EU Risk Management Plan

for

Cholestagel (colesevelam hydrochloride)

RMP version to be assessed as part of this application:	
RMP Version number:	2.0
Data lock point for this RMP:	30 Sep 2023
Date of final sign-off:	10 Nov 2023
Rationale for submitting an updated RMP:	Revision according to GVP Module V (Rev 2) Reclassification of a safety concern based on GVP Module V (Rev 2) Based on the GVP Module V (Rev 2), the EU RMP was transferred to the revised template. Updates other than those related to the revised template are summarised below.
Summary of significant changes in this RMP:	Part II SVII Recategorisation of the following safety concerns: Pancreatitis previously categorised as important potential risk has been reclassified to important identified risk and was further removed from the list of safety concerns. Constipation, intestinal obstruction, myalgia, deficiencies of fat-soluble vitamins, hypertriglyceridemia previously categorised

	as important identified risks were removed from the list of safety concerns. Rhabdomyolysis, bleeding tendency increased (due to malabsorption of vitamin K), consequences of low serum cholesterol levels, cholelithiasis/ cholecystitis previously categorised as important potential risks were removed from the list of safety concerns. Use of Cholestagel in pregnant and lactating women, use of Cholestagel in children younger than 12 years, use of Cholestagel in patients with renal or hepatic impairment were removed as missing information.

Other RMP versions under evaluation:	
RMP Version number:	None
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP:	
Version number:	1.0
Approved with procedure:	EMEA/H/C/000512/II/0014
Date of approval (opinion date):	05 Nov 2009

QPPV name:	[redacted]
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

Abbreviation	Explanation
ASCVD	Atherosclerotic Cardiovascular Disease
CAD	Coronary Artery Disease
FH	Familial Hypercholesterolaemia
HeFH	Heterozygous Familial Hypercholesterolaemia
HoFH	Homozygous Familial Hypercholesterolaemia
LDL-C	Low-Density Lipoprotein Cholesterol
LLT	Lipid-lowering Therapy
MTD	Maximum Therapeutic Dose
PL	Package Leaflet
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I. 1: Product(s) overview

Active substance(s) (INN or common name)	Colesevelam hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	Lipid modifying agents, bile acid sequestrants (C10AC04)
Marketing Authorisation Holder	CHEPLAPHARM Arzneimittel GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Cholestagel
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Colesevelam hydrochloride is a bile acid sequestrant.
	Summary of mode of action: Colesevelam hydrochloride is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. The LDL-C (low-density lipoprotein cholesterol) lowering mechanism of bile acid sequestrants has been previously established as follows: As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-α-hydroxylase, is upregulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effects of increasing transcription and activity of the cholesterol biosynthetic enzyme, hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase, and increasing the number of hepatic low-density lipoprotein receptors. A concomitant increase in very low-density lipoprotein synthesis can occur. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels.
	Important information about its composition: Each film-coated tablet contains 625 mg colesevelam (as hydrochloride).
Hyperlink to the Product Information	Summary of Product Characteristics (SmPC) https://www.ema.europa.eu/en/documents/product-information/cholestagel-epar-product-information_en.pdf

Indication(s) in the EEA	Current: Cholestagel co-administered with a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) is indicated as adjunctive therapy to diet to provide an additive reduction in low-density lipoprotein cholesterol (LDL-C) levels in adult patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone. Cholestagel as monotherapy is indicated as adjunctive therapy to diet for reduction of elevated total-cholesterol and LDL-C in adult patients with primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well-tolerated. Cholestagel can also be used in combination with ezetimibe, with or without a statin, in adult patients with primary hypercholesterolaemia, including patients with familial hypercholesterolaemia.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: *Combination therapy* The recommended dose of Cholestagel for combination with a statin with or without ezetimibe is 4 to 6 tablets per day. The maximum recommended dose is 6 tablets per day taken as 3 tablets twice per day with meals or 6 tablets taken once per day with a meal. *Monotherapy* The recommended starting dose of Cholestagel is 6 tablets per day taken as 3 tablets twice per day with meals or 6 tablets once per day with a meal. The maximum recommended dose is 7 tablets per day.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): *Film-coated tablet* Off-white, capsule-shaped film-coated tablets imprinted with “C625” on one side. Each tablet contains 625 mg colesevelam (as hydrochloride).
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI – Epidemiology of the indication(s) and target population(s)

Patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone or in whom a statin is considered inappropriate or is not well tolerated

Incidence:

Primary hypercholesterolaemia is associated with an underlying genetic cause and may be categorised as familial hypercholesterolaemia (FH) and non-familial (polygenic) hypercholesterolaemia (non-FH). The prevalence of the FH allele is estimated to be 0.2–0.5% in the general population regardless of the ethnic background [1]. It is calculated that ~1 child with FH is born per minute world-wide [2].

Prevalence:

According to data from the World Health Organization (WHO), the global prevalence of elevated total cholesterol (>190 mg/dL; 4.9 mmol/L) was 39% and was the highest in Europe (54%) [3].

Only a small proportion of hypercholesterolaemic patients have familial hypercholesterolaemia. In fact, overall contemporary data suggests that heterozygous FH (HeFH) affects ~1:200−300 individuals globally, which could mean that >30 million individuals worldwide could be affected of HeFH. Homozygous FH (HoFH) is, on the contrary, much less frequent than HeFH, from 1:1,000,000 people, based on historical prevalence data, to 1:160,000–300,000, as suggested from recent studies [2].

In a contemporary review, including 21 studies from Europe (9 studies), North America (4), Australia (3), Asia (2), South Africa (1), or pooled from international cohorts (2 studies) the estimated HeFH prevalence in individual studies ranged from 0.05% to 5.62%. A meta-analysis of 19 of these studies yielded an overall FH prevalence in the general population of 0.40% (1:250 individuals, 95% confidence interval [CI]: 1:192 to 1:345) [4].

An overview of HeFH prevalence in the general population from contemporary studies is shown in Figure 1.

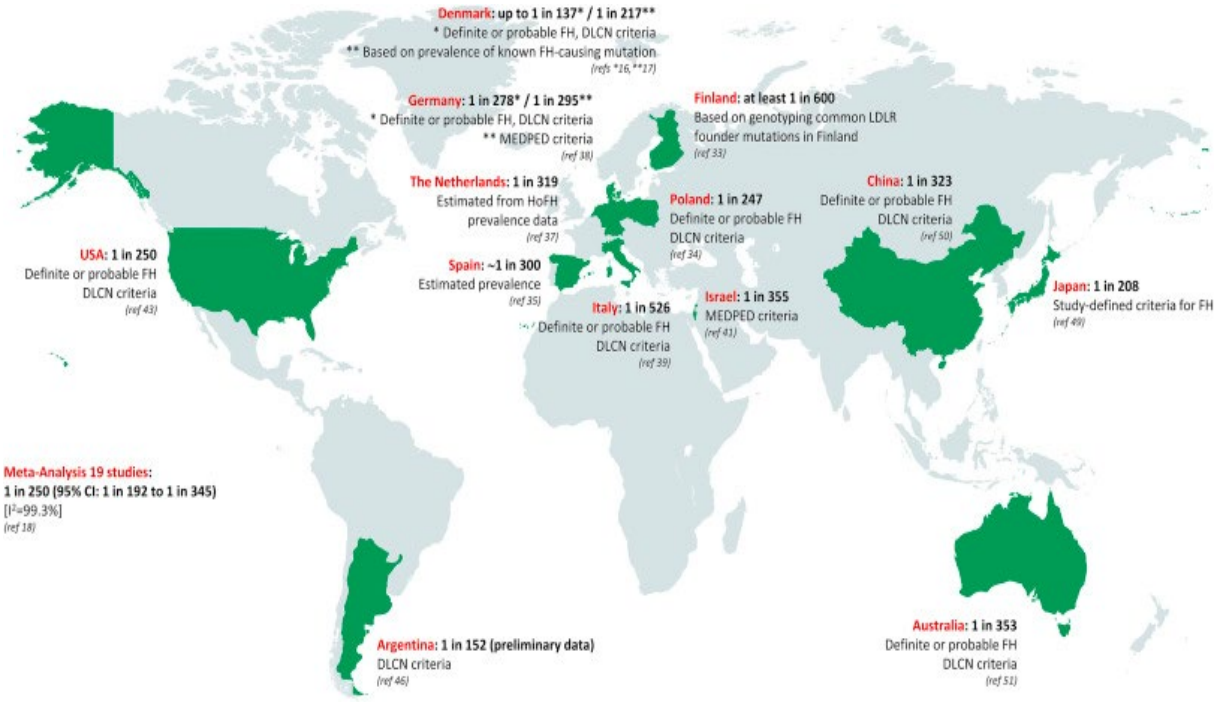

Figure 1: Overview (non-systemic review) of overall prevalence rates reported from contemporary studies for heterozygous familial hypercholesterolaemia in the general population (according to Vallejo-Vaz 2018)

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Non-FH can occur as a result of several risk factors, such as physical inactivity, smoking, hypertension, and diabetes, whereas FH occurs because of a specific genetic defect. FH is a common autosomal genetic disorder of low-density lipoprotein cholesterol (LDL-C) metabolism-related genes, such as those encoding the low-density lipoprotein (LDL) receptor, apolipoprotein (Apo) B-100, and proprotein convertase subtilisin/kexin type 9 (PCSK9) [1].

The prevalence of FH seems to vary with ethnicity and geographically, with higher prevalence reported in subpopulations with founder effects/communities sharing ascendants or in those with higher rates of consanguinity (e.g. Africans in South Africa, Christian Lebanese, Tunisians, some French-Canadian) [2].

The FH frequency is similar in men and women, but varies with age, with an increase in prevalence that peaked between ages 60 and 69 and declining thereafter. The age-dependent effect could be explained by insufficient dyslipidaemia screening in children and adolescents and age-related declines could be associated with premature mortality [4].

The main existing treatment options*:*

For patients with hypercholesterolaemia a healthy lifestyle, an optimum weight, no smoking, exercising for 150 minutes per week, and a diet low in saturated and trans-fatty acids and enriched in fibre, fruit, and vegetables and fatty fish is recommended [5].

Lipid-lowering therapy (LLT) with statins as a first-line treatment is a mainstay of hypercholesterolaemia treatment. As a second line, the cholesterol absorption inhibitor ezetimibe and bile sequestrants can be added to statins. However, these therapies may not

be sufficient in all patients. This may be due to the fact that some patients are statin-intolerant and stop taking their medication. Additionally, some patients may have very high baseline LDL-C concentrations and the maximum tolerated statin dose is insufficient to reduce LDL-C to goal levels; therefore, alternative LLTs may be needed in certain individuals. Long-term persistence with statins is important for efficacy; however, 50% or more of patients discontinue statin treatment within 1 year of initiation [6, 7].

A new target for LDL-C lowering therapy is the enzyme PCSK9 [1, 7].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Patients with severe hypercholesterolaemia are known to be at relatively high risk for developing atherosclerotic cardiovascular disease (ASCVD). ASCVD including myocardial infarction, stroke and peripheral arterial disease remains the foremost cause of death among chronic diseases. Its prevalence is increasing in many countries. Worldwide, cardiovascular disease (CVD) affected 523 million individuals in 2019 [8].

Familial hypercholesterolaemia is an autosomal co-dominant condition which results in life-long elevations in LDL-C from birth leading to premature cardiovascular disease (from age 30 in men and age 40 in women) and premature deaths. The risk of developing coronary artery disease (CAD) is associated with increased LDL-C and is 20-fold higher in untreated FH patients [1, 8].

HoFH is caused by the mutation of two alleles of LDL receptor. They can be classified as receptor negative (i.e., those with no LDL-receptor activity) and receptor defective (i.e., those with markedly reduced but detectable receptor activity). The presentation is usually in childhood with cutaneous xanthomas on the hands, wrists, elbows, knees, heels, and buttocks. Individuals with HoFH have extreme elevations in LDL-C – typically > 13 mmol/L (500 mg/dL) – and manifestations of ASCVD or aortic or supra-aortic stenosis before the age of 20 which is invariably fatal by aged 40 if untreated. Recently available data on HoFH from 38 countries showed that the average age of diagnosis was 12 years, with average LDL-C levels of 14.7 mmol/L (570 mg/dL) and with 9% already having evidence of ASCVD or aortic valve disease at diagnosis [8, 9].

HeFH is caused by the inheritance of one LDL-receptor mutant allele. The high LDL-C levels are usually in the range of 200 – 400 mg/dL with normal triglycerides. Patients with HeFH are generally asymptomatic in childhood and early adulthood, and recognition is based on hypercholesterolaemia on routine screening with the development of xanthomas or cardiovascular conditions [9, 10].

Important co-morbidities:

Hypercholesterolaemia is considered one of the main risk factors for many forms of cardiovascular disease (that is CHD, cerebrovascular disease and peripheral artery disease), which share atherosclerosis as the underlying pathology. About 5% of heart attacks under the age 60 and as many as 20% under age 45 are due to FH [9, 11].

In an observational study among 3,721 Canadian patients with hypercholesterolaemia who have been prescribed statins co-morbidities were common: it was found that 68% of the statin-

treated patients were at high risk for CAD, 46.4% had established CVD, 33.9% had diabetes and 59.5% had hypertension [12].

Amongst 87 adult patients (≥18 years) with genetically confirmed HeFH, 30 (34%) had one or more cardiovascular (CV) event and 36 (41%) had co-morbidities, i.e. atherosclerosis (n=6), hypertension (n=9), diabetes mellitus (n=3), thyroid disorder (n=6), and other (n=12). Of the 170 patients with genetically unconfirmed HeFH, 42 (25%) had one or more CV event and 101 (59%) had co-morbidities like atherosclerosis (n=9), peripheral vascular disease (n=1), hypertension (n=21), diabetes mellitus (n=9), thyroid disease (n=13), and other (n=48) [13].

Part II: Module SII – Non-clinical part of the safety specification

Toxicity:

Key issues identified from acute or repeat-dose toxicity studies

No single-dose toxicity studies were conducted. This omission was justified by the high doses used in the repeat-dose studies (2 to 3.6 g/kg/day). This is 27 to 50 times the human maximum therapeutic dose (MTD) of approximately 73 mg/kg/day for a 60 kg person. Furthermore, the mouse micronucleus study included doses up to 5 g/kg/day administered on two successive days.

The physico-chemical properties of colesevelam are such that it is unlikely to be absorbed after oral administration as it was confirmed by [^{14}C]- studies in rats, dogs, 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 and could reasonably be attributed to the binding of bile acids and the prevention of absorption of fat-soluble vitamins, vitamin E and K in particular. However, investigations of fat-soluble vitamins in human studies did not indicate any evidence of reductions.

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 maximum doses used in the toxicology studies were in the range of 2 to 3.6 g/kg/day. Occurring toxic effects included anaemia, haemorrhages in fast growing male rats, and elevated plasma levels of liver enzymes (plasma alanine amino transferase and aspartate amino transferase) without any hepatic histopathological or organ weight alterations. The slight increases in liver transaminases have been identified in patients receiving colesevelam hydrochloride and other bile sequestrants. The high chloride content of colesevelam hydrochloride resulted in increased plasma and urinary chloride concentrations at high dose levels [14].

In conclusion, colesevelam hydrochloride is not absorbed and its effects are most likely limited to those secondary to its biological action of bile sequestration (reduced plasma cholesterol, reduction of fat-soluble vitamin absorption and minor effects on liver enzymes) and to palatability or its bulk in animal diets. In addition, its chloride content results in higher plasma chloride and increased compensatory chloride excretion. These effects obviously require to be noted, but they are unlikely to be of more than minor significance for humans except in a minority of patients. This has been confirmed by the results of clinical trials.

Based on the preclinical studies the only established toxic effect of the compound is haemorrhage associated with vitamin K depletion that is observed in rats at doses that are

50-fold multiples of the maximum approved human dose. Because of these findings, the principal safety concern in humans was the interference with the absorption of fat-soluble vitamins. Given the doses at which haemorrhage occurred in animals, chronic massive overdoses of Cholestagel would be required to see a possible effect.

Reproductive/ developmental toxicity

The reproductive toxicology studies did not indicate any changes in reproductive parameters.

Genotoxicity

The Ames test and Chinese Hamster Ovary (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.

Carcinogenicity

In the mouse study, there are no treatment-related tumour findings up to 3 g/kg/day, which equals 40 times the MTD.

The rat carcinogenicity studies showed no increase in tumours at 1.2 g/kg/day. At doses >2.4 g/kg/day an increase in C-cell thyroid adenomas was observed, but only in animals surviving to the termination of the study. The difference, if reproducible, is likely to relate to better survival to termination rather than directly to colesevelam. C-cell adenoma and C-cell hyperplasia are common age-related lesions in many strains of rat [15].

In a 104-week carcinogenicity study with colesevelam hydrochloride in Harlan Sprague-Dawley rats, a statistically significant increase in the incidence of pancreatic acinar cell adenoma was seen in male rats at doses >1.2 g/kg/day (approximately 20 times the approved human dose) (trend test only). Spontaneous neoplasms of the exocrine pancreas have been reported to occur infrequently in most stocks and strains of laboratory rats. In general, rats have pancreatic tumour incidences of less than 1% at 2 years of age. There have been reports of relatively high (up to 40% in aged Wistar rats) incidence of these tumours [15].

The C-cell and pancreatic adenomas are preclinical effects which were observed at exposures considered sufficiently in excess of the maximum human exposure, indicating little or no relevance to clinical use.

Safety pharmacology:

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

Repeat dose toxicity studies on the degradants:

Toxicity studies on 4 degradants of colesevelam hydrochloride (decylamine HCl, didecylamine HCl, decylamino-6-hexytrimethyl ammonium chloride hydrochloride, and aminohexyltrimethylammonium chloride hydrochloride) were conducted. Each impurity has been tested up to 15 mg/kg/day. No treatment-related effects have been observed in the repeat-dose toxicity study.

Part II: Module SIII – Clinical trial exposure

The authorised product was divested to CHEPLAPAHRM and thus CHEPLAPHARM as current MAH did not perform the clinical development for this product.

Clinical trial exposure is based on number of patients participating in Genzyme sponsored clinical trials with Cholestagel and in Daiichi-Sankyo sponsored clinical trials with Welchol.

The initial phase II and III studies were conducted by Geltex Pharmaceuticals, Inc. (identified with GTC numbers) and were the basis for the initial approval of Welchol (May 2000 in the US). Geltex was acquired by Genzyme Corporation in December 2000. Genzyme sponsored 2 post approval studies (identified with CHOL numbers).

Additional phase IV studies were conducted by the American licensee, Daiichi-Sankyo, Inc., (identified with WEL numbers), following the marketing approval of Welchol in the US. Welchol was approved by the US Food and Drug Administration (FDA) on 18 Jan 2008 for the indication to improve glycaemic control in adults with Type 2 diabetes mellitus (T2DM).

A series of studies was conducted to explore the use of colesevelam alone and in combination with HMG-CoA (3-Hydroxy-3-Methylglutaryl Coenzyme A) reductase inhibitors. These studies are listed below.

- GTC-09-201 was designed to demonstrate the efficacy and safety of colesevelam at 4 doses ranging from 0.25 g to 6.75 g per day.
- GTC-37-201 was designed to demonstrate the efficacy and safety of colesevelam at 4 doses ranging from 1.5 g to 3.8 g per day.
- GTC-37-202 was designed to determine the efficacy of alternate dosing schedules of colesevelam once a day in the morning or evening and split daily dosing with both breakfast and dinner.
- GTC-48-301 was a pivotal phase III dose-ranging study designed to determine the long-term efficacy and safety of colesevelam in a large patient population.
- GTC-48-302 was a pivotal phase III study, designed in a similar manner as GTC-37-202, to confirm the efficacy of once a day and split daily doses.
- GTC-37-203, GTC-48-204 and GTC-48-205 were designed to determine the efficacy and safety of colesevelam in combination with HMG-CoA reductase inhibitors: lovastatin, simvastatin, and atorvastatin, respectively.
- GTC-37-901 was an uncontrolled dose titration extension study designed to evaluate the efficacy of colesevelam over one year.
- An additional clinical study, GTC-44-201, was conducted in normal healthy volunteers to test the tolerability of the tablet formulation of colesevelam.
- WEL-403 was a phase IV randomised, double-blind, placebo-controlled, parallel-group study of the combination of colesevelam and fenofibrate compared to fenofibrate and placebo in patients with mixed hyperlipidaemia.
- WEL-405 was a phase IV randomised, double-blind, placebo-controlled, parallel-group study of the combination of colesevelam and simvastatin compared to simvastatin and placebo in patients with primary hyperlipidaemia.

- WEL-406 was a phase IV randomised, double-blind, placebo-controlled, parallel-group study of the combination of colesevelam and atorvastatin compared to atorvastatin and placebo in patients with primary hyperlipidaemia.
- WEL-407 was a phase IV randomised, double-blind, placebo-controlled, parallel-group study of the combination of colesevelam and pravastatin compared to pravastatin and placebo in patients with primary hyperlipidaemia.
- WEL-408 was a phase IV randomised, double-blind, placebo-controlled, parallel-group study of the combination of colesevelam and ezetimibe compared to ezetimibe and placebo in patients with primary hyperlipidaemia.
- WEL-409 was a phase III randomised, open label study in diabetic patients to estimate the treatment effect on haemoglobin A1c (HbA1c) of colesevelam, rosiglitazone maleate, or sitagliptin on a background of metformin monotherapy.
- WEL-410, was a phase IV randomised, double-blind, placebo-controlled efficacy study of colesevelam administered to paediatric patients aged 10 to 17 years with heterozygous FH who were on a stable dose of a paediatric-approved statin monotherapy (atorvastatin, lovastatin, simvastatin or pravastatin), or who were treatment naive to lipid-lowering therapy.
- CHOL00107 was a phase IV randomised, double-blind, placebo-controlled, parallel-group study of colesevelam administered to patients with FH as add-on therapy to a maximally tolerated and stable regimen of a statin and ezetimibe for which their LDL-cholesterol level is still above their target.

The following trials were the foundation for the approval by the FDA of colesevelam for glycaemic control (measured by A1C) in adults with T2DM in combination with metformin, sulfonylureas, or insulin, either alone or in combination with other antidiabetic agents.

- Glucose-Lowering Effect of WelChol Study (GLOWS) was a randomised, single-blind, placebo run-in and a double-blind, placebo-controlled, parallel group study. This was the proof-of-concept study for the diabetes indication and was the predecessor to the 3 clinical trials described below, which studied the efficacy and safety of colesevelam as add-on therapy when combined with metformin, a sulfonylurea, and insulin-based therapies in people with T2DM.
- WEL-301 was a phase III, multi-centre, randomised, double-blind, placebo-controlled, parallel-group study to determine the efficacy and safety of colesevelam in patients with inadequately controlled T2DM, who were receiving metformin monotherapy or metformin combined with additional oral anti-diabetes mellitus drugs.
- WEL-302 was a phase III, multi-centre, randomised, double-blind, placebo-controlled, parallel-group study to determine the efficacy and safety of colesevelam in T2DM with inadequate glycaemic control on insulin therapy alone or insulin therapy combined with other oral anti-diabetic agents.
- WEL-303 was a phase III, multi-centre, randomised, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of colesevelam in T2DM with inadequate glycaemic control on sulfonylurea monotherapy or sulfonylurea therapy in combination with oral anti-diabetic agents.

The clinical development programme also involved several studies investigating possible interactions with other medicinal products. The following drugs were examined:

- lovastatin, an HMG-CoA reductase inhibitor likely to be co-administered with colesevelam;
- 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;
- valproic acid, an anti-seizure medication that has been reported to interact with cholestyramine;
- fenofibrate, another lipid-lowering treatment likely to be co-administered with colesevelam;
- glyburide, pioglitazone, and repaglinide, oral hypoglycaemics likely to be administered with colesevelam in patients with metabolic syndrome;
- the oral contraceptive norethindrone/ethinylestradiol;
- levothyroxine for patients with hypothyroidism;
- and ciclosporin as immunosuppressive therapy.

As a result of a post-marketing commitment required by the FDA (Food and Drug Administration), Daiichi-Sankyo, Inc., conducted four drug-drug interaction studies with colesevelam and glimepiride (WEL-A-U111), glipizide (WEL-A-U115), olmesartan (WEL-A-U117), and metformin (WEL-A-U119).

CHOL00207 was a phase I open label, randomised, single dose, 2-way crossover, 2-sequence pharmacokinetic study on the interaction of colesevelam and ciclosporin in healthy volunteers.

Total colesevelam exposure in the pivotal clinical trials

In the 7 original Geltex randomised, placebo-controlled phase II and phase III studies (GTC-37-201, GTC-37-202, GTC-37-203, GTC-48-204, GTC-48-205, GTC-48-301, and GTC-48-302), 1,350 patients with hypercholesterolaemia were treated and 1,188 patients completed the protocols. A total of 952 patients were treated with colesevelam. Of these, 807 patients were treated with colesevelam alone, and 145 patients were treated with a colesevelam/HMG-CoA reductase inhibitor combination.

Average duration of exposure per patient is summarised by treatment group in Table SIII. 1 and by dose group in Table SIII. 2.

Table SIII. 1: Summary of differences in duration of exposure by treatment category in the pivotal clinical trials

Treatment category	Number of patients (N)	Exposure days (Mean ± SD)
Placebo	258	76 ± 63
Colesevelam only	807	89 ± 66
Colesevelam/ HMG-CoA reductase inhibitor	145	34 ± 10
HMG-CoA reductase inhibitor only	140	35 ± 9

HMG-CoA, 3-Hydroxy-3-Methylglutaryl Coenzyme A; SD, Standard Deviation.

Table SIII. 2: Summary of differences in duration of exposure by colesevelam dose group in the pivotal clinical trials

Colesevelam dose group	Number of patients (N)	Exposure days (Mean ± SD)*
Placebo	258	76 ± 63
Low 1.5 g	120	33 ± 8
Medium 2.3 g to 3.0 g	419	103 ± 67
High 3.8 g to 4.5 g	413	96 ± 67

* P<0.0001, P-value based on ANOVA (Analysis of Variance). SD, Standard Deviation.

The interaction studies conducted during the initial clinical development programme involved a total of 540 subjects treated with colesevelam.

Total colesevelam exposure in the post-approval clinical trials

Phase III studies

In the 3 phase III studies to investigate the effect of colesevelam on glucose levels in T2DM patients (WEL-301, 302, and 303), a total of 1,064 patients aged 18 to 75 years were enrolled of whom 536 were assigned to the colesevelam group (3.75 g/day) and 528 to the placebo group. The mean scheduled duration of treatment exposure was 158.7 days.

Phase IV studies

In the 5 phase IV double-blind, randomised, placebo-controlled combination-therapy studies, i.e. WEL-403, WEL-405, WEL-406, WEL-407, and WEL-408, 241 patients were randomised to colesevelam and 177 were randomised to placebo. In both groups, 93% of patients completed the study.

In the study evaluating the lipid-lowering effect and safety of colesevelam therapy administered to paediatric patients with HeFH (WEL-410), 194 children aged 10 to 17 years were randomised after a 4-week stabilisation period (period I), 65 to placebo, 65 to colesevelam 1.875 g/day, and 64 to colesevelam 3.75 g/day for 8 weeks (period II). In total, 186 subjects (95.9%) completed period II, and 184 were enrolled in period III and all received colesevelam 3.75 g/day for 18 weeks. Overall, 173 (89.2%) completed the entire 26-week study.

In the phase IV study investigating the efficacy and safety of colesevelam as add-on therapy in patients with FH (CHOL00107), 85 patients (86 were enrolled) were in the safety population, 45 (53%) in the colesevelam group and 40 (47%) in the placebo group. For both treatment groups, the median duration of treatment exposure for the double-blind phase was 84 days; the mean (SD) treatment duration in days for the colesevelam group was 80.8 (17.13) and for the placebo group was 82.5 (13.32).

Part II: Module SIV – Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

No exclusion criteria are considered important.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Excluded from the clinical development programme, no exposure data available
Breastfeeding women	
Patients with relevant co-morbidities: • Patients with hepatic impairment • Patients with renal impairment	Excluded from the clinical development programme, no exposure data available
• Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not excluded from the clinical development programme, no exposure data available
Population with relevant different ethnic origin	Not excluded from the clinical development programme, no exposure data available
Subpopulations carrying relevant genetic polymorphisms	Not excluded from the clinical development programme, no exposure data available
Children below the age of 18 years	Excluded from the clinical development programme, no exposure data available*

* Phase 4 study (WEL-410) from 2007 indicated that treatment of paediatric patients with heterozygous familial hypercholesterolaemia aged 10 – 17 years is safe and efficacious for lipid-lowering therapy, Paediatric Committee of the EMA acknowledged paediatric development as completed.

Part II: Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

[redacted]

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no potential for misuse of colesevelam for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The risks considered important for inclusion in the list of safety concerns in the initial RMP submission are presented in Table SVII. 1.

Table SVII. 1: Summary of safety concerns in the initial RMP submission (RMP 1.0, 2009)

Important identified risk	• Constipation • Intestinal obstruction • Myalgia • Deficiencies of fat-soluble vitamins • Hypertriglyceridaemia
Important potential risks	• Rhabdomyolysis • Pancreatitis • Bleeding tendency increased (due to malabsorption of vitamin K) • Consequences of low serum cholesterol • Cholelithiasis / cholecystitis
Missing information	• Use of Cholestagel in pregnant and lactating women • Use of Cholestagel in children younger than 12 years • Use of Cholestagel in patients with renal or hepatic impairment

The risks were reclassified according to Good Pharmacovigilance Practice (GVP) Module V Revision 2 (R2). For current classification of these risks, please see chapter SVII.1.1 and chapter SVII.1.2.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Nervous system disorders: headache
- Gastrointestinal disorders: flatulence, vomiting, diarrhoea, abdominal pain, abnormal stools, nausea, abdominal distension

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Gastrointestinal disorders: dysphagia, pancreatitis
- Investigations: serum transaminase increased

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Constipation
- Intestinal obstruction
- Myalgia
- Rhabdomyolysis
- Bleeding tendency increased (due to malabsorption of vitamin K)
- Deficiencies of fat-soluble vitamins
- Hypertriglyceridaemia
- Low serum cholesterol
- Cholelithiasis / cholecystitis

Known risks that do not impact the risk-benefit profile:

- Hypersensitivity reactions in patients with known hypersensitivity to any of the ingredients

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table SVII. 2: Important identified risks

Important identified risk	Risk-benefit impact
None	Not applicable

Table SVII. 3: Important potential risks

Important potential risk	Risk-benefit impact
None	Not applicable

Table SVII. 4: Missing information

Missing information	Risk-benefit impact
None	Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns have been identified since this module of the RMP was last submitted. However, some of the previous safety concerns have been reclassified based on the cumulative data and / or reassessed based on the requirements for the presentation in the RMP as outlined in the GVP Module V (R2):

Constipation previously classified as important identified risk is removed from the list of safety concerns.

- The risk is fully characterised and appropriately managed, i.e. already properly labelled. Based on GVP Module V (R2), it no longer meets the definition of an important safety concern to be presented in the EU RMP i.e. it does not require additional PV activities, additional risk minimisation activities or routine risk minimisation activities recommending specific clinical measures to address the risk. No additional pharmacovigilance activities are ongoing or planned.

Intestinal obstruction previously classified as important identified risk is removed from the list of safety concerns.

- The risk is fully characterised and appropriately managed, i.e. already properly labelled. Based on GVP Module V (R2), it no longer meets the definition of an important safety concern to be presented in the EU RMP i.e. it does not require additional PV activities, additional risk minimisation activities or routine risk minimisation activities recommending specific clinical measures to address the risk. No additional pharmacovigilance activities are ongoing or planned.

Myalgia previously classified as important identified risk is removed from the list of safety concerns.

- The risk is fully characterised and appropriately managed, i.e. already properly labelled. Based on GVP Module V (R2), it no longer meets the definition of an important safety concern to be presented in the EU RMP i.e. it does not require additional PV activities, additional risk minimisation activities or routine risk minimisation activities recommending specific clinical measures to address the risk. No additional pharmacovigilance activities are ongoing or planned.

Deficiencies of fat-soluble vitamins previously classified as important identified risk is removed from the list of safety concerns.

- The risk is fully characterised and appropriately managed, i.e. already properly labelled. Based on GVP Module V (R2), it no longer meets the definition of an important safety concern to be presented in the EU RMP i.e. it does not require additional PV activities, additional risk minimisation activities or routine risk minimisation activities recommending specific clinical measures to address the risk. No additional pharmacovigilance activities are ongoing or planned.

Hypertriglyceridaemia previously classified as important identified risk is removed from the list of safety concerns.

- The risk is fully characterised and appropriately managed, i.e. already properly labelled. Based on GVP Module V (R2), it no longer meets the definition of an important safety concern to be presented in the EU RMP i.e. it does not require additional PV activities, additional risk minimisation activities or routine risk minimisation activities recommending specific clinical measures to address the risk. No additional pharmacovigilance activities are ongoing or planned.

Pancreatitis previously classified as important potential risk is to be reclassified as important identified risk and is removed from the list of safety concerns.

- Pancreatitis was identified as a new adverse drug reaction (ADR) by the CHMP following assessment of the Cholestagel PSUR covering the period from 10 Sep 2009 to 09 Sep 2010. Subsequently, pancreatitis was listed as ADR in section 4.8 of the SmPC. The risk is fully characterised and appropriately managed, i.e. already properly labelled. Based on GVP Module V (R2), it no longer meets the definition of an important safety concern to be presented in the EU RMP i.e. it does not require additional PV activities, additional risk minimisation activities or routine risk minimisation activities recommending specific clinical measures to address the risk. No additional pharmacovigilance activities are ongoing or planned.

Rhabdomyolysis previously classified as important potential risk is removed from the list of safety concerns.

- Based on post-marketing experience with Cholestagel, the scientific and clinical data do not support the initial supposition. Further, there is no reasonable expectation that any PV activity can further characterise the risk. Based on GVP Module V (R2), it no longer meets the definition of an important safety concern to be presented in the EU RMP i.e. it does not require additional PV activities, additional risk minimisation activities or routine risk minimisation activities recommending specific clinical measures to address the risk. No additional pharmacovigilance activities are ongoing or planned.

Bleeding tendency increased (due to malabsorption of vitamin K) previously classified as important potential risk is removed from the list of safety concerns.

- The risk is fully characterised and appropriately managed, i.e. adequately reflected in the SmPC. There is no reasonable expectation that any PV activity can further characterise the risk to an extent that it impacts the benefit risk. Based on GVP Module V (R2), it no longer meets the definition of an important safety concern to be presented in the EU RMP i.e. it does not require additional PV activities, additional risk minimisation activities or routine risk minimisation activities recommending specific clinical measures to address the risk. No additional pharmacovigilance activities are ongoing or planned.

Consequences of low serum cholesterol levels previously classified as important potential risk is removed from the list of safety concerns.

- Based on GVP Module V (R2), it no longer meets the definition of an important safety concern to be presented in the EU RMP i.e. it does not require additional PV activities, additional risk minimisation activities or routine risk minimisation activities recommending specific clinical measures to address the risk. No additional pharmacovigilance activities are ongoing or planned.

Cholelithiasis/cholecystitis previously classified as important potential risk is removed from the list of safety concerns.

- The scientific and clinical data do not support the initial supposition. Further, there is no reasonable expectation that any PV activity can further characterise the risk. Based

on GVP Module V (R2), it no longer meets the definition of an important safety concern to be presented in the EU RMP i.e. it does not require additional PV activities, additional risk minimisation activities or routine risk minimisation activities recommending specific clinical measures to address the risk. No additional pharmacovigilance activities are ongoing or planned.

Use of Cholestagel in pregnant and lactating women previously classified as missing information is removed from the list of safety concerns.

- The current EU SmPC states that caution should be exercised when prescribing to pregnant or breast-feeding women. There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile.

Use of Cholestagel in children younger than 12 years previously classified as missing information is removed from the list of safety concerns.

- The current EU SmPC provides safety and efficacy data of Cholestagel that were assessed in an 8-week multi-centre, randomised, double-blind, placebo-controlled study in 194 boys and post-menarchal girls, aged 10-17 years, with heterozygous familial hypercholesterolaemia on a stable dose of statins or treatment-naïve to lipid-lowering therapy. However, no recommendations on a posology can be made. There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile.

Use of Cholestagel in patients with renal or hepatic impairment previously classified as missing information is removed from the list of safety concerns.

- There is no reasonable expectation that the existing or future feasible PV activities could further characterise the safety profile.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risks

Not applicable.

Important Potential Risks

Not applicable.

SVII.3.2 Presentation of the missing information

Not applicable.

Part II: Module SVIII – Summary of the safety concerns

Table SVIII. 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The Marketing Authorisation Holder (MAH) proactively identifies and evaluates potential safety issues from Adverse Event (AEs) / Adverse Drug Reactions (ADRs) and other available safety data and assesses the potential impact of this data on the risk profile of Company products. Established routine pharmacovigilance and signal generation activities are used to capture and review safety information, including cases entered onto the Company Global Safety Database and information retrieved for other sources including Regulatory Authorities.

Specific adverse reaction follow-up questionnaires:

Not applicable

Other forms of routine pharmacovigilance activities:

Not applicable

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are considered necessary.

III.3 Summary table of additional pharmacovigilance activities

There are no additional pharmacovigilance activities for Cholestagel; therefore, this section is not applicable.

Table Part III. 1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for Post-Authorisation Efficacy Studies

The efficacy of Cholestagel in the approved indications and target populations has been proven in clinical studies as well as in its post-marketing experience on many of thousands of patients. Therefore, there is currently no need for further post-authorisation efficacy study.

Since there are no planned and ongoing post-authorisation studies, imposed by the competent authority as a condition of marketing authorisation or which are specific obligations in the context of conditional marketing authorisation or marketing authorisation under exceptional circumstances, this section is not applicable.

Table Part IV. 1: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study **Status**	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due Date**
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine risk minimisation measures

Important Identified Risks

Table Part V. 1: Description of routine risk minimisation measures by safety concern - Important identified risks

Safety concern	Routine risk minimisation activities
None	Not applicable

Important Potential Risks

Table Part V. 2: Description of routine risk minimisation measures by safety concern - Important potential risks

Safety concern	Routine risk minimisation activities
None	Not applicable

Missing Information

Not applicable.

V.2 Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V. 3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Not applicable.		
Important potential risks		
Not applicable.		
Missing information		
Not applicable.		

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Cholestagel (colesevelam hydrochloride)

This is a summary of the risk management plan (RMP) for Cholestagel. The RMP details important risks of Cholestagel, how these risks can be minimised, and how more information will be obtained about Cholestagel's risks and uncertainties (missing information).

Cholestagel's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cholestagel should be used.

This summary of the RMP for Cholestagel should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cholestagel's RMP.

I. The medicine and what it is used for

Cholestagel is authorised for the treatment of adults with primary hypercholesterolaemia:

- Cholestagel co-administered with a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) is indicated as adjunctive therapy to diet to provide an additive reduction in low-density lipoprotein cholesterol (LDL-C) levels in adult patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone.
- Cholestagel as monotherapy is indicated as adjunctive therapy to diet for reduction of elevated total-cholesterol and LDL-C in adult patients with primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well-tolerated.
- Cholestagel can also be used in combination with ezetimibe, with or without a statin, in adult patients with primary hypercholesterolaemia, including patients with familial hypercholesterolaemia.

It contains colesevelam as the active substance and it is given by oral route as a 625 mg film-coated tablet.

Further information about the evaluation of Cholestagel’s benefits can be found in Cholestagel’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage
https://www.ema.europa.eu/en/medicines/human/EPAR/cholestagel.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Cholestagel, together with measures to minimise such risks and the proposed studies for learning more about Cholestagel's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Cholestagel is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Cholestagel are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cholestagel. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important Identified Risks

There are no important identified risks for Cholestagel.

Important Potential Risks

There are no important potential risks for Cholestagel.

Missing Information

There is no missing information for Cholestagel.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Cholestagel.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Cholestagel.

Part VII: Annexes

Table of Contents

Annex 1 EudraVigilance Interface

Annex 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 Other supporting data (including referenced material)

General references

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Annex 8 Summary of changes to the risk management plan over time

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Version	Approval date Procedure	Change
1.0	18 February 2010 EMEA/H/C/000512/II/0014	n/a
2.0	<At the time of authorisation> <procedure number> dd/mm/yyyy	Part II- Revised as per revision 2 of the GVP module V Safety concerns *Important Identified Risks* *1: Removed* Constipation, intestinal obstruction, myalgia, deficiencies of fat-soluble vitamins, hypertriglyceridemia *Important Potential Risk* *1: Reclassified and removed* Pancreatitis *2: Removed* Rhabdomyolysis, bleeding tendency increased (due to malabsorption of vitamin K), consequences of low serum cholesterol levels, cholelithiasis/cholecystitis *Missing information* *1: Removed*