SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Colesevelam Hydrochloride 1.25 g powder for oral suspension in sachet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 1.25 g of colesevelam hydrochloride.

Excipient with known effect

Each sachet contains 0.33 g of propylene glycol alginate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral suspension

Pale yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Colesevelam 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.

Colesevelam 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.

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

4.2 Posology and method of administration

Posology

Combination therapy

The recommended dose of Colesevelam for combination with a statin with or without ezetimibe is 2.5 g to 3.75 g per day. The maximum recommended dose is 3.75 g per day taken as 1.875 g twice per day with meals or 3.75 g taken once per day with a meal. Clinical trials have shown that Colesevelam and statins can be co-administered or dosed apart, and that Colesevelam and ezetimibe can be co-administered or dosed apart.

Monotherapy

The recommended starting dose of Colesevelam is 3.75 g per day taken as 1.875 g twice per day with meals or 3.75 g once per day with a meal. The maximum recommended dose is 4.375 g per day, which can be delivered by the co-administration of two 1.25 g sachets and one 1.875 g sachet.

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

When a drug interaction cannot be excluded with a concomitant medicinal product for which minor variations in the therapeutic level would be clinically important, or where no clinical data are available on co-administration, Colesevelam should be administered at least four hours before or at least four hours after the concomitant medication in order to minimize the risk of reduced absorption of the concomitant medication (see section 4.5).

Elderly population

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

Paediatric population

The safety and efficacy of Colesevelam in children aged 0 to 17 years has not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

Colesevelam powder should be suspended in still water, stirred well and the suspension taken orally with a meal. Colesevelam powder for oral suspension in sachet should not be taken in its dry form. To prepare, the entire content of one or more sachets is poured into a glass or cup, approximately 1 cup of water is added, stirred and drunk. If some quantity remains in the glass, a sufficient amount of water should be added, stirred and drunk completely in order to administer the complete dose.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

• Bowel or biliary obstruction

4.4 Special warnings and precautions for use

Secondary causes of hypercholesterolaemia

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

Interaction with ciclosporin

For patients on ciclosporin starting or stopping Colesevelam or patients on Colesevelam with a need to start ciclosporin: /Colesevelam reduces the bioavailability of ciclosporin (see also section 4.5).

Patients starting on ciclosporin already taking Colesevelam should have their ciclosporin blood concentrations monitored as normal and their dose adjusted as normal. Patients starting on Colesevelam already taking ciclosporin should have their blood concentrations monitored prior to combination therapy and frequently monitored immediately starting co-therapy with the ciclosporin dose adjusted accordingly. It should be noted that stopping Colesevelam therapy will result in increased ciclosporin blood concentrations. Therefore, patients taking both ciclosporin and Colesevelam should have their blood concentrations monitored prior to and frequently after when Colesevelam therapy is stopped with their ciclosporin dose adjusted accordingly.

Effects on triglyceride levels

Caution should be exercised when treating patients with triglyceride levels greater than 3.4 mmol/L due to the triglyceride increasing effect with Colesevelam. Safety

and efficacy are not established for patients with triglyceride levels greater than 3.4 mmol/L, since such patients were excluded from the clinical studies.

The safety and efficacy of Colesevelam 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 Colesevelam is used in patients with these disorders.

Constipation

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

Anticoagulants

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

Oral contraceptives

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

4.5 Interaction with other medicinal products and other forms of interaction

In general

Colesevelam may affect the bioavailability of other medicinal products. Therefore, when a drug interaction cannot be excluded with a concomitant medicinal product for which minor variations in the therapeutic level would be clinically important, Colesevelam should be administered at least four hours before or at least four hours after the concomitant medication to minimize the risk of reduced absorption of the concomitant medication. For concomitant medications which require administration via divided doses, it should be noted that the required dose of Colesevelam can be taken once a day.

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

Interaction studies have only been performed in adults.

In interaction studies in healthy volunteers, Colesevelam had no effect on the bioavailability of digoxin, metoprolol, quinidine, valproic acid, and warfarin. /Colesevelam decreased the Cmax and AUC of sustained-release verapamil by approximately 31% and 11%, respectively. Since there is a high degree of variability in the bioavailability of verapamil, the clinical significance of this finding is unclear.

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

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

Anticoagulant therapy

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

Levothyroxine

In an interaction study in healthy volunteers, /Colesevelam reduced the AUC and Cmax of levothyroxine when administered either concomitantly or after 1 hour. No interaction was observed when /Colesevelam was administered at least four hours after levothyroxine.

Oral contraceptive pill

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

Ciclosporin

In an interaction study in healthy volunteers, co-administration of Colesevelam and ciclosporin significantly reduced the AUC0-inf and Cmax of ciclosporin by 34% by 44%, respectively. Therefore, advice is given to closely monitor ciclosporin blood concentrations (see also section 4.4). In addition, based on theoretical grounds Colesevelam should be administered at least 4 hours after ciclosporin in order to further minimise the risks related to the concomitant administration of ciclosporin and

Colesevelam. Furthermore, Colesevelam should always be administered at the same times consistently since the timing of intake of Colesevelam and ciclosporin could theoretically influence the degree of reduced bioavailability of ciclosporin.

Statins

When Colesevelam was co-administered with statins in clinical studies, an expected add- on LDL-C lowering effect was observed, and no unexpected effects were observed.

Colesevelam had no effect on the bioavailability of lovastatin in an interaction study.

Antidiabetic agents

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

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

Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

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

Co-administration of Colesevelam and glyburide (also known as glibenclamide) caused a decrease in theAUC0-inf and Cmax of glyburide by 32% and 47%, respectively. No interaction was observed when Colesevelam was administered four hours after glyburide.

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

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

Ursodeoxycholic acid

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

Other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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

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

Nervous system disorders
Common: Headache
Gastrointestinal disorders
Very common: Flatulence*, constipation*
Common: Vomiting, diarrhoea*, dyspepsia*, abdominal pain, abnormal stools,
Uncommon: Dysphagia
Very rare: Pancreatitis
Not known: Intestinal obstruction*,**
Musculoskeletal and connective tissue disorders
Uncommon: Myalgia
Investigations
Common: Serum triglycerides increased
Uncommon :Serum transaminases increased

*see section below for further information

** adverse reactions from post-marketing experience

Description of selected adverse events

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

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic properties

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

Mechanism of action

The mechanism of action for the activity of colesevelam, the active substance in Colesevelam, has been evaluated in several in vitro and in vivo studies. These studies have demonstrated that colesevelam binds bile acids, including glycocholic acid, the major bile acid in humans. Cholesterol is the sole precursor of bile acids. During normal digestion, bile acids are secreted into the intestine. A major portion of bile acids is then absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation.

Colesevelam is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. The LDL-C lowering mechanism of bile acid sequestrants has been previously established as follows: As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-α-hydroxylase, is upregulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effects of increasing transcription and activity of the cholesterol biosynthetic enzyme, hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase, and increasing the number of hepatic

low-density lipoprotein receptors. A concomitant increase in very low density lipoprotein synthesis can occur. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels.

In a 6-month dose-response study in patients with primary hypercholesterolaemia receiving 3.8 or 4.5 g Colesevelam daily, a 15 to 18% decrease in LDL-C levels was observed, which was evident within 2 weeks of administration. In addition, Total-C decreased 7 to 10%, HDL-C increased 3% and triglycerides increased 9 to 10%. Apo B decreased by 12%. In comparison, in patients given placebo, LDL-C, Total-C, HDL-C and Apo-B were unchanged, while triglycerides increased 5%. Studies examining administration of Colesevelam as a single dose with breakfast, a single dose with dinner, or as divided doses with breakfast and dinner did not show significant differences in LDL-C reduction for different dosing schedules. However, in one study triglycerides tended to increase more when Colesevelam was given as a single dose with breakfast.

In a 6-week study 129 patients with mixed hyperlipidaemia were randomised to fenofibrate 160 mg plus 3.8 g Colesevelam or fenofibrate alone. The fenofibrate plus Colesevelam group (64 patients) demonstrated a 10% reduction on LDL-C levels versus 2% increase for the fenofibrate group (65 patients). Reductions were also seen for non-HDL-C, Total-C and Apo B. A small 5%, non-significant increase in triglycerides was noted. The effects of combination of fenofibrate and Colesevelam on the risks of myopathy or hepatotoxicity are not known.

Multi-centre, randomised, double-blind, placebo-controlled studies in 487 patients demonstrated an additive reduction of 8 to 16% in LDL-C when 2.3 to 3.8 g Colesevelam and a statin (atorvastatin, lovastatin or simvastatin) were administered at the same time.

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

The addition of Colesevelam 3.8 g daily to maximally-tolerated statin and ezetimibe therapy was assessed in a multi-centre, randomised, double-blind, placebo-controlled study in 86 patients with familial hypercholesterolaemia. A total of 85% of the patients were on either atorvastatin (50% of whom received 80 mg dose) or rosuvastatin (72% of whom received 40 mg dose).

Colesevelam resulted in a statistically significant LDL-C reduction of 11% and 11% at 6 and 12 weeks vs an increase of 7% and 1% in the placebo group; mean baseline levels were 3.75 mmol/L and 3.86 mmol/L, respectively. Triglycerides in the Colesevelam group increased by 19% and 13% at 6 and 12 weeks vs an increase of 6% and 13% in the placebo group, but the increases were not significantly different.

HDL-C and hsCRP levels were also not significantly different compared to placebo at 12 weeks.

Paediatric population

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

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

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

5.2 Pharmacokinetic properties

Colesevelam is not absorbed from the gastrointestinal tract.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucralose

Citric acid monohydrate

Propylene glycol alginate

Magnesium trisilicate hydrate

Silica, colloidal anhydrous

Medium chain triglycerides powder (medium chain triglycerides, gum acacia, silicon dioxide)

Orange flavour (flavouring preparations (natural orange flavouring, orange extract, citrus fruit extract, fruit extract), maltodextrin (maize), modified starch (waxy maize, E1450), vegetable oils (coconut, palm), butylated hydroxyanisole (E320).

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

21 months

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Sachet of white coated paper/PE/Aluminium/ Ionomer resin foil.

Pack sizes are:

1 box containing 30 sachets with 1.25 g powder for oral suspension

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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