2. Summary of benefits/efficacy

2.1 Summary of existing efficacy data

Ezetimibe is the first medication in the novel class of selective cholesterol-absorption inhibitors. Ezetimibe selectively inhibits the uptake of cholesterol from the intestinal lumen at the level of the enterocyte in the intestinal brush border while having no effect on other sterols or lipid-soluble vitamins. Ezetimibe 10 mg daily produces a consistent reduction in low density lipoprotein cholesterol (LDL-C) by approximately 15 to 20% when used as monotherapy or in combination with 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins) or fenofibrate and a 4 to 9% increase in high-density lipoprotein cholesterol. Ezetimibe decreases blood cholesterol by inhibiting its absorption in the small intestine. It reduces total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B and triglycerides and increases high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolemia. In patients with primary hypercholesterolemia, ezetimibe as monotherapy reduced LDL-C by 18%, reduced total cholesterol by 13%, reduced triglycerides by 9% and raised HDL by 1%. In patients with hypercholesterolemia, ezetimibe added to ongoing HMG-CoA reductase inhibitor therapy significantly lowered total cholesterol, LDLC, apolipoprotein B and triglycerides and increased HDL-C compared with HMG-CoA reductase inhibitor administration alone. Mean percent change from treated HMG-CoA reductase inhibitor therapy was -17% for total cholesterol, -25% for LDL-C, - 14% for triglycerides, and +3% for HDL-C (Brar MKS. 2004).

The applicant has not conducted any clinical trials (except for bioequivalence study) with their formulations of Ezetimibe Tablets since they are essentially similar to that of respective strength of EZETROL® (ezetimibe) tablets of MSD-SP Limited Hertford Road, UK Hoddesdon, Hertfordshire EN11 9BU, Vereinigtes Konigreich., efficacy data available in published literature was reviewed. The information given in the proposed SPC of the applicant's formulations of Ezetimibe Tablets reflects the information as per innovator SPC.
Ezetimibe is evaluated in two Phase I studies and two Phase II studies. The results of the two Phase I studies showed that there were no apparent increase in the overall incidence of adverse events as the dose of ezetimibe increased up to 10mg. Of the 30 subjects who received ezetimibe, 6 (20%) reported adverse events, which was similar to the incidence rate (4/15; 27%) observed for the subjects receiving placebo. The results of two phase II studies showed that ezetimibe was well tolerated and had an overall adverse event profile similar to that of placebo in subjects with primary hypercholesterolemia (ZetiaTM. NDA Review. 2001).

Primary Hypercholesterolemia

Efficacy and safety of ezetimibe monotherapy in the management of primary hypercholesterolemia were established in 2 multicenter, randomized, double-blind, placebocontrolled studies of 12 weeks' duration in approximately 1700 patients with primary hypercholesterolemia. In these studies, patients who received ezetimibe (10 mg daily) had mean reductions of approximately 12–13% in total cholesterol, 18% in LDL-cholesterol, 15–16% in apo B, and 7–9% in triglyceride concentrations;1 2 8 increases in high-density lipoprotein (HDL)-cholesterol concentrations in patients receiving ezetimibe were negligible (1%). In most patients with primary hypercholesterolemia, maximal or near-maximal reductions in serum lipoprotein and apolipoprotein concentrations are achieved within 2 weeks and maintained during continued therapy. Reductions in LDL cholesterol concentrations appear to be consistent across age, gender, and baseline LDL-cholesterol concentrations (Ezetimibe AHFS 2012). The effect of ezetimibe (10 mg/day) on human cholesterol absorption was investigated in mildly hypercholesterolemic individuals. Fractional cholesterol absorption rate was measured by the continuous dual-isotope feeding method using deuterium-labeled cholesterol and sitostanol. Fractional cholesterol absorption rates averaged 49.8±13.8% on placebo and 22.7±25.8% on ezetimibe, indicating a reduction of 54% ($p<0.001$). LDL and total cholesterol levels following ezetimibe treatment were reduced 20.4% and 15.1%, respectively, whereas campesterol and sitosterol were decreased by 48% and 41%, respectively. The reduction of plasma concentrations of the non-cholesterol sterols, sitosterol and campesterol, which are not endogenously synthesized, suggests a direct effect on the absorption of these sterols by ezetimibe. In a pooled analysis from two controlled Phase III ezetimibe monotherapy studies in patients with primary hypercholesterolemia, 10 mg/day for 12 weeks reduced LDL cholesterol levels 18.2%, and significantly decreased triglyceride and apo B levels and increased HDLcholesterol levels (Davis H R. 2004).

Ezetimibe at 10 mg/day induced an about 20% reduction in LDL cholesterol. In addition, ezetimibe decreased triglyceride (TG) by about 8% and increased high-density lipoprotein (HDL) cholesterol by about 5%. In patients with primary dyslipidemias, ezetimibe (10 mg/day) therapy for 16 weeks reduced total, LDL and non- HDL cholesterol values as well as apolipoprotein B concentrations. Patients with TG values >150 mg/dL had significantly greater reductions in the concentrations of small, dense LDL particles compared to those with normal TG levels (49% vs. 19%, respectively; $p < 0.05$). With respect to individual LDL subfractions, cholesterol was significantly reduced by ezetimibe in cholesterol in nearly all LDL subfractions. These results indicate that ezetimibe significantly reduces LDL cholesterol by inhibiting the reabsorption of biliary cholesterol (Miura S I et al., 2008).

Clinical studies have confirmed cholesterol absorption inhibition in humans. These inhibitory effects of ezetimibe on cholesterol absorption in humans were established in a double-blind, placebo controlled crossover study of 18 patients with mild hypercholesterolemia. After 2 weeks of daily treatment with 10 mg ezetimibe, fractional cholesterol absorption rates were significantly decreased by 54%, compared to placebo ($P < 0.001$). This was accompanied by significant decreases in plasma LDL-C (24%) and total cholesterol (15%) rom baseline ($P < 0.001$). Moreover, significant reductions in plasma campesterol (48%) and sitosterol (41%) suggested ezetimibe's potential for treating rare disorders of lipid metabolism, such as homozygous sitosterolemia (Lipka LJ et al., 2003).

In a pooled analysis of two multicenter, placebo-controlled, double-blind, randomized, parallel-group trials, a total of 432 patients (243 in study A and 189 in study B) with baseline

LDL-C 130 to 250 mg/dL and triglycerides <300 mg/dL received either ezetimibe (0.25, 1, 5, or 10 mg daily) or placebo before a morning meal in a dose-response study (study A) or ezetimibe (5 or 10 mg daily) or placebo either in the morning or at bedtime (study B). There was a significant reduction in LDL-C by 15.7 and 18.5% with the 5 and 10 mg ezetimibe, respectively, for 12 weeks (P < 0.01 versus placebo, P < 0.05 for 10 mg versus 5 mg ezetimibe). These doses also produced a significant increase in HDL-C by 2.9 and 3.5% at 12 weeks versus placebo (P < 0.05). Non-significant decreases in triglycerides were observed as well. There were no significant differences on lipid parameters between the morning and evening doses for the 5- or 10-mg dose. Also, 10 mg ezetimibe achieved a 15% reduction in LDL-C in 67.8% of patients and ≥25% reduction in 22% of patients (Gupta EK et al., 2002). A multicenter, randomized, double-blind, placebo-controlled trial was conducted at 54 centers in the United States. The study consisted of 3 phases: a 2–12-week initial screening/drugwashout phase (no treatment); a 4-week single-blind, placebo run-in phase; and a 12-week double-blind treatment phase. Patients are randomly assigned to treatment with either ezetimibe 10 mg or placebo in a 3:1 ratio accordingly. Ezetimibe reduced the plasma concentration of direct LDL-C from baseline to endpoint by a mean of 17.7%, compared with an increase of 0.8% with placebo (P<0.01). The effects of ezetimibe on LDL-C were generally consistent across all subgroups analyzed, regardless of risk factor status, gender, age, race, baseline lipid profile, hypertension, diabetes mellitus, body mass index, menopausal status, known coronary heart disease, and number of cardiovascular risk factors. Compared with placebo, ezetimibe also significantly decreased calculated LDL-C, apo B, total cholesterol, and Lp(a) and significantly increased HDL-C and HDL2-C (P≤0.01). With this we can conclude that an effective LDL-C-lowering agent with favorable effects on other lipid variables (Knopp RH et al., 2003).

A multicenter randomized, double-blind controlled trial comparing ezetimibe 10 mg/d with placebo is conducted. 827 patients were randomized (622 active drug). Mean baseline LDL-C was 163 mg/dL, apo B 161 mg/dL, apo A-1 151 mg/dL, HDL-C 50 mg/dL, and triglycerides 160 mg/dL. Ezetimibe reduced LDL-C by 18% compared with a 0.8% increase with placebo, reduced apo B by 15%, LDL-C: HDL-C by 18%, and Lp (a) by 7.5%, and increased HDL2-C by 5% (all p¬0.01 vs. baseline with no effect by placebo). The effect on LDL-C was not influenced by gender, age, menopause, BMI, diabetes, baseline lipids or the number of risk factors. Treatment adverse events were reported in 61% on ezetimibe and 65% on placebo. Ezetimibe had no effect on plasma cortisol before and after corticotropin stimulation and no effect on the levels on lipid soluble vitamins. Ezetimibe significantly reduces LDL-C and favorably affects other lipids, is well tolerated and an effective new option for lipid management (Knopp R H et al., 2003).

In a randomized, double-blind versus placebo study, estimated the individual amount of absorbed cholesterol after 2 weeks of ezetimibe therapy (10 mg/die) in 18 patients affected by mild hypercholesterolemia. The amount of absorbed cholesterol dosed in the faeces was between 24.9 and 74.7% in the placebo group and between 2.3 and 48.7% in the ezetimibe group. After 2 weeks of therapy, the average uptake of fractioned cholesterol was 22.7% in the ezetimibe group and 49.8% in the placebo group. The reduction in cholesterol uptake in the ezetimibe group was 54% (p<0.001) (Nodari S et al., 2007).

Homozygous familial Hypercholesterolemia

Efficacy and safety of ezetimibe combined with atorvastatin or simvastatin for the management of homozygous familial hypercholesterolemia were established in a

randomized, double-blind study of 12 weeks' duration in a limited number of patients with a clinical and/or genotypic diagnosis of homozygous familial hypercholesterolemia who were already receiving atorvastatin (40 mg daily) or simvastatin (40 mg daily), with or without concomitant LDL apheresis. In this study, patients were randomized to receive 1 of 3 regimens: atorvastatin (80 mg daily) or simvastatin (80 mg daily) monotherapy; ezetimibe (10 mg daily) with either atorvastatin (40 mg daily) or simvastatin (40 mg daily); or ezetimibe (10 mg daily) with either atorvastatin (80 mg daily) or simvastatin (80 mg daily). The addition of ezetimibe (10 mg daily) to therapy with atorvastatin (40 or 80 mg daily) or simvastatin (40 or 80 mg daily) was more effective in reducing LDL-cholesterol concentrations (21% additional reduction based on pooled data from 40-mg and 80-mg groups) than increasing the dosage of atorvastatin or simvastatin monotherapy from 40 to 80 mg daily (7% additional reduction based on pooled data from 40-mg and 80-mg groups). In the entire group of patients receiving higher dosages (80 mg daily) of atorvastatin or simvastatin in combination with ezetimibe (10 mg daily), LDL-cholesterol concentrations were reduced by approximately 27% compared with a 7% reduction with statin monotherapy. Comparable reductions in LDL-cholesterol concentrations were observed in the subgroup of patients with genotype-confirmed homozygous familial hypercholesterolemia (Ezetimibe AHFS 2012).

This double-blind, randomised, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40mg). Patients were randomised to one of three treatment groups, atorvastatin or simvastatin (80mg), EZETROL 10mg administered with atorvastatin or simvastatin (40mg), or EZETROL 10mg administered with atorvastatin or simvastatin (80mg). EZETROL, administered with atorvastatin (40 or 80mg) or simvastatin (40 or 80mg), significantly reduced LDL-C compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80mg (EZETROL®, 2012).

The addition of ezetimibe to 40 mg of atorvastatin or simvastatin was evaluated in patients with homozygous familial hypercholesterolemia (HoFH). Patients with HoFH on 40 mg of statin had their statin dose doubled were given ezetimibe (10 mg) or both for 12 weeks. Compared with increasing the statin dose to 80 mg, the addition of ezetimibe to 40 or 80 mg of statin resulted in an additional 14% LDL-cholesterol reduction (20.7% vs. 6.7%), and adding ezetimibe to 80 mg statin an additional 21% LDL reduction occurred (27.5 vs. 7%). LDLcholesterol lowering through the inhibition of cholesterol absorption by ezetimibe does not require the expression of LDL receptors, and offers an addition treatment option for patients with HoFH (Davis H R. 2004).

Homozygous Familial Sitosterolemia

Homozygous familial sitosterolemia is an inherited recessive disorder characterized by the inability to excrete plant sterols from enterocytes in the intestinal lumen; patients present with elevated levels of plant sterols in plasma and tissue. The effects of ezetimibe have been studied in a multicenter, double-blind, placebo-controlled, randomized trial in patients with homozygous sitosterolemia (plasma sitosterol levels >5 mg/dL). Patients were permitted to continue lipid lowering regimens involving diet, bile acid resins, statins, ileal bypass surgery, or LDL-C apheresis during the study Compared with those who received placebo (n = 7), patients who received ezetimibe 10 mg/d PO (n = 30) for 8 weeks had an 11% reduction in TC ($P < 0.01$), a 27% reduction in mean plasma campesterol ($P < 0.001$), and a 26% reduction

in sitosterol (P < 0.001), as well as a 35% increase in the lathosteroVcholestero1 ratio (P < 0.001) (Jeu LA et al., 2003).

Efficacy and safety of ezetimibe in the management of homozygous sitosterolemia were established in a randomized, double-blind study of 8 weeks' duration in a limited number of patients with homozygous sitosterolemia who had plasma sitosterol concentrations exceeding 5 mg/dL and were already receiving standard antilipemic therapy (dietary therapy, bile acid sequestrants, statins, ileal bypass surgery, and/or LDL apheresis). In this study, treatment with ezetimibe (10 mg daily) reduced plasma sitosterol and campesterol concentrations by 21 and 24%, respectively when compared with placebo-treated patients in whom increase of 4 and 3% is observed. Reductions in sitosterol and campesterol concentrations were consistent between patients receiving ezetimibe with or without bile acid sequestrants (Ezetimibe AHFS 2012).

Dose-Response Trial

In study A, ezetimibe 0.25 to 10 mg once daily decreased mean plasma concentrations of direct LDL-C by 9.9% to 18.7% compared with placebo after 12 weeks of treatment (P < 0.01). The degree of reduction in LDL-C was directly related to the dose of ezetimibe; that is, the response increased as the dose increased. The mean percentage change from baseline to end point ranged from -9.3% to -18.9% in the 4 ezetimibe treatment groups, compared with +3.6% in the placebo group. In study B, all 4 regimens of ezetimibe 5 or 10 mg administered AM or PM were effective in reducing mean plasma concentrations of direct LDL-C by 13.8% to 18.2% compared with placebo after 12 weeks of treatment (P < 0.01). The timing of administration of ezetimibe had no effect on the response to treatment. Table 4 details the efficacy of ezetimibe in reducing directly measured levels of LDL-C by >15% and >25%. More patients receiving ezetimibe 10 mg had LDL-C reductions >15% and >25% relative to ezetimibe 5 mg. In this pooled analysis, there was also a trend toward reduced TG concentrations in both groups compared with placebo, although this did not reach statistical significance (Bays HE, et al., 2001).

A pooled analysis of data from 2 studies of ezetimibe 5 and 10 mg daily compared with placebo for lowering LDL-C levels in patients with primary hypercholesterolemia. In study A, patients were randomized to receive either 0.25, 1, 5, or 10 mg oral ezetimibe or placebo administered before the morning meal (ASI). In study B, patients were randomized to receive either 5 or 10 mg oral ezetimibe or placebo administered before the morning meal (AM) or at bedtime (PM). In study A, ezetimibe 0.25 to 10 mg once daily decreased mean plasma concentrations of direct LDL-C by 9.9% to 18.7% compared with placebo after 12 weeks of treatment (P < 0.01). The degree of reduction in LDL-C was directly related to the dose of ezetimibe; that is, the response increased as the dose increased. In study B, all 4 regimens of Ezetimibe 5 or 10 mg administered AM or PM were effective in reducing mean plasma concentrations of direct LDL-C by 13.8% to 18.2% compared with placebo after 12 weeks of treatment. The decrease in plasma LDL-C levels was significantly greater with ezetimibe 10 mg compared with ezetimibe 5 mg (P < 0.05) (Bays HE et al., 2001).

Efficacy of Combination therapy

In 4 multicenter, randomized, double-blind, placebo-controlled studies in hypercholesterolemic patients, combination therapy with ezetimibe (10 mg daily) and a statin (i.e., atorvastatin 10–80 mg daily, lovastatin 10–40 mg daily, pravastatin 10–40 mg daily, or simvastatin 10–80 mg daily), initiated concurrently and continued for 12 weeks,

reduced total cholesterol, LDLcholesterol, apo B, and triglyceride concentrations and, except for the combination of ezetimibe and pravastatin, increased HDL-cholesterol concentrations compared with monotherapy with the corresponding statin. Following combination therapy with ezetimibe and either atorvastatin, simvastatin, pravastatin, or lovastatin, total reductions in LDL-cholesterol concentrations averaged 53–61, 46–58%, 34–42, or 34–46, respectively, compared with reductions of 37–54, 27–45, 21–31, or 20–30% (Ezetimibe AHFS 2012).

A possible molecular mechanism of the enhanced efficacy of ezetimibe plus simvastatin is decreased V(very)LDL and LDL apoB-100 concentrations through reduced VLDL production and the upregulation of LDL receptor-mediated LDL clearance. The additional decrease in plasma LDL cholesterol induced by ezetimibe showed wide inter-individual variability and was negatively correlated with the percent decrease in LDL cholesterol due to statin alone (Miura SI et al., 2008).

In a randomized, double-blind, multicenter study in type 2 DM patients, LDL cholesterol was reduced significantly more by adding ezetimibe 10 mg/day to simvastatin 20 mg/day than by doubling the dose of simvastatin to 40 mg/day. In addition, ezetimibe + simvastatin therapy also produced significant incremental reductions in non-HDL cholesterol, very LDL cholesterol and apolipoprotein B relative to simvastatin 40 mg/day (Miura SI et al., 2008).

A multicenter randomized, double-blind, placebo controlled, factorial design study was conducted at 31 sites in the United States. Coadministration of ezetimibe/simvastatin (pooled across all simvastatin doses) led to a mean percent reduction in LDL-C levels from baseline to study end point of –53.2% compared with a reduction of –38.5% with simvastatin alone (pooled across all doses); the incremental mean percent LDL-C reduction for pooled ezetimibe/simvastatin vs pooled simvastatin alone was –14.8% (P<.001). Moreover, the incremental mean percent reduction in LDL-C levels from baseline to study end point for ezetimibe/simvastatin vs simvastatin alone was significant (P<.001) at each dose of simvastatin (the mean percent reduction from baseline at study end point was –31.3%, –34.9%, –41.5%, and –45.6% for simvastatin at 10, 20, 40, and 80 mg, respectively, compared with –46.2%, –50.5%, –54.9%, and –60.8% for ezetimibe/simvastatin at 10/10, 10/20, 10/40, and 10/80 mg, respectively. This study showed that co-administration of ezetimibe/simvastatin, a treatment strategy that targets both synthesis and intestinal absorption of cholesterol, had greater lipid lowering efficacy than simvastatin monotherapy (Goldberg AC et al., 2004).

A Multicenter, double blind placebo-controlled study is conducted. Of the 182 patients that were screened, 60 were randomized to receive eze/simva 10/20 mg, and 60 were randomized to receive simvastatin 40 mg. A total of eight patients discontinued from the study after randomization. After 6 weeks, treatment with combination eze/simva 10/ 20 mg resulted in a significantly greater reduction in mean LDL-C level compared with doubling the dose of simvastatin to 40 mg (-27% vs -12%). In addition, the percentage of patients achieving LDL-C less than 100 mg/dL (<2.6 mmol/L) was significantly greater with eze/simva 10/20 treatment versus doubling the dose of simva to 40 mg (73% vs 25%). The percentage of subjects who achieved LDL-C less than 80 mg/dL (<2.0 mmol/L) after 6 weeks was significantly greater for the eze/simva 10/20 group compared with the simva 40 mg group (21% vs 4%: P = .010). The percent reduction in total cholesterol was significantly greater

with eze/simva 10/20 mg combination treatment compared with doubling simva to 40 mg after 6 weeks of treatment (216.9% vs 27.5%: P < .001) (Averna M et al., 2010).

Efficacy and safety of ezetimibe combined with atorvastatin or simvastatin for the management of homozygous familial hypercholesterolemia were established in a randomized, double-blind study of 12 weeks' duration in a limited number of patients with a clinical and/or genotypic diagnosis of homozygous familial hypercholesterolemia who were already receiving atorvastatin (40 mg daily) or simvastatin (40 mg daily), with or without concomitant LDL apheresis.1 4 In this study, patients were randomized to receive 1 of 3 regimens: atorvastatin (80 mg daily) or simvastatin (80 mg daily) monotherapy; ezetimibe (10 mg daily) with either atorvastatin (40 mg daily) or simvastatin (40 mg daily); or ezetimibe (10 mg daily) with either atorvastatin (80 mg daily) or simvastatin (80 mg daily).1 4 The addition of ezetimibe (10 mg daily) to therapy with atorvastatin (40 or 80 mg daily) or simvastatin (40 or 80 mg daily) was more effective in reducing LDL-cholesterol concentrations (21% additional reduction based on pooled data from 40-mg and 80-mg groups) than increasing the dosage of atorvastatin or simvastatin monotherapy from 40 to 80 mg daily (7% additional reduction based on pooled data from 40-mg and 80-mg groups). In the entire group of patients receiving higher dosages (80 mg daily) of atorvastatin or simvastatin in combination with ezetimibe (10 mg daily), LDL-cholesterol concentrations were reduced by approximately 27% compared with a 7% reduction with statin monotherapy. Comparable reductions in LDL-cholesterol concentrations were observed in the subgroup of patients with genotype-confirmed homozygous familial hypercholesterolemia (Murdoch D et al., 2004; Lyseng-Williamson KA., 2012; Nodari S et al., 2007).

In a double-blind, multicenter study on 1229 patients comparison was done between, ezetimibe/simvastatin and atorvastatin and it was found that ezetimibe/simvastatin was consistently superior to atorvastatin in reducing LDL-C levels at both the recommended usual starting and next highest doses in patients with type 2 diabetes and hypercholesterolemia. Ezetimibe/simvastatin reduced LDL-C levels by more than 50% from baseline at these doses, fulfilling the ADA recommendation of a 30% to 40% reduction from baseline. This study also confirmed the superior attainment of LDLC levels of less than 70 mg/dL in high-risk patients with ezetimibe/simvastatin vs atorvastatin (Goldberg RB et al., 2006).

Data from several randomized, double-blind studies in patients with primary hypercholesterolemia indicated that reductions in LDL cholesterol concentrations achieved with pooled doses of the fixed-combination preparation were greater than those achieved with pooled doses of atorvastatin, rosuvastatin, or simvastatin monotherapy. In one study, LDLcholesterol concentrations were reduced by 47–59% following therapy with the fixed combination preparation containing ezetimibe (10 mg) and simvastatin (10– 80 mg) and by 36–53% following monotherapy with atorvastatin (10–80 mg daily). In another study, LDLcholesterol concentrations were reduced by 52–61% following therapy with the fixed combination preparation containing ezetimibe (10 mg) and simvastatin (20–80 mg) and by 46–57% following monotherapy with rosuvastatin (10–40 mg daily). In the third study, LDL cholesterol concentrations were reduced by 45–60% following therapy with the fixed combination preparation containing ezetimibe (10 mg) and simvastatin (10–80 mg) and by 33–49% following monotherapy with simvastatin (10–80 mg daily). Despite its additive effects on LDL-cholesterol reduction, the fixed-combination preparation was not superior to

simvastatin monotherapy in reducing carotid intimal-medial wall thickness (cIMT). In a randomized, double-blind, active controlled study (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia, ENHANCE) in 725 patients with heterozygous familial hypercholesterolemia, treatment with the fixed-combination preparation containing ezetimibe (10 mg) and simvastatin (80 mg) for 2 years resulted in a change in cIMT (increase of 0.011 mm) that was not statistically different from the change in cIMT observed with simvastatin monotherapy (80 mg) (increase of 0.006 mm). However, reductions in LDLcholesterol concentrations achieved with the fixed-combination preparation (56%) were

substantially greater than those achieved with simvastatin monotherapy (39%) (Murdoch D et al., 2004; Lyseng-Williamson KA et al., 2012; Nodari S et al., 2007).

Comparison studies
A double-blind, multicenter, 6-week, parallel-group study, hypercholesterolemic patients were randomized to receive ezetimibe/simvastatin or rosuvastatin. At all doses and across doses, ezetimibe/simvastatin reduced LDL cholesterol significantly more than rosuvastatin. Ezetimibe/simvastatin also produced significantly greater reductions in total cholesterol, non-HDL cholesterol and apolipoprotein B. In clinical trials, ezetimibe/simvastatin produced greater reductions in LDL cholesterol than did monotherapy. This combination therapy may have the strongest lipid-lowering effect (Miura SI et al., 2008).

A double-blind, 6-week, parallel group trials are conducted in hypercholesterolemic patients who are randomized to milligram equivalent doses of ATORVA versus EZE 10 mg/SIMVA and maximum doses of ROSUVA versus EZE/SIMVA. Within each trial, baseline characteristics were similar among groups. At all dose comparisons, significantly more patients receiving EZE/SIMVA reached LDL-C <70 mg/dL and achieved both LDL-C <70 mg/dL and either Apo-B <90 mg/dL, TC/HDL-C <4.0, or Apo-B/Apo-A-I<0.7 (EZE/SIMVA versus ATORVA) compared to ATORVA and ROSUVA. For most dose comparisons, significantly more patients receiving EZE/SIMVA attained both LDL-C<70 mg/dL and either non–HDLC<100 mg/dL or CRP<2 mg/L compared to ATORVA or ROSUVA. Hence treatment with EZE/SIMVA will help patients achieve recommended levels of these other emerging risk factors, better than the statin monotherapies ATORVA or ROSUVA (Davidson MH et al., 2002).

2.2 Uncertainties about efficacy

There is no experience on safety and efficacy when administered to children under 10 years of age, limited clinical experience in paediatric and adolescent patients (aged 10 to 17 years old), no experience in patients with moderate or severe hepatic insufficiency, no experience on safety and efficacy of co-administration of ezetimibe and fibrates and no experience in pregnant and lactating women.

3. Summary of safety concerns

3.1 Important Identified Risks

Risks	What is known	Preventability
Elevation of transaminase blood	Treatment with Ezetimibe	Prescribers should

levels when ezetimibe is administered together with a statin	Mylan is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score>9) liver dysfunction, due to possible transaminase elevations.	check the transaminase blood level before treatment start and during the treatment.
Myopathy and rhabdomyolysis (especially during co-administration with a statin)	In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis (unexplained muscle pain, tenderness, weakness or muscle breakdown resulting in kidney damage) have been reported. These muscle problems can be serious and may become a potentially life-threatening condition. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis.	If myopathy is suspected based on muscle symptoms or is confirmed by creatine phosphokinase (CPK) levels increased more than 10 times the normal limit, ezetimibe, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with ezetimibe should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

3.2 Important Potential Risks

N/A

3.3 Important missing information

Risks	**What is known**
No experience on safety and efficacy when administered to children under 10 years of age	Because insufficient data are available, the use of ezetimibe in children under 10 years of age is not recommended.
No experience in patients with moderate or severe hepatic insufficiency	Treatment with Ezetimibe Mylan is not recommended in patients with moderate or severe liver dysfunction.

No experience on safety and efficacy of co-administration of ezetimibe and fibrates	The safety and efficacy of the combined use of Ezetimibe Mylan and fibrates (medicines for lowering cholesterol) have not been established.
No experience in pregnant and lactating women	Treatment with Ezetimibe Mylan is contraindicated in pregnant and lactating patients.

4. Summary of risk minimisation measures by safety concern

No additional risk minimisation measure has been suggested for ezetimibe. Routine risk minimisation measure includes addition of information in various safety sections of the SPC and PIL to make healthcare professional and patient aware about the safety concerns.

5. Planned post authorisation development

This being a generic drug application, no post authorisation development has been planned.

6. Summary of changes to the Risk Management Plan over time

This is the initial RMP prepared for generic Ezetimibe Mylan 10mg tablets application.