The underlisted safety variations have been submitted by Marketing Authorization Holders (MAHs) and approved by the Food and Drugs Authority in line with the Variation Guidelines for Allopathic Medicines.These safety variations are being shared with healthcare professionals and patients.

Safety Updates

| No. | Name of Drug | Active Ingredient(s) | Updated Section | Update | Date of Update | MAH |
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| 1 | Coartem | Artemether/ Lumefantrine | Pregnancy, lactation, females and males of reproductive potential | Revision of text to read ''Risk Summary-Based on animal data, Coartem is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections WARNINGS AND PRECAUTIONS and NON-CLINICAL SAFETY DATA).<br>Coartem should not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. However, it should not be withheld in life-threatening situations where no other suitable and effective antimalarials are available (see section WARNINGS AND PRECAUTIONS). During the second and the third trimester, treatment should be considered if the expected benefit to the mother outweighs the risk to the fetus.<br>Reproductive toxicity studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats. Other artemisinin derivatives have in addition demonstrated teratogenic potential with an increased risk during early gestation).'' under the sub heading Pregnancy.<br><br>Revision of text to read "Human Data<br>A meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy assessed adverse pregnancy outcomes. The data showed that compared to quinine, artemisinin treatment, including artemether-lumefantrine, was not associated with an increased risk of miscarriage, stillbirth or congenital anomalies. However, due to the limitations of these studies, the risk of adverse pregnancy outcomes for artemether-lumefantrine exposed women in early pregnancy cannot be excluded.<br>Data from observational and open label studies in over 1200 pregnant women exposed to artemether-lumefantrine in their second- or third trimester, and pharmacovigilance data have not demonstrated an increase in adverse pregnancy outcomes or teratogenic effects." | 09-Oct-20 | Novartis |
| | | | Instructions for use and handling, and disposal | Revision of text to read "For the treatment of children and infants, the 24 tablet pack of 20 mg/120 mg tablets may be prescribed. The prescriber and pharmacist should instruct the parent or caregiver on the posology for their child and that a variable specific number of tablets should be given to the child based upon the child's body weight for the full treatment. Therefore, some tablets may remain in the pack at the end of the full treatment course. After successful treatment the remaining tablets should be discarded or returned to the pharmacist (see section DOSAGE REGIMEN AND ADMINISTRATION). " under this section. | | |

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| 2 | Inegy | Ezetimibe/Simvastatin | Special warnings and precautions for use | Revision of text to read "Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine." under the heading Excipients.<br><br>Addition of text to read " INEGY contains less than 1 mmol (23 mg) sodium per tablet, that is to say essentially sodium-free." under the heading Excipients. | 09-Oct-20 | MSD |
| | | | Interaction with other medicinal products and other forms of interaction | Addition of " Ticagrelor-Doses greater than 10/40 mg INEGY daily are not recommended" to a table titled Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis.<br><br>Addition of text to read " Ticagrelor: Co-administration of ticagrelor with simvastatin increased simvastatin Cmax by 81 % and AUC by 56 % and increased simvastatin acid Cmax by 64 % and AUC by 52 % with some individual increases equal to 2 to 3 fold. Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg daily could cause adverse reactions of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. The concomitant use of ticagrelor with doses of simvastatin greater than 40 mg is not recommended." under the sub-heading Effects of other medicinal products on INEGY. | | |

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| 2 | Inegy | Ezetimibe/Simvastatin | Undesirable effects | Revision of text to read " INEGY (or co-administration of ezetimibe and simvastatin equivalent to INEGY) has been evaluated for safety in approximately 12,000 patients in clinical trials.<br><br>The following adverse reactions were observed in clinical studies of INEGY in patients treated with INEGY (n = 2,404) and at a greater incidence than placebo (n = 1,340), in patients treated with INEGY (n = 9,595) and at a greater incidence than statins administered alone (n = 8,883) in clinical studies of ezetimibe or simvastatin, and/or reported from post-marketing use with INEGY or ezetimibe or simvastatin. These reactions are presented in Table 1 by system organ class and by frequency. The frequencies of adverse events are ranked according to the following: Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1000, < 1/100), Rare (≥ 1/10,000, < 1/1000), Very Rare (< 1/10,000) including isolated reports. , and Not Known (cannot be estimated from the available data)."<br><br>Revision of text in Adverse Reaction table, Table 1.<br><br>Addition of text under the Adverse reaction table to read " * In a clinical trial, myopathy occurred commonly in patients treated with simvastatin 80 mg/day compared to patients treated with 20 mg/day (1.0% vs 0.02%, respectively) (see sections 4.4 and 4.5).<br>** There have been very rare reports of immune-mediated necrotising myopathy (IMNM), an autoimmune myopathy, during or after treatment with some statins. IMNM is clinically characterised by: persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotising myopathy without significant inflammation; improvement with immunosuppressive agents (see section 4.4)."<br><br>Reclassification of text concerning adverse reactions under Post-marketing Experience into the Adverse reaction table, Table 1. | 09-Oct-20 | MSD |

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| | Inegy | Ezetimibe/Simvastatin | Undesirable effects | Revision of text to read "An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopaenia, eosinophilia, red blood cell sedimentation rate increased, arthritis and arthralgia, urticaria, photosensitivity reaction, pyrexia, flushing, dyspnoea and malaise. Increases in HbA1c and fasting serum glucose levels have been reported with statins, including simvastatin.<br><br>There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use, including simvastatin. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).<br><br>The following additional adverse events have been reported with some statins:<br>• Sleep disturbances, including nightmares<br>• Sexual dysfunction<br>• Diabetes mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30 kg/m2, raised triglycerides, history of hypertension)." under the sub-heading Post-marketing Experience. | 09-Oct-20 | MSD |
| | | | Pharmacodynamic properties | Revision of text to read "All patients were randomised in a 1:1 ratio to receive either ezetimibe/simvastatin 10/40 mg (n = 9,067) or simvastatin 40 mg (n = 9,077) and followed for a median of 6.0 years." and "The average LDL-C value at the time of study qualifying event was 80 mg/dL (2.1 mmol/L) for those on lipid-lowering therapy (n = 6,390) and 101 mg/dL (2.6 mmol/L) for those not on previous lipid- lowering therapy (n = 11,594). " under the heading Clinical efficacy and safety: Prevention of Cardiovascular Events. | | |
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| 3 | Ezetrol | Ezetimibe | Qualitative and quantitative composition | Addition of text to read "Ezetrol contains less than 1 mmol (23 mg) sodium per tablet." under this section. | 12-Oct-20 | MSD |

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| 3 | Ezetrol | Ezetimibe | Special warnings and precautions for use | Revision of text to read "In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18 144 patients with coronary heart disease and ACS event history were randomised to receive ezetimibe/simvastatin 10/40 mg daily (n = 9,067) or simvastatin 40 mg daily (n = 9,077). During a median follow-up of 6,0 years, the incidence of consecutive elevations of transaminases (≥ 3 X ULN) was 2,5 % for ezetimibe/simvastatin and 2,3 % for simvastatin (see section 4.8).<br><br>In a controlled clinical study in which over 9,000 patients with chronic kidney disease were randomised to receive Ezetrol 10 mg combined with simvastatin 20 mg daily (n = 4,650) or placebo (n = 4,620) (median follow-up period of 4,9 years), the incidence of consecutive elevations of transaminases (> 3 X ULN) was 0,7 % for Ezetrol combined with simvastatin and 0,6 % for placebo (see section 4.8).<br>" under Liver Enzymes.<br><br>Revision of text to read "In IMPROVE-IT, 18,144 patients with coronary heart disease and ACS event history were randomised to receive ezetimibe/simvastatin 10/40 mg daily (n = 9,067) or simvastatin 40 mg daily (n = 9,077). During a median follow-up of 6,0 years, the incidence of myopathy was 0,2 % for ezetimibe/simvastatin and 0,1 % for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN or two consecutive observations of CK ≥ 5 and < 10 times ULN. The incidence of rhabdomyolysis was 0,1 % for ezetimibe/simvastatin and 0,2 % for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN with evidence of renal injury, ≥ 5 times ULN and < 10 times ULN on two consecutive occasions with evidence of renal injury or CK ≥ 10,000 IU/L without evidence of renal injury (see section 4.8).<br><br>In a clinical trial in which over 9,000 patients with chronic kidney disease were randomised to receive Ezetrol 10 mg combined with simvastatin 20 mg daily (n = 4,650) or placebo (n = 4,620) (median follow-up 4,9 years), the incidence of myopathy/rhabdomyolysis was 0,2 % for Ezetrol combined with simvastatin and 0,1 % for placebo (see section 4.8)." under Skeletal Muscle.<br><br>Revision of text to read "Ezetrol contains less than 1 mmol (23 mg) sodium per tablet, that is to say essentially sodium-free." under Excipients. | 12-Oct-20 | MSD |

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| 3 | Ezetrol | Ezetimibe | Undesirable effects | Revision of text to read "Ezetrol administered alone or co-administered with a statin:<br>The following adverse reactions were observed in patients treated with Ezetrol (n = 2,396) and at a greater incidence than placebo (n = 1,159) or in patients treated with Ezetrol co-administered with a statin (n = 11,308) and at a greater incidence than statin administered alone (n = 9,361). Post-marketing Adverse reactions were derived from reports containing Ezetrol either administered alone or with a statin. Adverse reactions observed in clinical studies of Ezetrol (as a monotherapy or co-administered with a statin) or Ezetrol reported from post-marketing use either administered alone or with a statin are listed in Table 1. These reactions are presented by system organ class and by frequency." under the heading Tabulated list of adverse reactions (clinical studies and post-marketing experience).<br><br>Revision of Adverse Reaction Table<br><br>Revision of text to read "In the IMPROVE-IT study (see section 5.1), involving 18,144 patients treated with either ezetimibe/simvastatin 10/40 mg (n = 9,067; of whom 6 % were up-titrated to ezetimibe/simvastatin 10/80 mg) or simvastatin 40 mg (n = 9,077; of whom 27 % were up-titrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6,0 years." under Patients with Coronary Heart Disease and ACS Event History.<br><br>Revision of text to read "In the IMPROVE-IT study (see section 5.1), involving 18,144 patients treated with either ezetimibe/simvastatin 10/40 mg (n = 9,067; of whom 6 % were up-titrated to ezetimibe/simvastatin 10/80 mg) or simvastatin 40 mg (n = 9,077; of whom 27 % were up-titrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6,0 years." under Patients with Chronic Kidney Disease. | 12-Oct-20 | MSD |

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| 3 | Ezetrol | Ezetimibe | Pharmacodynamic properties | Revision of text to read "The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a multicentre, randomised, double-blind, active-control study of 18,144 patients enrolled within 10 days of hospitalisation for acute coronary syndrome (ACS; either acute myocardial infarction [MI] or unstable angina [UA]). Patients had an LDL-C ≤ 125 mg/dlL (≤ 3,2 mmol/lL) at the time of presentation with ACS if they had not been taking lipid-lowering therapy or ≤ 100 mg/dl (≤ 2,6 mmol/lL) if they had been receiving lipid-lowering therapy. All patients were randomised in a 1:1 ratio to receive either ezetimibe/simvastatin 10/40 mg (n = 9,067) or simvastatin 40 mg (n = 9,077) and followed for a median of 6,0 years.<br>Patients had a mean age of 63,6 years; 76 % were male, 84 % were Caucasian and 27 % were diabetic. The average LDL-C value at the time of study qualifying event was 80 mg/dl (2,1 mmol/lL) for those on lipid-lowering therapy (n = 6,390) and 101 mg/dl (2,6 mmol/lL) for those not on previous lipid-lowering therapy (n = 11,594). Prior to the hospitalisation for the qualifying ACS event, 34 % of the patients were on statin therapy. At one year, the average LDL-C for patients continuing on therapy was 53,2 mg/dlL (1,4 mmol/lL) for the ezetimibe/simvastatin group and 69,9 mg/dlL (1,8 mmol/lL) for the simvastatin monotherapy group. Lipid values were generally obtained for patients who remained on study therapy." under Prevention of Cardiovascular Events.<br><br>Revision of text to read "The SHARP protocol-specified primary comparison was an intention-to-treat analysis of "major vascular events" (MVE; defined as non-fatal MI or cardiac death, stroke or any revascularisation procedure) in only those patients initially randomised to the Ezetrol combined with simvastatin (n = 4,193) or placebo (n = 4,191) groups. Secondary analyses included the same composite analysed for the full cohort randomised (at study baseline or at year 1) to Ezetrol combined with simvastatin (n = 4,650) or placebo (n = 4,620) as well as the components of this composite." under Prevention of Major Vascular Events in Chronic Kidney Disease (CKD). | 12-Oct-20 | MSD |