile acids are reabsorbed in the terminal ileum, the bulk of sterol excretion occurs by faecal excretion of bile acids. Reabsorbed bile acids return to the liver via the portal vein, and are then recycled into bile. In this process, termed the enterohepatic circulation, bile acids are recirculated multiple times during a single day. Previous studies have established that bile acid sequestrants increase faecal bile acid excretion at least 4-fold. Enhancing excretion of cholesterol in the form of bile acids decreases the amount of bile acids that reaches the liver after uptake in the ileum and return to the liver via the portal vein. This has two benefits: an increase in bile acid synthesis from cholesterol, and a compensatory increase in LDL cholesterol uptake by the liver via the LDL receptor. The net effect is to decrease serum LDL cholesterol levels. Therefore, the fundamental mechanism by which bile acid sequestrants lower serum LDL cholesterol is by increasing bile acid excretion.

Primary pharmacology
Study GTC-48-802 was a multiple dose, open-label, parallel-design study. Patients with mild to moderate hypercholesterolaemia (LDL cholesterol 3.36-5.68 mmol/L and triglycerides <3.39 mmol/L) were entered into the NCEP Step 1 diet for six weeks. Patients were randomised to either Cholestagel 2.3 g/day or 3.8 g/day. 24 patients entered the treatment phase of the study.
LDL cholesterol decreased by 0.36 mmol/L and 0.54 mmol/L (14 %) for the 2.3 g/day group and the 3.8 g/day group, respectively. Total cholesterol declined by 0.31 mmol/L for the 2.3 g/day group and 0.36 mmol/L for the 3.8 g/day group. Triglycerides increased by a mean of 0.03 mmol/L for the 2.3 g/day group and 0.55 mmol/L for the 3.8 g/day group. Faecal bile acids increased as compared to baseline for both groups. Cholestagel increased the absolute amount of faecal bile acids but the change and percent change in total faecal fatty acids and faecal neutral sterols were not statistically significant. The physiological post-prandial rise in serum bile acids was blunted with Cholestagel dose-dependently. Change in serum oxysterol from baseline to endpoint was not statistically significant for either treatment group with the exception of 27-OH cholesterol, which decreased

significantly in the 3.8 g group. There were statistically significant median increases of mevalonic acid levels from baseline to endpoint for both the 2.3 g/day group (1.170 mmol/day, p=0.001) and 3.8 g/day group (1.110 mmol/day, p=0.0015).

Secondary pharmacology
No specific studies have been conducted evaluating secondary pharmacological actions of Cholestagel. It should be recognised that Cholestagel belongs to the bile sequestrants class with a well-known and recognized mechanism of primary and secondary pharmacological actions.

Relationship between plasma concentration and effect
The relationship between plasma concentration and effect is not applicable for this compound. Cholestagel is an insoluble polymeric substance that is not expected to be absorbed. The non-absorbable nature has been demonstrated in the non-clinical pharmacokinetic studies. A clinical pharmacology absorption study was conducted to confirm the results of the non-clinical testing *(see section on clinical efficacy).*

Pharmacodynamic interactions with other medicinal products or substances
No specific pharmacodynamic interaction studies were conducted.

Clinical efficacy

Introduction
In randomised, placebo-controlled Phase 2/3 studies, 1350 patients with hyperlipidaemia were treated and 1188 patients completed the protocols. A total of 952 patients were treated with Cholestagel, 807 patients were treated with Cholestagel alone, and 145 patients were treated with a Cholestagel /HMG-CoA reductase inhibitor combination. In these studies, a total of 689 patients who received Cholestagel monotherapy, and 133 patients who received Cholestagel in combination with HMG CoA-reductase inhibitors completed their protocols.

Overview of Clinical Efficacy and Safety Programme

Study	**Objective(s) of the Study;** **Primary endpoint**	**Study Design; Type of Control; Duration of Treatment**	**Test Product(s); Dosage regimen; Route of Administration**	**Diagnosis of Patients;** ***(n)***
GTC-37-201 Efficacy/Safety (Phase 2) (Monotherapy)	Assess safety and efficacy of new formulation; Change and % change in serum LDL-C from baseline to completion of treatment period.	Randomised, double-blind, parallel design; Placebo controlled; 6 weeks	Capsules, 1.5 g, 2.3 g, 3.0 g, and 3.8 g per day as split doses, oral	Primary hypercholesterolemia; LDL-C ≥ 4.14 mmol/l 149 (120 test drug, 29 placebo)

GTC-37-202 Efficacy/Safety (Phase 2) (Monotherapy)	Assess safety and efficacy of once per day dosing; Change and % change in serum LDL-C from baseline to completion of treatment period.	Randomised, double-blind, parallel design; Placebo controlled; 4 weeks	Capsules, 1.5 g given in A.M., 1.5 g given in P.M., and 0.75 g BID, oral	Primary hypercholesterolemia; LDL-C ≥ 4.14 mmol/l and ≤ 5.69 mmol/l 122 (90 test drug; 32 placebo)
GTC-48-301 Efficacy/Safety (Phase 3) (Monotherapy)	Assess safety and efficacy in a large pivotal trial; Change in serum LDL-C from baseline to completion of treatment	Randomized, double-blind, parallel design; Placebo controlled; 6 months	Capsules, 2.3 g, 3.0 g, 3.8 g and 4.5 g per day as split doses, oral	Primary hypercholesterolemia; LDL-C ≥ 3.36 mmol/l and ≤ 5.69 mmol/l 494 (400 test drug; 94 placebo)
GTC-48-302 Efficacy/Safety (Phase 3) (Monotherapy)	Assess safety and efficacy of once per day dosing in a pivotal trial; Change in serum LDL-C from baseline to completion of treatment period.	Randomized, double-blind, parallel design; Placebo controlled; 6 weeks	Capsules, 3.8 g given in A.M., 3.8 g given in P.M., and 1.9 g BID, oral	Primary hypercholesterolemia; LDL-C ≥ 3.75 mmol/l and ≤ 6.46 mmol/l 98 (75 test drug; 23 placebo)
GTC-37-203 Efficacy/Safety (Phase 2) (Combination Therapy)	Determine the efficacy and safety of co-admin-istration of Cholestagel and lovastatin; Change in serum LDL-C from baseline to completion of treatment period.	Randomized, double-blind, parallel design; Placebo controlled; 4 weeks	Cholestagel capsules, 2.3 g; lovastatin capsules, 10 mg; Cholestagel 2.3 g + lovastatin 10 mg dosed together; Cholestagel 2.3 g + lovastatin 10 mg dosed apart; all oral	Primary hypercholesterolemia; LDL-C ≥ 4.14 mmol/l and ≤ 5.69 mmol/l 135 (83 test drug with or without lovastatin; 26 lovastatin only; 26 placebo)
GTC-48-204 Efficacy/Safety (Phase 2) (Combination Therapy)	Determine the combined efficacy and safety of co-admin-istration of Cholestagel and simvastatin; Change in serum LDL-C from baseline to completion of treatment period.	Randomized, double-blind, parallel design; Placebo controlled; 6 weeks	Cholestagel capsules 2.3 g or 3.8 g per day as split doses; simvastatin tablets 10 mg or 20 mg; Cholestagel 2.3 g + simvastatin 20 mg; Cholestagel 3.8 g + simvastatin 10 mg; all oral	Primary hypercholesterolemia; LDL-C ≥ 4.14 mmol/l 258 (148 test drug with or without simvastatin; 75 simvastatin only; 35 placebo)

GTC-48-205 Efficacy/Safety (Phase 2) (Combination Therapy)	Determine the combined efficacy and safety of co-admin-istration of Cholestagel and atorvastatin; Change in serum LDL-C from baseline to completion of treatment period.	Randomized, double-blind, parallel design; Placebo controlled; 4 weeks	Cholestagel capsules 3.8 g per day as split dose; atorvastatin capsules 10 mg or 80 mg per day; Cholestagel 3.8 g + atorvastatin 10 mg; all oral	Primary hypercholesterolemia; LDL-C ≥ 4.14 mmol/l 94 (36 test drug with or without atorvastatin; 39 atorvastatin only; 19 placebo)
GTC-37-901 Efficacy/Safety (Extension study) (Monotherapy)	Assess safety and efficacy of long-term use; Change in serum LDL-C from baseline to completion of treatment period.	Open-label, dose-titration; non-controlled; 50 weeks	Capsules, 1.5 to 3.8 g per day as split doses, oral	Primary hypercholesterolemia; 260
GTC-44-201 Efficacy/Safety (Monotherapy)	Assess the safety/efficacy and tolerability of Cholestagel tablets	Open-label, fixed dose; non-controlled; 28 days	Tablets; 1.9 g b.i.d;, oral.	Healthy Subjects; 20

Dose response studies

Five placebo-controlled phase 2 studies were undertaken in which efficacy and safety of Cholestagel was evaluated. The Phase 2 studies are regarding objectives, treatment, study design and endpoint assessment similar to the two pivotal Phase 3 studies. For this reason all Phase 2 and 3 studies are presented and discussed combined in the following sections.

Main studies (Phase 2 and Phase 3)

Description of the studies

Study GTC-48-301 was a pivotal Phase 3 dose-response study designed to determine the long-term efficacy and safety of Cholestagel. Study GTC-48-302 was a pivotal Phase 3 dose-regime study, designed in a similar manner as GTC-37-202, to confirm the efficacy of once a day and split daily doses. Three studies with colesevelam and HMG-CoA reductase inhibitors (GTC-37-203, GTC-48-204, GTC-48-205) are also considered as main studies, as they have been conducted to support the add-on indication. Two open-label studies (GTC-37-901 and GTC-44-201) are considered as supportive efficacy studies.
All studies, except GTC-37-901 and GTC-44-201, were double blind and placebo-controlled. In some studies, patients were stratified prior to randomisation into categories of baseline LDL cholesterol. No comparative studies with other bile acid sequestrants were performed.
In all studies, all patients underwent a physical exam before and after therapy and a medical history was obtained. All patients were placed on a controlled diet low in fat and dietary cholesterol for at least 2 weeks prior to dose initiation and all patients were required to adhere to a low-fat, low-cholesterol diet while being enrolled in the studies. At least two baseline lipid values were obtained, and serum lipid values during treatment were obtained at intervals of at least 2 weeks duration.

METHODS

Study Participants

Inclusion criteria. The patient population studied constitute ambulatory men or women 18 years of age or older with polygenic hypercholesterolaemia who met the lipid criteria for mild to moderate Fredrickson Type IIa hyperlipoproteinaemia. Premenopausal and postmenopausal women, elderly, and racial minorities were included. There was no upper limit of age for inclusion.

Exclusion criteria: Pregnant women and children were excluded. Hypertriglyceridaemia; poorly controlled diabetes mellitus or hypertension; clinically significant liver or renal disease; vasculitis; HIV infection; MI or CABG/PTCA within 2 months of screening; any clinically significant unstable medical condition; history of dysphagia, swallowing disorders, or intestinal motility disorders; participated in a study of another investigational drug during the past 30 days; use of other lipid-lowering medication during the study; use of probucol in the year prior to screening or fibrates in the month prior to screening; active ethanol or drug abuse; breast-feeding; previous exposure to cholestagel; any evidence of active malignancy except for basal cell carcinoma of the skin.

A history of malignancy was not an exclusion criterion. Although certain relevant high-risk cardiovascular subjects populations are excluded, specific efficacy/safety issues are not to be expected taking into account the experience with the commercially available bile acid sequestrants.

Treatments

One clinical study was conducted with the tablet formulation (GTC-44-201). In the main efficacy studies, patients were instructed to take Cholestagel immediately prior to or with meals. The maximum monotherapy dose of 4.5 g per day was selected based on the results of a dose-ranging study, GTC-37-201, which suggested that a dose of 4.5 g per day would result in LDL cholesterol reductions of approximately 20% without a significant incidence of adverse events. Doses greater than 4.5 g per day were not studied. Constipation may increase with higher doses. A previous dose-ranging study with the prototype polymer (GTC-09-201) demonstrated that the incidence of constipation increased at 6.75 g per day.

Outcomes/endpoints

The primary efficacy parameter was the change in fasting serum LDL cholesterol from the baseline to the completion of the Cholestagel treatment period.

The secondary efficacy endpoints were in all studies percent change in LDL cholesterol, changes and percent changes in total cholesterol, HDL cholesterol and triglycerides. In addition, apolipoprotein B, Lp(a), apolipoprotein A-1 and LDL particle size were studied in GTC-37-201, GTC-48-204, GTC-48-205, GTC-48-301. The extent of lipid alterations was expressed as mean and median change and percent change from baseline to endpoint.

Statistical methods

The sample size was chosen to expose a sufficient number of patients to colesevelam for six months to meet the ICH Notes for guidance on population exposure, suggesting a number of patients in aggregate with other studies to be 300-600 patients. No formal power calculation was performed.

Both the intent to treat (ITT) and evaluable populations were used for the analysis of efficacy. The ITT population was defined as those patients who were randomised, took at least one dose of study medication, and had at least one post-baseline fasting lipid evaluation. The evaluable population was defined as those patients who completed the study and were at least 80% overall compliant to study medication. Assessment of study results refers to the ITT population.

In the main studies treatment groups, the change and percent change from baseline to endpoint were analysed using a paired t-test. Baseline was defined as the average of the Day –7 and Day 0 values. If applicable, the difference in change and percent change between groups was analysed using analysis of variance (ANOVA) with factor for treatment. If treatment factor was statistically significant, all of the paired comparisons between the treatment groups were performed using contrasts from the one-way ANOVA model, if appropriate. Both ANOVA and the paired t-test are based on a normal distribution assumption. If there was at least one treatment group non-normally distributed at the significance level of 0.01, the Kruskal-Wallis test replaced the ANOVA, the Wilcoxon Signed Rank test replaced the paired t-test, and the contrast of ANOVA was replaced by the Wilcoxon Rank-Sum test. Additional analyses have been conducted using a two-way ANOVA model with factors like

center, age-sex subgroups, race subgroups, baseline LDL cholesterol subgroups and treatment with treatment center interaction.

RESULTS

GTC-37-201: A Randomized, Double-Blind, Placebo-Controlled Evaluation of Cholestagel in Patients with Primary Hypercholesterolemia

Of the 149 patients treated, 137 (92%) completed the study. Colesevelam demonstrated a statistically significant and dose-related reduction in mean LDL cholesterol and mean total cholesterol compared to baseline with a maximum of 15%, p=0.0001 (0.79 mmol/L, p=0.0001) in the colesevelam 3.8 g treatment group for LDL cholesterol and a maximum of 8%, p=0.0001 (0.55 mmol/L, p=0.0001) in the colesevelam 3.8 g treatment group for total cholesterol. All but the colesevelam 1.5 g treatment group showed statistically significant reductions in LDL and total cholesterol compared to placebo. Median triglycerides increased significantly with 10%, p=0.021 (0.17 mmol/L, p=0.038) from baseline in the colesevelam 3.8 g treatment group and were significantly different from placebo (p=0.027 for percent change and p=0.017 for change).

GTC-37-202: A Randomized, Double-Blind, Placebo-Controlled Trial of Once-per-Day Versus Split Dosing of Cholestagel in Patients with Primary Hypercholesterolemia

Of the 122 patients randomised, 121 patients (99%) completed the study. Statistically significant mean reduction and percent reduction from baseline to endpoint in LDL cholesterol were noted for all of the colesevelam treatment groups compared to placebo, but the reduction was only 6-7% (0.31-0.36 mmol/L). This study was not powered to detect differences between the active treatment groups. Change and percent change in triglycerides from baseline to endpoint increased significantly with 17%, p= 0.005 (0.28 mmol/L, p=0.01) for the colesevelam qd in AM group.

GTC-48-301: A Randomized, Double-Blind Trial of Cholestagel versus Placebo in Patients with Primary Hypercholesterolemia

494 patients entered the treatment period, and 382 (77%) completed the study. Of the 494 patients randomised into the study, 467 were considered part of the ITT population and 353 were part of the evaluable population. Sustained reductions in LDL cholesterol ≥9% were obtained with Cholestagel at doses of 2.3 g and ≥15% at doses of 3.8 g and 4.5 g per day. However, only a limited number of the patients in the pivotal 6-month study reached the clinically more relevant target of LDL cholesterol <3mmol/L.

More than 50% of patients achieve at least a 15% reduction in LDL cholesterol regardless of baseline LDL cholesterol, and 6% of patients in the Cholestagel 4.5 g group and 14% of patients in the Cholestagel 3.8 g group were non-responders. There was no difference in mean percent reduction in LDL cholesterol across the strata of LDL-C levels of <4.15 mmol/L and LDL cholesterol ≥4.15 and ≤4.92 mmol/L. No conclusions can be drawn from the patient population with LDL cholesterol >4.92 mmol/L due to the small numbers of patients. Small, statistically significant increases in HDL cholesterol were also noted.

GTC-48-302: A Randomized, Double-Blind, Placebo-Controlled Trial of Once Per Day versus Split Dosing of Colesevelam Hydrochloride in Patients with Primary Hypercholesterolemia

One hundred seventy seven (177) patients were entered into the diet period; 98 were randomised into the drug treatment period; and 90 (92%) completed the trial.

Reductions in mean change and mean percent change in LDL cholesterol were statistically significant for each of the active treatment groups. The changes in the lipid parameters LDL cholesterol, total cholesterol, triglycerides, and HDL cholesterol do not show statistically significant differences between the three Cholestagel dosing regimens. Percent change in LDL cholesterol was similar in the evaluable population with LDL reductions of 20%, 16% and 19% for AM, PM and BID treatment groups, respectively. It appears that triglycerides increased more in the colesevelam 3.8 g AM treatment group compared to the colesevelam 3.8 g PM treatment group.

GTC-37-203: A Randomized, Double-Blind, Placebo-Controlled Trial of Cholestagel and Lovastatin Alone and in Combination in Patients with Primary Hypercholesterolemia

135 patients were randomised into the treatment period, and 126 (93%) completed the study.

The change and percent change in LDL Cholesterol were statistically significant for each of the active treatment groups. There was a 7% reduction in LDL cholesterol in the colesevelam 2.3 g treatment group compared with a 22% reduction for the lovastatin alone group.. The two combination treatment groups achieved the clinical target LDL cholesterol of 3 mmol/L even with low doses of both lovastatin and colesevelam. However, patients not responding adequately on lovastatin treatment alone should have had colesevelam as add-on therapy.
Combination therapy was more efficacious in reducing LDL cholesterol and total cholesterol than were the individual components alone. Combination therapy did not increase triglyceride levels in contrast to colesevelam given alone. There was no clinically significant change or percent change from baseline to endpoint for Lp(a). Changes in apolipoprotein A-1 mirrored changes observed for HDL cholesterol. Changes in apolipoprotein B mirrored changes observed for LDL cholesterol.

GTC-48-204: A Randomized, Double-Blind, Placebo-Controlled Trial of Cholestagel and Simvastatin Alone and in Combination in Patients with Primary Hypercholesterolemia
258 were randomised into the treatment period, and 241 (93%) patients completed the study.
Reductions in median change and percent change in LDL cholesterol were statistically significant for each of the active treatment groups. Paired comparisons between treatment groups demonstrated that both combination regimens (Cholestagel 2.3 g/Simvastatin 20 mg and Cholestagel 3.8 g/Simvastatin 10 mg) resulted in statistically superior reductions of LDL and total cholesterol compared to the monotherapies. The percent LDL cholesterol reductions in the colesevelam 2.3 g and 3.8 g treatment groups (8% and 16% respectively) are similar to the results in the pivotal 6 month study (9% and 15% respectively). Even the lowest simvastatin dose was more effective in reducing LDL cholesterol compared to colesevelam 3.8 g. The two combination treatment groups both achieved the clinical target LDL cholesterol of <3 mmol/L.
However, the study is limited by not investigating colesevelam as add on therapy to patients not reaching the clinical target LDL cholesterol on different simvastatin doses.
The combination of colesevelam and simvastatin reduced LDL cholesterol and total cholesterol more than either colesevelam or simvastatin alone.
The combination of Cholestagel 3.8 g/simvastatin 10 mg increased HDL cholesterol more than the individual treatments. However, the Cholestagel 2.3 g/simvastatin 20 mg did not increase HDL cholesterol more than the individual treatments.

GTC-48-205: A Randomized, Double-Blind, Placebo-Controlled Trial of Cholestagel and Atorvastatin Alone and in Combination in Patients with Primary Hypercholesterolemia
94 patients were randomised into the treatment period, and 89 (95%) completed the trial.
Reductions in median change and percent change in LDL cholesterol were statistically significant for each of the active treatment groups. The combination regimen of Cholestagel 3.8 g plus atorvastatin 10 mg resulted in greater LDL cholesterol reduction that either Cholestagel 3.8 g or atorvastatin 10 mg alone. The co-administration of Cholestagel and atorvastatin decreased LDL cholesterol by 47.6%. In addition, Cholestagel and atorvastatin in combination showed the highest median increase (10.8%) in HDL cholesterol.
The 12% reduction in LDL cholesterol in the colesevelam 3.8 g treatment group is similar to the result in the pivotal 6 month study (15%). Even the lowest dose of atorvastatin was more effective in reducing LDL cholesterol than colesevelam 3.8 g.
All treatment groups including atorvastatin achieved the clinical target LDL cholesterol of <3 mmol/L. However, the study is limited by not investigating colesevelam as add on therapy in patients not reaching the clinical target LDL cholesterol on different atorvastatin doses.

GTC-37-901: An Extended Use Study of Cholestagel in Patients with Primary Hypercholesterolemia
Two hundred seventy-two (272) patients from GTC-37-201, GTC-37-202, and GTC-37-203 were screened for this study, 260 patients were treated, and 186 (72%) completed the study. In this titration-based study, the Cholestagel dose was to be titrated to achieve a 15-30% LDL cholesterol reduction from the baseline value. Only 50% of patients were actually titrated per protocol to the maximum prescribed dose of 3.8 g/day by the final treatment interval (Week 42 to 50). Reductions in percent change in LDL cholesterol of –0.53 mmol/L and 12.0%, respectively, were observed at an average daily prescribed Cholestagel dose of 2.8 g/day. Cholestagel demonstrated a sustained LDL lowering effect over a 50-week treatment period.

The overall mean prescribed daily dose of colesevelam for the study was 2.8 g, and the mean prescribed daily dose in the last 8 weeks was 3.3 g. Only 48.6% of the patients in the All study visits convention and 39.5% of the patients in the colesevelam only visits convention achieved the protocol goal and experienced a >15% reduction in LDL cholesterol from baseline to endpoint. Of the 97 patients who were titrated to the maximum protocol dose of 3.8 g, 67% of the patients in the All study visits convention and only 46.4% of the patients in the colesevelamonly visits convention experienced a >15% reduction in LDL cholesterol from baseline to endpoint.
The 10.9% reduction in LDL cholesterol for the colesevelam only treatment group is similar to the 12% reduction in the colesevelam 3.0 g treatment group in the pivotal 6-month study.
The increase in triglycerides in colesevelam only treated patients was significant and the increase was similar to the results in the other clinical studies.

GTC-44-201: An Open-Label, Fixed-Dose, Safety Trial of Colesevelam Hydrochloride Tablets in Normal Volunteers

LDL cholesterol at the end of this study was reduced by 12% from baseline levels ($P \leq 0.001$) and triglycerides were increased by 30% from baseline ($P < 0.05$). 16 of the 20 randomised subjects had LDL cholesterol concentrations ≥3.36 mmol/l at screening (Day –7). Within this hypercholesterolaemic population, Cholestagel administration resulted in a mean decrease in LDL cholesterol of 15% ($P < 0.0001$), and a mean decrease in total cholesterol of 8%, supporting the efficacy of the tablet formulation. This is consistent with comparable efficacy of the capsule and tablet formulations of Cholestagel. LDL-cholesterol was reduced with 12% from baseline to endpoint ($p<0.001$). Triglycerides increased with 30% from baseline to endpoint ($P < 0.05$).
The study is too small to properly assess efficacy, but the lipid values suggest that the efficacy for tablets is similar to capsules.

Analysis performed across trials (pooled analyses and meta-analysis)

In the pooled safety analysis the Applicant also measured lipid variables. Colesevelam treatment was associated with statistically significant decreases in LDL and total cholesterol concentrations and statistically significant increases in HDL cholesterol and triglyceride concentrations from baseline to endpoint as compared to placebo.

Comparison of Efficacy Results of all Studies

Monotherapy

Changes in lipid variables in mmol/L (%) from baseline to endpoint in placebo-controlled monotherapy studies

DOSE	N	LDL-C MEAN	TOTAL-C MEAN	HDL-C MEDIAN	TG MEDIAN
37-201, Phase 2, 6 wks					
Placebo	29	0.07 (1)	0.04 (0)	-0.01 (-1)	-0.07 (-6)
Colesevelam 1.5 g	30	-0.22 (-4) *	-0.16 (-2)	-0.03 (-2)	0.16 (10)
Colesevelam 2.3 g	29	-0.40 (-8) *	-0.38 (-5) *	0.00 (0)	0.07 (3)
Colesevelam 3.0 g	30	-0.59 (-11) *	-0.53 (-8) *	0.04 (3)	0.01 (1)
Colesevelam 3.8 g	29	-0.79 (-15) *	-0.55 (-8) *	0.04 (4) §	0.17 (10) *

37-202, Phase 2, 4 wks					
Placebo	32	0.04 (1)	0.06 (1)	-0.03 (-3)	0.01 (0)
Colesevelam 1.5 g AM	30	-0.36 (-7) *	-0.21 (-3) *	0.01 (0)	0.28 (17) *
Colesevelam 1.5 g PM	30	-0.35 (-7) *	-0.26 (-4) *	0.03 (2)	0.09 (6)
Colesevelam 1.5 g b.i.d.	30	-0.31 (-6) *	-0.32 (-4) *	0.00 (0)	-0.03 (-2)
48-301, Phase 3, 6 mth					
Placebo	88	-0.01 (0)	0.04 (1)	-0.01 (-1)	0.05 (5)
Colesevelam 2.3 g	99	-0.36 (-9) *	-0.26 (-4) *	0.04 (3) *	0.13 (9) *
Colesevelam 3.0 g	91	-0.50 (-12) *	-0.40 (-6) *	0.05 (4) *	0.08 (5) §
Colesevelam 3.8 g	95	-0.62 (-15) *	-0.47 (-7) *	0.04 (3) *	0.17 (10) *
Colesevelam 4.5 g	94	-0.72 (-18) *	-0.61 (-10) *	0.04 (3) *	0.12 (9) *
48-302, Phase 3, 6 wks					
Placebo	22	0.11 (3)	0.20 (3)	0.00 (0)	-0.02 (-1)
Colesevelam 3.8 g AM	25	-0.79 (-18) *	-0.61 (-9) *	0.05 (3)	0.25 (15) *
Colesevelam 3.8 g PM	23	-0.63 (-15) *	-0.51 (-8) *	0.12 (8) §	0.12 (6)
Colesevelam 3.8 g b.i.d.	24	-0.83 (-18) *	-0.64 (-9) *	0.12 (8) *	0.10 (8)

* $P < 0.05$

§ Only statistically significant for percent change

P values based on t-test (normality met) and Wilcoxon signed-rank test (normality not met).

LDL-C: In all studies, statistically significant reductions in LDL cholesterol from baseline to endpoint were observed with all colesevelam administrations, and these were dose-related. Colesevelam monotherapy of 3.8 g and 4.5 g per day resulted in mean LDL cholesterol reductions of 15-18% which is considered to be a clinically meaningful reduction. However, the clinical target LDL cholesterol of <3 mmol/L was not reached with colesevelam monotherapy in the majority of patients.
The degree of percent LDL cholesterol lowering is consistent from one trial to another. Further, the data indicate that the efficacy of once daily dosing is similar to twice daily dosing, although the studies are too small to draw any firm conclusions.

Total-C: A 10% decrease in total cholesterol from baseline to endpoint was achieved with the highest colesevelam dose.

HDL-C: Minor elevations in HDL cholesterol occurred, but not consistent in all trials. Even small elevation in HDL cholesterol would be expected to have a potential clinical benefit. Published meta-analyses have demonstrated that a 1% increase in HDL cholesterol correspond to a 2-3% decrease in the risk of CHD mortality.

Triglycerides: There was an increase in triglycerides in all colesevelam monotherapy treatment groups with a maximum of 17% from baseline. In the one-year uncontrolled study median serum concentrations of triglycerides increased with 12% in patients treated with 3.8 g colesevelam.
The increase in triglycerides that occur with bile acid sequestrant therapy is thought to be due to increased synthesis of VLDL particles. The correlation between colesevelam doses and percent change in triglycerides is weaker than that for LDL cholesterol. It is therefore impossible to predict the occurrence of a large increase in triglycerides in patients treated with colesevelam.

HDL-C/Triglycerides: Usually HDL-cholesterol decreases when triglycerides increase as cholesterol ester formed on HDL transfers to other lipoproteins via cholesterol ester transfer protein in exchange for triglycerides. However, when colesevelam is used, HDL-cholesterol is slightly increased.

Apolipoprotein B: The pivotal 6 month study showed a 12% median reduction in Apolipoprotein B from baseline to endpoint in the colesevelam 3.8 g and 4.5 g treatment groups which corresponds to the LDL cholesterol reduction. Apolipoprotein B was unaffected in the placebo group.

Combination therapy

Changes in lipid variables in mmol/L (%) from baseline to endpoint in placebo-controlled combination studies

DOSE	N	LDL-C MEAN	TOTAL-C MEAN	HDL –C MEDIAN	TG MEDIAN
37-203 Phase 2, 4 wks					
Placebo	26	0.02 (0)	0.04 (1)	0.01 (1)	0.01 (1)
Colesevelam 2.3 g	29	-0.34 (-7) *	-0.19 (-3)	0.06 (5) *	0.27 (16) §
Lovastatin 10 mg	26	-1.00 (-22) *	-0.97 (-14) *	0.05 (5)	0.01 (0)
Colesevelam 2.3 g/lov 10mg together	27	-1.54 (-34) *	-1.41 (-21) *	0.05 (4)	-0.02 (-1)
Colesevelam 2.3 g/lov 10mg apart	23	-1.37 (-32) *	-1.37 (-21) *	0.03 (2)	-0.02 (-2)
48-204 Phase 2, 6 wks					
Placebo	33	-0.18 (-4) *	-0.16 (-2)	-0.04 (-3)	0.09 (6)
Colesevelam 2.3 g	36	-0.44 (-8) *	-0.28 (-4) *	0.05 (3) *	0.21 (11)
Colesevelam 3.8 g	37	-0.79 (-16) *	-0.63 (-9) *	0.01 (2)	0.19 (11) *
Simvastatin 10 mg	35	-1.23 (-26) *	-1.29 (-19) *	0.04 (3) *	-0.26 (-17) *
Simvastatin 20 mg	39	-1.57 (-34) *	-1.60 (-23) *	0.08 (7) *	-0.19 (-12) *
Colesevelam 2.3 g/simvastatin 20mg	37	-2.07 (-42) *	-2.05 (-29) *	0.05 (4) *	-0.16 (-12) *
Colesevelam 3.8 g/ simvastatin 10mg	34	-2.07 (-42) *	-2.00 (-28) *	0.13 (10) *	-0.19 (-12)
48-205 Phase 2, 4 wks					
Placebo	19	0.16 (3)	0.29 (4) *	0.05 (4) *	0.16 (10)
Colesevelam 3.8 g	16	-0.56 (-12) *	-0.37 (-6) *	0.03 (3) *	0.22 (10)
Atorvastatin 10 mg	18	-1.77 (-38) *	-1.89 (-27) *	0.10 (8) *	-0.43 (-24) *
Colesevelam 3.8 g/ atorvastatin 10 mg	18	-2.31 (-48) *	-2.15 (-31) *	0.11 (11) *	-0.02 (-1)
Atorvastatin 80 mg	20	-2.48 (-53) *	-2.70 (-39) *	0.06 (6) *	-0.58 (-33) *

*P <0.05

§ Only statistically significant for percent change

P values based on t-test (normality met) and Wilcoxon signed-rank test (normality not met).

The strategy used with Cholestagel and HMG-CoA reductase inhibitors was to span the range of low to standard doses with both agents. While no one HMG-CoA reductase inhibitor was used at doses

across the spectrum, the dose combinations with lovastatin, simvastatin, and atorvastatin complemented each other. In all of these cases, combination therapy was more efficacious than were the individual components alone. In GTC-48-205, a standard monotherapy dose of Cholestagel (3.8 g per day) was combined with a starting dose of atorvastatin (10 mg per day) and achieved a 48% mean reduction in LDL cholesterol. Low-dose Cholestagel with standard-dose simvastatin in GTC-48-204, and low-dose Cholestagel with low-dose lovastatin in GTC-37-203 also resulted in additive efficacy.

HMG-COA REDUCTASE INHIBITOR DOSE	CHOLESTAGEL DOSE	% LDL CHOLESTEROL DECREASE FROM CHOLESTAGEL	% LDL CHOLESTEROL DECREASE FROM HMG-COA R.I.	PREDICTED DECREASE	ACTUAL DECREASE IN CLINICAL STUDIES FOR COMBINATION
Lovastatin 10 mg	Cholestagel 2.3 g (dosed together)	7%	22%	27%	34%
Lovastatin 10 mg	Cholestagel 2.3 g (dosed apart)	7%	22%	27%	32%
Simvastatin 20 mg	Cholestagel 2.3 g	8%	34%	39%	42%
Simvastatin 10 mg	Cholestagel 3.8 g	16%	26%	38%	42%
Atorvastatin 10 mg	Cholestagel 3.8 g	12%	38%	45%	48%

To predict the additive effects of colesevelam and HMG-CoA reductase inhibitors in combination, the following formula in which two drugs, A and B, are assumed to act independently were used:
(Initial LDL cholesterol level)X(1-x)=(LDL cholesterol level with drug A monotherapy), where x is the percentage of reduction in LDL cholesterol after use of drug A, divided by 100.
(LDL cholesterol level with monotherapy)X(1-y)=(LDL cholesterol level with combination therapy), where y is the percentage of reduction in the LDL cholesterol level after use of drug B, divided by 100.

For all combinations of Cholestagel and an HMG-CoA reductase inhibitor, the actual decrease in LDL cholesterol was the same or exceeded the predicted decrease. At least an additive increase in efficacy was concluded. Within the 95% confidence limits for the regression, all of the results fall above the line of additivity, supporting that Cholestagel in combination with lovastatin, simvastatin, and atorvastatin results in at least additive efficacy.

The studies demonstrate the additive efficacy of combination therapy with HMG-CoA reductase inhibitors and colesevelam. However, a limitation to the strategy used is that there are no add-on studies in patients not reaching satisfactory LDL-cholesterol levels on HMG-CoA reductase monotherapy.

Historical comparison with other available drugs
An important limitation of the colesevelam development plan was the lack of direct comparison between colesevelam and another bile acid sequestrant. Cholestyramine has documented survival benefit in the Lipid Research Clinics Coronary Primary Prevention Trial. On a g/g basis Cholestagel is more potent in reducing LDL and total cholesterol when compared to other bile acid sequestrants. When data from the largest and longest controlled primary prevention study with bile acid sequestrants (the LRC-CPPT) is analysed, Cholestagel suggests to be 3- to 4- fold more potent than

cholestyramine. However, a historical comparison might speculate that Colestipol and Cholestyramine are more efficacious in the highest licensed dose when compared with Cholestagel.

Non-responders
In the pivotal 6 month study, GTC-48-301, 37 % of the patients treated with 4.5 g colesevelam/day and 46% of those treated with 3.8 g colesevelam/day did not reach at least 15% reduction in LDL cholesterol. The reason for poor response in patients could be due to an excessive hepatic cholesterol synthesis or poor compliance. Increased hepatic cholesterol synthesis is thought to increase VLDL production and triglyceride levels when patients are treated with bile acid sequestrants.

AM/PM once daily dosing: LDL-cholesterol reductions were similar with both dosing regimens and compared to twice daily dosing. In the GTC-37-202 study median triglycerides increased with 17% from baseline to endpoint in the colesevelam 1.5 g AM group compared to 6% in the colesevelam 1.5 g PM group. In the GTC-48-302 study triglycerides increased with 15% in the colesevelam 3.8 g AM group compared to 6% in the colesevelam 3.8 g PM group.

Long-term efficacy
The pivotal 6 month study demonstrated a sustained reduction in LDL cholesterol over a 6-month period compared to placebo. The overall mean prescribed daily dose of colesevelam for the 1 year extension study was 2.8 g and the mean prescribed daily dose in the last 4 weeks was 3.3 g. Only 48.6% of the patients taking Cholestagel alone or Cholestagel in combination with a HMG-CoA reductase inhibitors and 39.5% of the patients taking only Cholestagel achieved the protocol goal i.e. >15% reduction in LDL cholesterol from baseline to endpoint. Of the 97 patients who were titrated to the maximum protocol dose of 3.8 g, 67% of the patients taking Cholestagel in combination with a HMG-CoA reductase inhibitor and only 46.4% of the patients in the Cholestagel only group experienced a >15% reduction in LDL cholesterol from baseline to endpoint.

Comparison of Results in Subpopulations
Correlations between demographic categories and LDL cholesterol reduction were made for major subgroups of hyperlipidaemic patients in the US population: men <65, men =65, women <65, women =65, Caucasians, Non-Caucasians, premenopausal and postmenopausal women on hormone replacement, and postmenopausal women without hormone replacement. Data were also collected on patients in different baseline LDL cholesterol categories: <4.14 mmol/l, 4.14-4.91 mmol/l, and >4.91 mmol/l. These data show that Cholestagel produces a dose-related decrease in LDL cholesterol for all of the subgroups tested.
As colesevelam is not absorbed, no dose adjustments should be necessary in patient with impaired renal function. Some of the colesevelam effect is based on liver synthesis. The efficacy in patients with liver failure has not been investigated.
A separate study in diabetic patients would have been of value as many published studies have demonstrated a significant association between increased triglycerides and CHD, particularly in patients with diabetes.
Studies in children have not been conducted. However, about 1 in 500 in the European population has familiar hypercholesterolaemia. The most important clinical feature of familial hypercholesterolaemia is the development of premature and extensive atherosclerosis. Considering the need for therapeutic options in children with familiar hypercholesterolaemia, studies in paediatric patients are encouraged on the condition that effects on serum triglyceride concentration are studied closely.
The Applicant has committed to perform a Post-Approval study in the hypercholesterolaemic paediatric population within specified timeframes.

Discussion on clinical efficacy

One study including 24 patients with hypercholesterolaemia was conducted to assess the effects of Cholestagel on sterol metabolism in humans, and hence to assess the mechanism of action of Cholestagel as a hypocholesterolaemic agent. Cholestagel decreased LDL cholesterol and total cholesterol in a dose-related fashion. Fecal bile acids were increased but not statistically significant. With Cholestagel, the physiological post-prandial rise in serum bile acid salts was blunted in a dose-dependent manner. The increase in urine mevalonic acid showed that Cholestagel induced a

compensatory increase in total body cholesterol synthesis. Dose response was limited as a higher dose than 4.5 g was not studied. Constipation may increase with higher doses. There was a marked increase in fatty acid excretion but the difference was not statistically significant, probably due to the small numbers of patients and the large standard deviations. No steatorrhea has been noted. However, increased fatty acid excretion has the potential of increasing excretion of fat soluble vitamins and can be a clinical problem especially when treating patients with a susceptibility to fat soluble vitamin deficiencies.
There were no significant differences between postprandial serum triglycerides at baseline and after 2 or 4 weeks of colesevelam treatment. However, postprandial lipid values were measured up to 4 hours only, while the triglycerides were still increasing
The results from the study indicate a similar mechanism of action of colesevelam as for other bile acid sequestrants even though increased synthesis of bile acids have not been shown and a direct comparison have not been made.

The study with radiolabelled colesevelam demonstrated that the colesevelam is negligibly absorbed and eliminated via the gastrointestinal tract system. However, in this study the proposed maximum dose was not investigated.

Colesevelam reduced the bioavailability of verapamil and the metabolite norverapamil, but did not significantly reduce the bioavailability of quinidine, valproic acid, digoxin, warfarin, metoprolol, or lovastatin. 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, cannot be excluded with a concomitant medicinal product, that medication should be administered at least one hour before or four hours after Cholestagel to minimize the risk of reduced absorption of the concomitant medication. Drug-drug interaction studies were performed with an insufficient number and inadequate selection of drugs. The selection of drugs tested in *in vivo* studies should have been based on known interactions with other bile acid sequestrants. The Applicant has committed to perform further interaction studies post-marketing with Cholestagel.
The applicant has conducted five Phase 2 studies in which efficacy and safety of Cholestagel was evaluated. The Objectives, treatment, design and endpoint assessment of the Phase 2 studies are similar to the two Phase 3 main studies: one dose-ranging study designed to determine the long-term efficacy and safety of Cholestagel and another designed to confirm the efficacy of once daily versus split daily doses. The efficacy data are limited as only 1264 unique subjects/patients have been exposed to colesevelam.

The primary efficacy parameter was the change in fasting serum LDL cholesterol from the baseline to the completion of the Cholestagel treatment period. The significance assigned to this endpoint reflects the strong correlation established between elevated LDL cholesterol and coronary heart disease (CHD), and the evidence from clinical trials showing that reductions in LDL cholesterol have a beneficial effect on morbidity and mortality from CHD. The chosen variable is therefore considered a reasonable primary surrogate endpoint, but is acceptable only if no significant deleterious effects on other lipid variables such as HDL, cholesterol and triglycerides occur. Secondary efficacy parameters included total cholesterol, HDL cholesterol, triglycerides, and apolipoproteins.

Although the primary efficacy variable was the change in LDL cholesterol from baseline to endpoint, the Applicant has focused on percent change in LDL cholesterol. A given percent change in LDL cholesterol corresponds to a smaller absolute reduction in patients with a moderate LDL cholesterol at baseline compared to patients with a high baseline LDL cholesterol. In addition, the association between LDL cholesterol and risk of CHD is not linear, and a certain change in LDL cholesterol leads to a larger reduction in risk of CHD for patients with a high baseline value than for patients with a lower LDL cholesterol at baseline.

Colesevelam monotherapy at doses of 3.8 g and 4.5 g per day lowers LDL-cholesterol by 15-18%, which is considered a clinically relevant reduction. Similar LDL cholesterol reductions were achieved whether Cholestagel was dosed once per day or split between breakfast and dinner. However, the overall effect of colesevelam monotherapy is too small to reach the clinical target of <3 mmol/L.

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%.
Doses greater than 4.5 g per day were not studied. Constipation may increase with higher doses.
The effects of Cholestagel on mortality or morbidity are not known.
Initiation of add-on treatment with Cholestagel subsequent to statin therapy has not been specifically studied. However, combination therapy with an HMG-CoA reductase inhibitor was shown to be more efficacious than were the individual components alone and triglycerides were not increased in patients receiving combination therapy due to the triglyceride lowering effects of HMG-CoA reductase inhibitors. The incremental benefit from adding an HMG-CoA reductase inhibitor to Cholestagel is similar to the benefit from Cholestagel monotherapy. 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.
Median percent reductions with each combination were 49% with Cholestagel 3.8 g/atorvastatin 10 mg; 42% with both Cholestagel 3.8 g/simvastatin 10 mg and Cholestagel 2.3 g/simvastatin 20 mg; 33% with Cholestagel 2.3 g/lovastatin 10 mg dosed together; and 31% with Cholestagel 2.3 g/lovastatin 10 mg dosed apart. However, as expected HMG-CoA reductase inhibitors were more potent in reducing LDL cholesterol and total cholesterol and had a larger increase in HDL cholesterol compared to colesevelam. In addition, with respect to triglycerides these were reduced. HMG-CoA reductase inhibitors have outcome studies with morbidity/mortality endpoints, whereas colesevelam studies are only based on the surrogate endpoint LDL cholesterol.

Cholestagel has not been compared directly to other bile acid sequestrants in clinical trials. The primary disadvantages of currently prescribed bile acid sequestrants are unpalatability, the large daily dose needed and the high incidence of gastrointestinal side effects. The effects of Cholestagel on lipids are similar to currently available bile acid sequestrants. When compared with historical data colestipol and colestyramine in their highest dose are, more efficacious when compared with Cholestagel. Cholestagel monotherapy doses of 3.8 g and 4.5 g per day resulted in median reductions of LDL of more than 15%. At the highest approved dosage, colestyramine (24 g per day) and colestipol (30 g per day) lower LDL cholesterol on average 15 to 30%. The chosen maximum dose of Colestagel is driven by an improved tolerability profile relative to other bile acid sequestrants. This strategy can be debated from an efficacy point of view because the relative low incidence of side effects can be attributed to a too low dose leading to a debatable efficacy profile.

Of concern is the increase in triglycerides seen during colesevelam treatment. 2% of Cholestagel only and no placebo patients experienced treatment emergent serum triglyceride levels of ≥ 6 mmol/L; 7% of Cholestagel and 5% of placebo patients experienced treatment emergent serum triglyceride levels ≥ 4 mmol/L. However, these pharmacodynamic effects are well known with the other bile acid binding resins. Further, triglycerides did not increase when colesevelam was combined with a HMG-CoA reductase inhibitor.
In very rare cases, elevation in triglycerides and/or cholesterol was spontaneously reported in USA postmarketing reports after launching in September 2000. Some of these patients had extreme elevations in triglycerides, which were seen both when colesevelam was given alone, and when given in combination with simvastatin. There is growing evidence of the importance of triglycerides as a risk factor for CHD, and some of the benefit of reducing LDL-cholesterol might to some extent be counteracted by the triglyceride increasing effect of colesevelam. However, if HMG-CoA reductase inhibitors are contraindicated/not tolerated, a high LDL-cholesterol level is probably a bigger risk factor than a moderate increase in triglycerides. Increased hepatic cholesterol synthesis would probably increase the VLDL production and might explain the extreme serum triglyceride levels seen in some patients. 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.

It has to be pointed out that the effects of Cholestagel on mortality and morbidity are not known. For this reason HMG-CoA reductase inhibitors should remain the first line treatment in patients with

hypercholesterolaemia. Despite the efficacy of the HMG-CoA reductase inhibitors, many patients with severe hypercholesterolaemia may not respond sufficiently and will require combination therapy, using an-add on approach, to achieve target LDL cholesterol levels.
Colesevelam could be an alternative to HMG-CoA reductase inhibitors in patients where these are contraindicated or not tolerated. The major drawback of currently available bile acid resins or sequestrants is their lack of tolerability. Side effects of bile acid binding resins (colestipol, colestyramine) are primarily related to gastrointestinal intolerance, which include symptoms of nausea, bloating, abdominal pain, and constipation. The resins must be taken in large quantities as a gritty powder mixed in water or as numerous large tablets. The improved potency of colesevelam might allow for once per day dosing and thereby increase compliance compared to other bile acid sequestrants.

Cholestagel belongs to the bile sequestrants class with a well-known and recognised mechanism of primary and secondary pharmacological actions. No unexpected pharmacological properties are present. It is recommended by various expert panels to use this class of agents with statins. A number of already registered bile acid sequestrants (cholestyramine and colestipol) are indicated for the add-on indication. It has been demonstrated also for Cholestagel that the combination with statins is more effective than the monocomponents. Post-marketing data from the US do not indicate any specific problems with regard to efficacy while a significant number of patients were already on the maximum approved dose.
Cholestagel is indicated for co-administration with an HMG-CoA reductase inhibitor (statin) as adjunctive therapy to diet to provide an additive reduction in LDL-cholesterol (LDL-C) levels in patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone,
and as monotherapy as adjunctive therapy to diet for reduction of elevated total and LDL-cholesterol in patients with isolated primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well tolerated.
It is not considered necessary to perform an add-on study in patients who have responded insufficiently to the optimal dosage before registration. However, in order to gather further efficacy and safety the Applicant has committed to perform a Post Approval Study of Cholestagel as add-on therapy to an optimal dose of statin.

Prior to initiating therapy with Cholestagel as combination therapy or monotherapy, patients should be placed on a cholesterol-lowering diet and a lipid profile performed to assess total-cholesterol (total-C), HDL-cholesterol (HDL-C) and triglyceride levels. During therapy, this 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. Current European guidelines should be consulted to establish treatment approaches and goals for individual patients.
Cholestagel tablets should be taken orally with a meal and liquid. When a drug interaction cannot be excluded with a concomitant medicinal product, that medication should be administered at least one hour before or four hours after Cholestagel to minimize the risk of reduced absorption of the concomitant medication.
Combination therapy: Therapy with Cholestagel may be initiated when standard doses of the HMG-CoA reductase inhibitor are inadequate or not well tolerated; the SPC for that particular HMG-CoA reductase inhibitor should be consulted. 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. Co-administration with atorvastatin, lovastatin or simvastatin in clinical trials shows that Cholestagel can be dosed at the same time as one of these HMG-CoA reductase inhibitors or the two medicinal products can be 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.

Clinical safety

Cholestagel is a member of a class of bile acid sequestrant drugs that are used principally for treatment of elevated LDL cholesterol. An established drawback of currently available bile acid sequestrants, Questran (cholestyramine) and Colestid (colestipol), is lack of tolerability. Because these drugs are not absorbed, the risk of systemic toxicity is low. However, these marketed bile acid sequestrants can

interfere with the absorption of fat-soluble vitamins and other drugs including phenylbutazone, thyroid hormone, digitalis, warfarin, thiazide diuretics, and some antibiotics. Given the history of bile acid sequestrants, the areas of safety concern during the development of Cholestagel were related to gastrointestinal tolerance, interference with the absorption of fat-soluble vitamins, and drug interactions. Safety data are tabulated for Cholestagel, Cholestagel in combination with HMG-CoA reductase inhibitors versus placebo and for increasing doses of Cholestagel in the monotherapy studies.

Patient exposure

A total of 1870 patients were treated in the entire clinical development programme:

- 1350 patients in the placebo-controlled efficacy trials (GTC-37-201, GTC-37-202, GTC-37-203, GTC-48-204, GTC-48-205, GTC-48-301, and GTC-48-302),
- 260 patients in a non-randomised, non-placebo-controlled extension study (GTC-37-901) 187 of these patients had previously been exposed to Cholestagel in one of the efficacy trials,
- 24 patients in a randomised, non-placebo-controlled pharmacodynamic study (GTC-48-802),
- 20 healthy subjects in a non-randomised, non-placebo-controlled trial of Cholestagel tablets that included an efficacy endpoint, and so are numbered as a Phase 2 study (GTC-44-201),
- 216 healthy subjects that received either a single dose (172 subjects) or multiple doses (44 subjects) of Cholestagel.

The 1350 patients included in the integrated safety analysis represent 98% of the total of 1374 patients treated, and all patients included in Phase 2 and 3 clinical studies. The 952 patients exposed to Cholestagel alone or in combination with HMG-CoA reductase inhibitors in the integrated safety analysis represent 98% of the 976 patients exposed to multiple doses of Cholestagel in clinical studies. The two uncontrolled clinical studies excluded from the pooled safety analysis are Studies GTC-48-802 (24 patients) and GTC-37-901 (260 patients).

The demographic characteristics of the patients included in the safety analysis represented reasonably those likely to be treated with antihypercholesterolaemic medications, although the prevalence of male subjects might be somewhat low. Over 25% of the patients treated were greater than or equal to 65 years of age, and 4.3% were greater than or equal to 75 years of age. Cholestagel only treatment categories had significantly longer average exposure than the combination Cholestagel/HMG-CoA reductase inhibitor. Age, sex, hormonal status, race, and the percentage of overweight patients and smokers were reasonably balanced across studies. There were substantial percentages of patients in the three baseline LDL cholesterol categories that could be considered to represent mild (<4.14 mmol/l), moderate (4.14 to 4.91 mmol/l), and severe (>4.91 mmol/l) degrees of elevated LDL cholesterol. The distributions among the three categories were dissimilar across studies as a result of protocol design.

Adverse events

In general, the percentages of patients reporting common adverse events were similar in the placebo and Cholestagel only treatment categories. Only constipation and dyspepsia were reported by a higher percentage among Cholestagel only patients. These events were generally mild and did not often result in drug discontinuation. There was no significant increase in laxative or antacid use.

Constipation was reported by a slightly higher percentage of patients in the colesevelam/HMG-CoA reductase inhibitor treatment group (10.3%) compared to the HMG-CoA only treatment group (7.9%). Compared with placebo, the percentage of patients reporting these adverse events were increased by approximately 5%. The gastrointestinal side effects do not seem to be markedly dose-related, and increasing the dose to 4.5 g seems to be acceptable with regard to such adverse events.

Myalgia seems to be more frequent in the colesevelam/HMG-CoA reductase inhibitor group and the HMG-CoA reductase inhibitor only group (6.2% and 3.6% respectively) compared to the colesevelam only group and placebo group (2.1% and 0.4% respectively). It was suggested that myalgia was more frequently reported for the Cholestagel/HMG-CoA reductase inhibitor group as compared with HGM-CoA reductase inhibitor alone; however, a statistical comparison showed the difference to be non-significant (p=0.29).

Serious adverse event/deaths/other significant events

There were 3 deaths in three different centres and in three different studies: aspiration pneumonia secondary to a cerebrovascular accident, myocardial infarction and homicide. All deaths were considered unrelated to study medication.
A total of 1.9% of placebo patients and 1.4% of Cholestagel only patients experienced serious adverse events. A total of 0.7% of both the Cholestagel/HMG-CoA reductase inhibitor and HMG-CoA reductase inhibitor only patients experienced serious adverse events. In total, there were 18 serious adverse events during study treatment in the seven placebo-controlled studies. These serious adverse events were similar to what could be expected in a general population over the treatment period.
All but one of these serious adverse events were considered not related or remote to study medication. The one exception was a patient on placebo who experienced abdominal pain that was considered possibly related to treatment. However, 5 patients had a cardiovascular event when taking colesevelam compared to none in the placebo group. All of these patients took medium or high doses of colesevelam (2.3-4.5 g). Due to the small number of events it is not possible to draw any conclusion regarding the differences noted.

Laboratory findings
Cholestagel increased mean AST, ALT, and alkaline phosphatase levels slightly when used alone using dichotomised endpoints. However, the changes were small and not considered clinically relevant. Demographic subgroups had similar isolated laboratory changes. These changes were anticipated because bile acid sequestrants are known to cause slight increases in liver function tests. There is no plausible physiological explanation of why Cholestagel would cause liver toxicity because it is not absorbed and cannot accumulate in tissues. Cholestagel used in combination with HMG-CoA reductase inhibitors did not alter the magnitudes of the increases in liver function tests observed with the HMG-CoA reductase inhibitor.

There are isolated case reports of hyperchloraemic metabolic acidosis due to increased chloride intake with cholestyramine in patients taking cholestyramine for the indication of pruritis associated with liver disease, and has most often been associated with concomitant use of spironolactone. Typical dietary chloride intake is 4000 to 6000 g/day. For Cholestagel an additional risk is not anticipated because of the lower doses of Cholestagel administered.
Vitamin K status was indirectly measured using PT and PTT. The baseline and endpoint means were within the normal ranges and the magnitudes of the changes were relatively small. The incidence of notable high PT and PTT is numerically only slightly higher in the colesevelam treated patients compared to placebo. However, from non-clinical studies anaemia and haemorrhage associated with vitamin K depletion have been observed in rats and dogs at doses that are 40-fold and 8-fold, respectively, greater than the maximum recommended human dose.
Because of this finding, the principal safety concern in humans is the interference with the absorption of fat-soluble vitamins.

Safety in special populations
The safety of colesevelam has not been established in risk patients, pregnant women, lactating women or children. Since the safety of colesevelam in patients with liver failure is not established, an appropriate statement has been included in the warning section in the SPC. However, specific safety issues are not to be expected taking into account the experience with the commercially available bile acid sequestrants. There are only very limited data on patients with type II diabetes mellitus and documented atherosclerosis and more extensive data would have been of value. The Applicant has committed to perform a Post-Approval study in the hypercholesterolaemic paediatric population.

Interactions
The only overt toxicity in nonclinical testing of Cholestagel was interference with the absorption of fat-soluble vitamins. Absorption of fat-soluble vitamins is dependent upon bile acids. As a result, fat-soluble vitamin serum concentrations were considered key safety parameters, and fat-soluble Vitamins were measured in the Cholestagel clinical studies.
The Cholestagel and Cholestagel/HMG-CoA reductase inhibitor groups did not have statistically significant changes in PT, Vitamin A or Vitamin E levels. There were small statistically but not

clinically relevant decreases in PTT for the Cholestagel and Cholestagel/HMG-CoA reductase inhibitor groups. However, it should be recognised that the reduction will be directly related to the dose administered.
Drug-drug interaction studies were performed with a limited number and selection of medicinal products. Only single-dose studies were performed. Postmarketing reports have indicated possible drug-drug interactions with colesevelam. Drugs reported more than once include levothyroxin sodium, phenytoin, gabapentin, and warfarin, the interaction with warfarin possibly caused by reduced absorption of fat-soluble vitamins (e.g. vitamin K).
The Applicant has committed to perform further interaction studies with Cholestagel.

Discontinuation due to adverse events
Of the 1350 patients treated, 82 (6.1%) discontinued due to an adverse event. The percentage of patients discontinuing due to an adverse event ranged from 1.0% in GTC-37-202, a 4-week treatment study, to 9.9% in GTC-48-301, the 6-month treatment study. The absolute majority of Cholestagel treated patients terminated due to digestive system related adverse events. Constipation is the major complaint and at times is severe. Other, less frequent gastrointestinal complaints comprises abdominal discomfort (abdominal pain and cramping), intestinal gas (bloating and flatulence), indigestion and heartburn, diarrhoea and loose stools, and nausea and vomiting.

Post marketing experience
On 26 May 2000, colesevelam hydrochloride was approved, in capsule and tablet form for marketing in the U.S. The tablets are marketed under the tradename WelChol and the capsules are not being marketed. There have been ten periodic adverse event reports since launch. The reported incidence of labelled adverse events is <0.05%.

The majority of adverse events have been gastrointestinal in nature as would be expected from the results of the pivotal 6-month study (GTC-48-301). Cases received describing elevations in triglycerides and/or cholesterol were very rare. The baseline triglyceride levels were higher for these patients than median baseline levels in the submitted studies, which might suggest that patients with high baseline triglyceride levels are more prone to colesevelam induced hypertriglyceridaemia. The changes in HDL cholesterol values of these patients are of interest, but are not presented. Elevations in triglycerides are a matter of concern as an increase in triglycerides is correlated with an increase in CHD and patients with triglyceride levels above 10 mmol/L are at high risk of developing pancreatitis. Published data suggest that the combination of high TG and low HDL-C levels is a powerful risk factor for cardiac events or CHD deaths, even when LDL cholesterol levels are normal. Furthermore, elevated triglycerides are a CHD risk factor, regardless of the HDL cholesterol level.
One patient with no history of excessive alcohol consumption was hospitalised with a diagnosis of acute pancreatitis 2 days after he started Welchol therapy. The physician associated the use of Welchol to the event.
Some of the case reports indicate possible drug-drug interactions with colesevelam. Drugs reported more than once include levothyroxin sodium, phenytoin, gabapentin, and warfarin, the interaction with warfarin possibly caused by reduced absorption of fat-soluble vitamins (e.g. vitamin K).

Long term safety
The absence of a control group in the extended one-year study makes it difficult to draw conclusions. However, no clinically significant mean changes in chemistry, haematology, vitamin or coagulation variables were reported in the GTC-37-901 study. The safety results of this study support the results of the placebo-controlled studies.

Discussion on clinical safety

Cholestagel monotherapy was associated with a 3% increase over placebo in the percentage of patients terminating early due to an adverse event. Cholestagel in combination with HMG-CoA reductase inhibitors was associated with a 3% increase over HMG-CoA reductase inhibitor alone in the percentage of patients terminating early due to an adverse event. The side effects that were notably increased in frequency relative to placebo treated patients are constipation and dyspepsia. Compared with placebo, the percentage of patients reporting these adverse events are increased approximately by 5%. Constipation

and dyspepsia are generally mild or moderate in intensity and rarely resulted in study termination. These increases were related to intolerance for the medicinal product rather than toxicity. One in 30 patients discontinued due to side effects that could be attributed to Cholestagel treatment either alone or in combination with HMG-CoA reductase inhibitors. 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. The risk of constipation should especially be considered in patients with coronary heart disease and angina pectoris.

Cholestagel was associated with some statistically significant changes in some serum chemistry parameters. However, in general the magnitudes of the changes were small and the mean values remained within the normal range at baseline and endpoint of the analysis. Cholestagel increased mean AST, ALT, and alkaline phosphatase levels slightly when used alone using dichotomised endpoints. These changes were anticipated because bile acid sequestrants are known to cause slight increases in liver function tests. It should be noticed that there is no plausible physiological explanation of whether Cholestagel would cause liver toxicity because it is not absorbed and cannot accumulate in tissues. Cholestagel in combination with HMG-CoA reductase inhibitors did not alter the magnitudes of the increases in liver function tests as observed with the HMG-CoA reductase inhibitor. The Cholestagel and Cholestagel/HMG-CoA reductase inhibitor groups did not show statistically significant changes in PT, Vitamin A or Vitamin E levels. There were small statistically significant but clinically irrelevant decreases in PTT for the Cholestagel group. 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. Further, anticoagulant therapy should be monitored closely in patients receiving warfarin or similar agents, since bile acid sequestrants have been shown both to reduce absorption of vitamin K and to interfere with warfarin's anticoagulant effect.

There was an increase in myalgia for the Cholestagel/HMG-CoA reductase inhibitor group as compared with HGM-CoA reductase inhibitor alone; however, a statistical comparison showed the difference to be non-significant (p=0.29). Noteworthy is that Cholestagel only treatment categories had significantly longer average exposure than the combination Cholestagel/HMG-CoA reductase inhibitor. There are isolated case reports of hyperchloraemic metabolic acidosis in patients with pruritis associated with liver disease due to increased chloride intake with cholestyramine predominantly in concomitant use of spironolactone. Typical dietary chloride intake is 4000 to 6000 g/day. Additional risk with Cholestagel is not anticipated because of the lower doses of Cholestagel administered.

Of concern is the increase in triglycerides seen during colesevelam treatment. 2% of Cholestagel only and no placebo patients experienced treatment emergent serum triglyceride levels of $\geq$ 6 mmol/L; 7% of Cholestagel and 5% of placebo patients experienced treatment emergent serum triglyceride levels $\geq$ 4 mmol/L. However, these pharmacodynamic effects are well known with the other bile acid binding resins. 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.

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.
Drug-drug interaction studies were performed with a limited number and selection of medicinal products. The Applicant has committed to perform further interaction studies with Cholestagel. When a drug interaction cannot be excluded with a concomitant medicinal product, that medication should be administered at least one hour before or four hours after Cholestagel to minimize the risk of reduced absorption of the concomitant medication.

Cholestagel belongs to the bile sequestrants class with a well-known and recognised mechanism of primary and secondary pharmacological actions. No unexpected pharmacological properties are present. It is recommended by various expert panels to use this class of agents with statins. A number of already registered bile acid sequestrants (cholestyramine and colestipol) are indicated for the add-on indication. Post-marketing data from the US do not indicate any specific problems with regard to safety while a significant number of patients were already on the maximum approved dose.
Cholestagel is indicated for co-administration with an HMG-CoA reductase inhibitor (statin) as adjunctive therapy to diet to provide an additive reduction in LDL-cholesterol (LDL-C) levels in patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone,
and as monotherapy as adjunctive therapy to diet for reduction of elevated total and LDL-cholesterol in patients with isolated primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well tolerated.
It is not considered necessary to perform an add-on study in patients who have responded insufficiently to the optimal dosage before registration. However, in order to gather further efficacy and safety the Applicant has committed to perform a Post Approval Study of Cholestagel as add-on therapy to an optimal dose of statin.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Overall, the limited programme of primary pharmacodynamic and pharmacokinetic studies provided adequate evidence for efficacy of colesevelam. Because of the lack of absorption of colesevelam hydrochloride no specific safety pharmacology studies were carried out and the pharmacology studies focused on the proof of concept. In addition, the pharmacokinetics studies described the absorption, distribution and excretion in rats and dogs and the pharmacokinetic drug interactions due to gastrointentinal sequestration of other drugs. As colesevelam is a stable polymer metabolism studies were not performed.
As sequestration of bile salts could reduce the absorption of fat-soluble vitamins (A, D, E and K) part of the toxicology studies also contained assays for plasma vitamin levels. Deficiencies in vitamin K levels, possibly leading to haemorrhages were assayed indirectly by measuring clotting parameters.
The maximum doses used in the toxicology studies were in the range of 2 to 3.6 g/kg/day. This is 27 to 50 times the maximum human therapeutic dose (MTD) of approximately 73 mg/kg/day for a 60 kg person. A comprehensive package of toxicology studies was submitted including repeated dose toxicity studies in rats and dogs for up to 6 months and 1 year, respectively, and a complete package of reproductive toxicity studies. The genotoxic potential was evaluated in an Ames test, a chromosome aberration assay in CHO cells and in a mouse micronucleus test. The carcinogenic potential was evaluated in two conventional carcinogenicity studies in mice and rats. Finally, degradation products in colesevelam were qualified in additional repeated dose toxicity and genotoxicity studies.

Efficacy

Pharmacodynamics: Colesevelam is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. 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.

Clinical efficacy: It has to be pointed out that Cholestagel has not been compared directly to other bile acid sequestrants in clinical trials and the effects of Cholestagel on mortality or morbidity are not known. For this reason HMG-CoA reductase inhibitors should remain the first line treatment in patients with hypercholesterolaemia.
Initiation of add-on treatment with Cholestagel subsequent to statin therapy has not been specifically studied. However, Cholestagel belongs to the bile sequestrants class with a well-known and recognised mechanism of primary and secondary pharmacological actions. No unexpected pharmacological properties are present. It is recommended by various expert panels to use this class of agents with statins. A number of already registered bile acid sequestrants (cholestyramine and colestipol) are indicated for the add-on indication. Post-marketing data from the US do not indicate any specific problems with regard to efficacy while a significant number of patients were already on the maximum approved dose of a statin. Moreover, 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.
Cholestagel is indicated for co-administration with an HMG-CoA reductase inhibitor (statin) as adjunctive therapy to diet to provide an additive reduction in LDL-cholesterol (LDL-C) levels in patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone,
and as monotherapy as adjunctive therapy to diet for reduction of elevated total and LDL-cholesterol in patients with isolated primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well tolerated.
In order to gather further efficacy and safety data the Applicant has committed to perform a Post Approval Study of Cholestagel as add-on therapy to an optimal dose of statin and in the hypercholesterolaemic paediatric population.

Safety

Safety data show a relatively mild adverse event profile and reasonable tolerability to Cholestagel.
Cholestagel belongs to the bile sequestrants class with a well-known and recognised mechanism of primary and secondary pharmacological actions. The side effects that were notably increased in frequency relative to placebo treated patients are constipation and dyspepsia. Compared with placebo, the percentage of patients reporting these adverse events are increased approximately by 5%. Constipation and dyspepsia are generally mild or moderate in intensity and rarely resulted in study termination.
Cholestagel increased mean AST, ALT, and alkaline phosphatase levels slightly when used alone using dichotomised endpoints. These changes were anticipated because bile acid sequestrants are known to cause slight increases in liver function tests. There were small statistically significant but clinically irrelevant decreases in PTT for the Cholestagel group. Caution should be exercised when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies, such as patients with malabsorption. Further, anticoagulant therapy should be monitored closely in patients receiving warfarin or similar agents, since bile acid sequestrants have been shown both to reduce absorption of vitamin K and to interfere with warfarin's anticoagulant effect.
There was an increase in myalgia for the Cholestagel/HMG-CoA reductase inhibitor group as compared with HGM-CoA reductase inhibitor alone; however, a statistical comparison showed the difference to be non-significant (p=0.29).
Of concern is the increase in triglycerides seen during colesevelam treatment. 2% of Cholestagel only and no placebo patients experienced treatment emergent serum triglyceride levels of $\geq$ 6 mmol/L; 7% of Cholestagel and 5% of placebo patients experienced treatment emergent serum triglyceride levels $\geq$ 4 mmol/L. However, these pharmacodynamic effects are well known with the other bile acid binding resins. Caution should be exercised when treating patients with triglyceride levels greater than 3.4 mmol/L due to the triglyceride increasing effect with Cholestagel.
In order to gather further efficacy and safety data the Applicant has committed to perform a Post Approval Studies of Cholestagel as add-on therapy to an optimal dose of statin and in the hypercholesterolaemic paediatric population.

Benefit/risk assessment

Following the review of the submitted documentation, and the final SPC and letter of undertaking, the CPMP agreed that Cholestagel has shown efficacy in patients with hypercholesterolaemia that is clinically relevant and that allows a conclusion on an acceptable benefit/risk.
Cholestagel belongs to the bile sequestrants class with a well-known and recognised mechanism of primary and secondary pharmacological actions. Cholestagel has not been compared directly to other bile acid sequestrants in clinical trials and the effects of Cholestagel on mortality or morbidity are not known. For this reason HMG-CoA reductase inhibitors should remain the first line treatment in patients with hypercholesterolaemia.
It has been demonstrated also for Cholestagel that the combination with statins is more effective than the monocomponents. Furthermore, post-marketing data from the US do not indicate any specific problems with regard to efficacy and/or safety while a significant number of patients were already on the maximum approved dose of a statin.
Despite the efficacy of the HMG-CoA reductase inhibitors, many patients with severe hypercholesterolaemia may not respond sufficiently and will require combination therapy, using an add-on approach, to achieve target LDL cholesterol levels. Colesevelam could be an alternative to HMG-CoA reductase inhibitors in patients where these are contraindicated or not tolerated. Cholestagel is indicated for co-administration with an HMG-CoA reductase inhibitor (statin) as adjunctive therapy to diet to provide an additive reduction in LDL-cholesterol (LDL-C) levels in patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone, and as monotherapy as adjunctive therapy to diet for reduction of elevated total and LDL-cholesterol in patients with isolated primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well tolerated.
The CPMP did not consider it necessary to perform an add-on study in patients who have responded insufficiently to the optimal dosage prior to registration. However, in order to gather further efficacy and safety data the Applicant has committed to perform a Post Approval Study of Cholestagel as add-on therapy to an optimal dose of statin. In addition, the Applicant has committed to perform a Post-Approval study in the hypercholesterolaemic paediatric population and to undertake additional interaction studies.

Recommendation

”Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk ratio of Cholestagel for “co-administration with an HMG-CoA reductase inhibitor (statin) as adjunctive therapy to diet to provide an additive reduction in LDL-cholesterol (LDL-C) levels in patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone”, and “as monotherapy as adjunctive therapy to diet for reduction of elevated total and LDL-cholesterol in patients with isolated primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well tolerated”, was favourable and therefore recommended the granting of the marketing authorisation.