SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ezehron Duo 20 mg/10 mg, tablet
Ezehron Duo 10 mg/10 mg, tablet
Ezehron Duo 5 mg/10 mg, tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ezehron Duo 20 mg/10 mg tablet
Each tablet contains 20 mg rosuvastatin (as calcium salt) and 10 mg of ezetimibe.

Excipients of known activity: lactose monohydrate (each tablet contains 228.29 mg lactose monohydrate)

Ezehron Duo 10 mg/10 mg tablet
Each tablet contains 10 mg rosuvastatin (as calcium salt) and 10 mg of ezetimibe.

Excipients of known activity: lactose monohydrate (each tablet contains 238.39 mg lactose monohydrate)

Ezehron Duo 5 mg/10 mg tablet
Each tablet contains 5 mg rosuvastatin (as calcium salt) and 10 mg of ezetimibe.

Excipients of known activity: lactose monohydrate (each tablet contains 243.89 mg lactose monohydrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Ezehron Duo 20 mg/10 mg tablet: white to off-white, round, biconvex, uncoated tablet. The diameter of the tablet is 11 mm.

Ezehron Duo 10 mg/10 mg tablet: white to off-white, oval, biconvex, uncoated tablet, engraved E1 on one side and 1 on the other side. The dimensions of the tablet are 15 mm x 7 mm

Ezehron Duo 5 mg/10 mg tablet: white to off-white, round, flat, uncoated tablet, engraved E2 on one side and 2 on the other side. The diameter of the tablet is 10 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia

Ezehron Duo is indicated as adjunct to diet for treatment of primary hypercholesterolemia as substitution therapy in adult patients adequately controlled with the individual substances given concurrently at the same dose level as in the fixed dose combination, but as separate products.

Prevention of Cardiovascular Events
Ezehron Duo is indicated to reduce the risk of cardiovascular events ~~(see section 5.1)~~ as substitution therapy in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), who are adequately controlled with the individual substances given concurrently at the same dose level as in the fixed dose combination, but as separate products.

4.2 Posology and method of administration

Posology
Ezehron Duo is indicated in adult patients whose hypercholesterolemia is adequately controlled with separately administered monocomponent preparations of the same doses as the recommended combination. The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with Ezehron Duo tablets.

The recommended daily dose is one tablet of the given strength with or without food.
Ezehron Duo are not suitable for initial therapy. Treatment initiation or dose adjustment if necessary should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible. Ezehron Duo 5 mg/10 mg, 10 mg/10 mg and 20 mg/10 mg tablet are not suitable for the treatment of patients requiring 40 mg dose of rosuvastatin.

Ezehron Duo should be taken either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

Paediatric population
The safety and efficacy of Ezehron Duo in children below the age of 18 years have not yet been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Use in the elderly
A start dose of 5 mg rosuvastatin is recommended in patients □70 years (see section 4.4). The combination is not suitable for initial therapy. Treatment initiation or dose adjustment if necessary should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Dosage in patients with renal insufficiency
No dose adjustment is necessary in patients with mild to moderate renal impairment.
The recommended start dose of rosuvastatin is 5 mg in patients with moderate renal impairment (creatinine clearance □60 ml/min). The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.
The use of rosuvastatin in patients with severe renal impairment is contraindicated for all doses (see sections 4.3 and 5.2).

Dosage in patients with hepatic impairment
No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with Ezehron Duo is not recommended in patients with moderate (Child Pugh score 7 to 9) or

severe (Child Pugh score >9) liver dysfunction (See sections 4.4 and 5.2.). Ezehron Duo is contraindicated in patients with active liver disease (see section 4.3).

Race
Increased systemic exposure of rosuvastatin has been seen in Asian subjects (see sections 4.4 and 5.2). The recommended start dose is rosuvastatin 5 mg for patients of Asian ancestry. The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.

Genetic polymorphisms
Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure (see Section 5.2). For patients who are known to have such specific types of polymorphisms, a lower daily dose of Ezehron Duo is recommended.

Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is 5 mg of rosuvastatin in patients with predisposing factors to myopathy (see section 4.4). The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.

Concomitant therapy
Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when Ezehron Duo tablets are administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir; (see Sections 4.4 and 4.5).
Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing Ezehron Duo tablets therapy. In situations where co-administration of these medicinal products with Ezehron Duo tablets is unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered (see Section 4.5).

Method of administration
For oral use.
Ezehron Duo tablets should be taken each day once at the same time of the day with or without food. The tablet should be swallowed whole with a drink of water.

4.3 Contraindications

Ezehron Duo tablet is contraindicated:

- in patients with hypersensitivity to the active substances (rosuvastatin, ezetimibe) or to any of the excipients listed in section 6.1.
- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3x the upper limit of normal (ULN).
- during pregnancy and breast-feeding and in women of childbearing, potential not using appropriate contraceptive measures.
- in patients with severe renal impairment (creatinine clearance □30 ml/min).
- in patients with myopathy.
- in patients receiving concomitant combination of sofosbuvir/velpatasvir/voxilaprevir (see section 4.5)

– in patients receiving concomitant ciclosporin. (See sections 4.4, 4.5 and 5.2).

4.4 Special warnings and precautions for use

Skeletal Muscle Effects

Effects on skeletal muscle e.g. myalgia, myopathy, and, rarely rhabdomyolysis have been reported in rosuvastatin-treated patients with all doses and in particular with doses □20 mg.

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. 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 a creatine phosphokinase (CPK) level > 10 times the ULN, ezetimibe, any statin, and any of these agents known to be associated with increased risk of rhabdomyolysis, 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 (see section 4.8).

Creatine Kinase Measurement

Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase, which may confound interpretation of the results.

If CK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5-7 days. If the repeat test confirms a baseline CK>5xULN, treatment should not be started.

Before treatment

Ezehron Duo, as other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

– renal impairment
– hypothyroidism
– personal or family history of hereditary muscular disorders
– previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
– alcohol abuse
– age >70 years
– situations where an increase in plasma levels may occur (see section 5.2)
– concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (>5xULN) treatment should not be started.

Whilst on treatment

Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are <5xULN). Routine monitoring of CK levels in asymptomatic patients is not warranted.

There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including rosuvastatin. IMNM is clinically characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with rosuvastatin and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolid antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of Ezehron Duo and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Ezehron Duo tablets with fibrates or niacin should be carefully weighed against the potential risks of such combinations.

Rosuvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of rosuvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Ezehron Duo tablets should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). Rosuvastatin/Ezetimibe should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Liver effects

In controlled co-administration trials in patients receiving ezetimibe with a statin, consecutive transaminase elevations (≥3X the upper limit of normal [ULN]) have been observed. It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment.

Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with Ezehron Duo tablets.

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, Ezehron Duo tablets is not recommended (see section 5.2).

Renal effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease (see section 4.8).

Race

Rosuvastatin pharmacokinetic studies show an increase in exposure in Asian subjects compared with

Caucasians (see sections 4.2 and 5.2).

Protease inhibitors
Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of Ezehron Duo in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating rosuvastatin in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of Ezehron Duo is adjusted (see sections 4.2 and 4.5).

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.
In the JUPITER study, the reported overall frequency of diabetes mellitus was 2.8% in rosuvastatin and 2.3% in placebo, mostly in patients with fasting glucose 5.6 to 6.9 mmol/L.

Fibrates
The safety and efficacy of ezetimibe administered with fibrates have not been established.
If cholelithiasis is suspected in a patient receiving Ezehron Duo and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see sections 4.5 and 4.8).

Anticoagulants
If Ezehron Duo tablet is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Ciclosporin: See section 4.3 and 4.5.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with rosuvastatin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of this reaction appears, Ezehron Duo should be discontinued immediately and an alternative treatment should be considered.
If the patient has developed a serious reaction such as SJS or DRESS with the use of Ezehron Duo, treatment with Ezehron Duo must not be restarted in this patient at any time.

Paediatric population
The safety and efficacy of Ezehron Duo tablets in children below the age of 18 years have not yet been

established, therefore its use is not recommended in this age group.

Liver disease and alcohol
Ezehron Duo should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

Lactose
Ezehron Duo tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications
Ciclosporin: During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see section 4.3). Concomitant administration did not affect plasma concentrations of ciclosporin.
Co-administration of Ezehron Duo with ciclosporin is contraindicated (see section 4.3).
In a study of eight post-renal transplant patients with creatinine clearance of > 50 ml/min on a stable dose of ciclosporin, a single 10-mg dose of ezetimibe resulted in a 3.4-fold (range 2.3 to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency who was receiving ciclosporin and multiple other medications, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin AUC (range 10 % decrease to 51 % increase) compared to a single 100-mg dose of ciclosporin alone. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted.

Not-recommended combinations
Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see section 4.5 Table). For instance, in a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin AUC and Cmax respectively. The concomitant use of rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of rosuvastatin dose adjustments based on the expected increase in rosuvastatin exposure (see Sections 4.2, 4.4, and 4.5 Table). The combination is not suitable for initial therapy. Treatment initiation or dose adjustment if necessary should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

*Transporter protein inhibitors***:** Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of Ezehron Duo with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see Sections 4.2, 4.4, and 4.5 Table).

Gemfibrozil and other lipid-lowering products: Concomitant use of rosuvastatin and gemfibrozil resulted in

a 2-fold increase in rosuvastatin C_{max} and AUC (see section 4.4). Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur.
Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (or equal to 1 g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone.

In patients receiving fenofibrate and ezetimibe, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease (see section 4.4 and 4.8). If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see section 4.8). Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1.5- and 1.7-fold respectively). Co-administration of ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe sometimes increased cholesterol in the gallbladder bile, but not all species (see section 5.3). A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

Daptomycin: The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors and daptomycin. Consideration should be given to suspending Rosuvastatin/Ezetimibe temporarily in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk. If co -administration cannot be avoided, CPK levels should be measured more frequently than once weekly and patients should be closely monitored for any signs or symptoms that might represent myopathy. (see section 4.4).

Fusidic Acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.
If treatment with systemic fusidic acid is necessary, rosuvastatine treatment should be discontinued throughout the duration of the fusidic acid treatment. **Also see section 4.4**

Other interactions
Antacid: The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied.
Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

Erythromycin: Concomitant use of rosuvastatin and eryhtromycin resulted in a 20% decrease in AUC_{0-t} and a 30% decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes: Results from *in vitro* and *in vivo* studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and

CYP3A4).
In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

Vitamin K antagonists: As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.
Concomitant administration of ezetimibe (10 mg once daily) had no effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If Ezehron Duo are added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of rosuvastatin and oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.
In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of oral contraceptives (ethinyl estradiol and levonorgestrel).

Colestyramine: Concomitant colestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding ezetimibe to colestyramine may be lessened by this interaction (see section 4.2).

Ezetimibe: Concomitant use of 10 mg Rosuvastatin and 10 mg ezetimibe resulted in a 1.2 fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects (Table 1). A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out (see section 4.4). The risk of these events may therefore be increased with concomitant use of ezetimibe and rosuvastatin. Appropriate clinical monitoring of these patients is recommended.

Ticagrelor: Ticagrelor might affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. Although the exact mechanism is not known, in some cases, concomitant use of ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and rhabdomyolysis .

Other medicinal products: Based on data from specific interaction studies no clinically relevant interaction between rosuvastatin and digoxin is expected.
In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, glipizide, tolbutamide, or midazolam, during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Interactions requiring rosuvastatin dose adjustments (see also Table below): When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses

should be adjusted. Start with a 5 mg once daily dose of rosuvastatin if the expected increase in exposure (AUC) is approximately 2-fold or higher. The maximum daily dose should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products, for example a 20 mg dose of rosuvastatin with gemfibrozil (1.9-fold increase), and a 10 mg dose of rosuvastatin with combination atazanavir/ritonavir (3.1-fold increase).

If medicinal product is observed to increase rosuvastatin AUC less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the rosuvastatin dose above 20 mg.

Table 1. Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasi magnitude) from published clinical trials

Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
2-fold or greater than 2-fold increase in AUC of rosuvastatin		
Sofosbuvir/velpatasvir/voxilaprevir (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) once daily for 15 days	10 mg single dose	7.4-fold ↑
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Darolutamide 600 mg BID, 5 days	5 mg, single dose	5.2-fold ↑
Regorafenib 160 mg, OD, 14 days	5 mg single dose	3.8-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Roxadustat 200 mg QOD	10 mg, single dose	2.9-fold ↑
Velpatasvir 100 mg OD	10 mg, single dose	2.7-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ Ritonavir 100 mg OD/ dasabuvir 400 mg BID, 14 days	5 mg, single dose	2.6-fold ↑
Teriflunomide	Not available	2.5-fold ↑
Grazoprevir 200 mg/elbasvir 50mg OD, 11 days	10 mg, single dose	2.3-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD, 7 days	5 mg OD, 7 days	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Capmatinib 400mg BID	10 mg, single dose	2.1-fold ↑

Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Fostamatinib 100 mg twice daily	20 mg, single dose	2.0-fold ↑
Tafamidis 61 mg BID on Days 1 & 2, followed by OD on Days 3 to 9	10 mg, single dose	2.0-fold ↑
Less than 2-fold increase in AUC of rosuvastatin		
Febuxostat 120mg OD	10 mg, single dose	1.9-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	1.4-fold ↑**
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	1.2-fold ↑**
Decrease in AUC of rosuvastatin		
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓

* Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone.
Data given as % change represent % difference relative to rosuvastatin alone.
Increase is indicated as "↑" no change as "↔" decrease as "↓"
**Several interaction studies have been performed at different rosuvastatin dosages, the table shows the most significant ratio
AUC = area under curve; OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Ezehron Duo is contraindicated in pregnancy and breast-feeding.
Women of childbearing potential should use appropriate contraceptive measures.

Pregnancy

Rosuvastatin:
Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity (see section 5.3). If a patient becomes pregnant during use of Ezehron Duo, treatment should be discontinued immediately.
Ezetimibe:
No clinical data are available on the use of ezetimibe during pregnancy.
Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development (see section 5.3).

Breast-feeding
Rosuvastatin:
Limited data from published reports indicate that Rosuvastatin is present in human milk. Rosuvastatin is excreted in the milk of rats. Due to rosuvastatin´s mechanism of action, there is a potential risk for adverse reactions in the infant. Rosuvastatin is contraindicated during lactation.
Ezetimibe:
Studies on rats have shown that ezetimibe is secreted into milk. It is not known if ezetimibe is secreted into human breast milk.

Fertility
Ezetimibe:
No clinical trial data are available on the effects of ezetimibe on human fertility. Ezetimibe had no effect on the fertility of male or female rats (see section 5.3).
Rosuvastatin:
There are no known effects on fertility after use of rosuvastatin.

4.7 Effects on ability to drive and use machines

Ezehron Duo tablets has no or negligible influence on the ability to drive and use machines. Studies to determine the effect of rosuvastatin and/or ezetimibe on the ability to drive and use machines have not been conducted. However, when driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

Summary of the safety profile
The adverse reactions seen with rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4% of rosuvastatin-treated patients were withdrawn due to adverse reactions.

In clinical studies of up to 112 weeks duration, ezetimibe 10 mg daily was administered alone in 2396 patients, or with a statin in 11,308 patients or with fenofibrate in 185 patients. Adverse reactions were usually mild and transient. The overall incidence of side effects was similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between ezetimibe and placebo.

According to available data 1200 patients took rosuvastatin and ezetimibe combination in clinical studies. As reported in the published literature, the most frequent common adverse events related to rosuvastatin-ezetimibe combination treatment in hypercholesterolemic patients are increased hepatic transaminases,

gastrointestinal problems and muscle pain. These are known undesirable effects of the active substances. However, a pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out (see section 5.2).

Tabulated list of adverse reactions

The frequencies of adverse events are ranked according to the following: 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); Not known (cannot be estimated from the available data).

MedDRA system organ class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Thrombocytopenia[2]		
Immune system disorders			hypersensitivity reactions including angioedema[2]		Anaphylaxis, rash, urticaria
Endocrine disorders	diabetes mellitus[1,2]				
Metabolism and Nutrition Disorders		decreased appetite[3]			
Psychiatric disorders					Depression[2,5]
Nervous system disorders	Headache[2,4], dizziness[2]	Paraesthesia[4]		Polyneuropathy[2], memory loss[2]	peripheral neuropathy[2] sleep disturbances (including insomnia and nightmares)[2,] myasthenia gravis
Eye disorders					ocular myasthenia
Vascular Disorders		hot flush[3]; hypertension			
Respiratory, thoracic and mediastinal disorders		Cough[3]			dyspnoea[2,5]
Gastrointestinal disorders	Constipation[2], nausea[2], abdominal pain[2,3] diarrhoea[3] flatulence[3]	Dyspepsia[3] gastrooesophageal reflux disease[3]; nausea[3] dry mouth[4]; gastritis[4]	Pancreatitis[2]		
Hepatobiliary disorders			Increased hepatic	Jaundice[2], hepatitis[2]	cholelithiasis[5;]

			transaminases[2]		cholecystitis[5]
Skin and subcutaneous tissue disorders		Pruritus[2,4], rash[2,4], urticaria[2,4]			Stevens-Johnson syndrome[2] erythema multiforme[5], drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Myalgia[2,4]	Arthralgia[3]; muscle spasms[3]; neck pain[3] back pain[4]; muscular weakness[4]; pain in extremity[4]	Myopathy (including myositis)[2], rhabdomyolysis[2,] lupus-like syndrome, muscle rupture		immune-mediated necrotizing myopathy[2], tendon disorders, sometimes complicated by rupture[2],
Renal and urinary disorders				Haematuria[2]	
Reproductive system and breast disorders				Gynecomastia[2]	
General disorders and administration site conditions	Asthenia[2], fatigue[3]	chest pain[3], pain[3], asthenia[4]; oedema peripheral[4]			
Investigations	ALT and/or AST Increased[4]	blood CPK increased[3]; gamma-glutamyltransferase increased[3]; liver function test abnormal[3]			

1 Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m^2, raised triglycerides, history of hypertension) – for rosuvastatin.

2 Adverse reaction profile for rosuvastatin based on data from clinical studies and extensive post-marketing experience.

3 Ezetimibe in monotherapy. Adverse reactions were observed in patients treated with ezetimibe (N=2396) and at a greater incidence than placebo (N=1159)

[4] Ezetimibe co-administered with a statin. Adverse reactions were observed in patients with ezetimibe co- administered with a statin (N=11308) and at a greater incidence than statin administered alone (N=9361).

[5] Additional adverse reactions of ezetimibe, reported in post-marketing experience. Because these adverse experiences have been identified from spontaneous reports, their true frequencies are not known and cannot be estimated.

The following adverse events have been reported with some statins:

- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent

Renal effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in □1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.
Haematuria has been observed in patients treated with rosuvastatin and clinical trial data show that the occurrence is low.

Skeletal Muscle Effects: Effects on skeletal muscle e.g. myalgia, myopathy (including myositis), and, rarely, rhabdomyolysis with and without acute renal failure have been reported in rosuvastatin-treated patients with all doses and in particular with doses □20 mg.

A dose-related increase in CK levels has been observed in patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK-levels are elevated (□5xULN), the treatment should be discontinued (see section 4.4).

Liver Effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient.

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) are higher at the 40 mg rosuvastatin dose.

Laboratory values
In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3X ULN, consecutive) was similar between ezetimibe (0.5%) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with ezetimibe co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see section 4.4).
In clinical trials, CPK >10X ULN was reported for 4 of 1,674 (0.2%) patients administered ezetimibe alone vs 1 of 786 (0.1%) patients administered placebo, and for 1 of 917 (0.1%) patients co-administered

ezetimibe and a statin vs 4 of 929 (0.4%) patients administered a statin alone. There was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone) (see section 4.4).

Paediatric population
The safety and efficacy of Ezehron Duo in children below the age of 18 years have not yet been established (see section 5.1).
Rosuvastatin:
Creatine kinase elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of children and adolescents compared to adults. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.
Ezetimibe:
Paediatric patients (6 to 17 years of age)
In a study involving paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia (n = 138), elevations of ALT and/or AST (≥ 3X ULN, consecutive) were observed in 1.1% (1 patient) of the ezetimibe patients compared to 0% in the placebo group. There were no elevations of CPK (≥ 10X ULN). No cases of myopathy were reported.

In a separate study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n = 248), elevations of ALT and/or AST (≥3X ULN, consecutive) were observed in 3% (4 patients) of the ezetimibe/simvastatin patients compared to 2% (2 patients) in the simvastatin monotherapy group; these figures were respectively 2% (2 patients) and 0% for elevation of CPK (≥ 10X ULN). No cases of myopathy were reported.
These trials were not suited for comparison of rare adverse drug reactions.

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 ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

There is no published literature data on rosuvastatin overdose.
There is no specific treatment in the event of overdose with rosuvastatin.
In clinical studies, administration of ezetimibe, 50 mg/day, to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated.
In animals, no toxicity was observed after single oral doses of 5,000 mg/kg of ezetimibe in rats and mice and 3,000 mg/kg in dogs.
A few cases of overdosage with ezetimibe have been reported: most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

In the event of an overdose, symptomatic and supportive measures should be employed. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents, combinations of various lipid modifying agents.
ATC code: C10BA06
Ezehron Duo is a lipid-lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol.

Mechanism of action
Rosuvastatin
Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.
Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Ezetimibe
Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe is orally active, and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g. statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Pharmacodynamic effects
Rosuvastatin
Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 1). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 2*: Dose response in patients with primary hypercholesterolaemia (type IIa and IIb)*
(adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-	ApoB	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5 mg	17	-45	-33	13	-35	-44	-38	4
10 mg	17	-52	-36	14	-10	-48	-42	4
20 mg	17	-55	-40	8	-23	-51	-46	5
40 mg	18	-63	-46	10	-28	-60	-54	0

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Ezetimibe
Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction. In a 2-week clinical study in 18 hypercholesterolaemic patients, Ezetimibe inhibited intestinal cholesterol

absorption by 54%, compared with placebo.
A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [^{14}C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat soluble vitamins A and D.

Rosuvastatin-ezetimibe co-administration
Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.
Administration of statin/ezetimibe combination is effective in reducing the risk of cardiovascular events in patients with coronary heart disease and ACS event history.

Clinical efficacy and safety
Rosuvastatin
Rosuvastatin is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolaemia.

From pooled phase III data, Rosuvastatin has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (mean baseline LDL-C about 4.8 mmol/L) to recognised European Atherosclerosis Society (EAS; 1998) guideline targets; about 80% of patients treated with 10 mg reached the EAS targets for LDL-C levels (<3 mmol/L).

In a large study, 435 patients with heterozygous familial hypercholesterolaemia were given Rosuvastatin from 20 mg to 80 mg in a force-titration design. All doses showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to a daily dose of 40 mg (12 weeks of treatment), LDL-C was reduced by 53%. Thirty three percent (33%) of patients reached EAS guidelines for LDL-C levels (<3 mmol/L).

In a force-titration, open label trial, 42 patients (including 8 paediatric patients) with homozygous familial hypercholesterolaemia were evaluated for their response to Rosuvastatin 20 - 40 mg. In the overall population, the mean LDL-C reduction was 22%.

In clinical studies with a limited number of patients, Rosuvastatin has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin (see section 4.4).

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of rosuvastatin on the occurrence of major atherosclerotic cardiovascular disease events was assessed in 17,802 men (≥50 years) and women (≥60 years).

Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years.
LDL-cholesterol concentration was reduced by 45% ($p<0.001$) in the rosuvastatin group compared to the placebo group.

In a post-hoc analysis of a high-risk subgroup of subjects with a baseline Framingham risk score >20% (1558 subjects) there was a significant reduction in the combined end-point of cardiovascular death,

stroke and myocardial infarction (p=0.028) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate per 1000 patient-years was 8.8. Total mortality was unchanged in this high-risk group (p=0.193). In a post-hoc analysis of a high-risk subgroup of subjects (9302 subjects total) with a baseline SCORE risk ≥5% (extrapolated to include subjects above 65 yrs) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.0003) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate was 5.1 per 1000 patient-years. Total mortality was unchanged in this high-risk group (p=0.076).

In the JUPITER trial, there were 6.6% of rosuvastatin and 6.2% of placebo subjects who discontinued use of study medication due to an adverse event. The most common adverse events that led to treatment discontinuation were: myalgia (0.3% rosuvastatin, 0.2% placebo), abdominal pain (0.03% rosuvastatin, 0.02% placebo) and rash (0.02% rosuvastatin, 0.03% placebo). The most common adverse events at a rate greater than or equal to placebo were urinary tract infection (8.7% rosuvastatin, 8.6% placebo), nasopharyngitis (7.6% rosuvastatin, 7.2% placebo), back pain (7.6% rosuvastatin, 6.9% placebo) and myalgia (7.6% rosuvastatin, 6.6% placebo).

Paediatric population
In a double-blind, randomised, multi-centre, placebo-controlled, 12-week study (n=176, 97 male and 79 female) followed by a 40-week (n=173, 96 male and 77 female), open-label, rosuvastatin dose-titration phase, patients 10 to 17 years of age (Tanner stage II-V, females at least 1-year post-menarche) with heterozygous familial hypercholesterolaemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10 to 13 years and approximately 17%, 18%, 40% and 25% were Tanner stage II, III, IV, and V, respectively.

LDL-C was reduced 38.3%, 44.6% and 50.0% by rosuvastatin 5, 10 and 20 mg, respectively, compared to 0.7% for placebo.

At the end of the 40-week, open-label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 2.8 mmol/L.

After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected (see section 4.4). This trial (n=176) was not suited for comparison of rare adverse drug events.

Rosuvastatin was also studied in a 2-year open-label, titration-to-goal study in 198 children with heterozygous familial hypercholesterolaemia aged 6 to 17 years (88 male and 110 female, Tanner stage <II-V). The starting dose for all patients was 5 mg rosuvastatin once daily. Patients aged 6 to 9 years (n=64) could titrate to a maximum dose of 10 mg once daily and patients aged 10 to 17 years (n=134) to a maximum dose of 20 mg once daily.

After 24 months of treatment with rosuvastatin, the LS mean percent reduction from the baseline value in LDL-C was -43% (Baseline: 236 mg/dL, Month 24: 133 mg/dL). For each age group, the LS mean percent reductions from baseline values in LDL-C were -43% (Baseline: 234 mg/dL, Month 24: 124 mg/dL), -45% (Baseline: 234 mg/dL, Month 24: 124 mg/dL), and -35% (Baseline: 241 mg/dL, Month 24: 153 mg/dL) in the 6 to <10, 10 to <14, and 14 to <18 age groups, respectively.

Rosuvastatin 5 mg, 10 mg, and 20 mg also achieved statistically significant mean changes from

baseline for the following secondary lipid and lipoprotein variables: HDL-C, TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, non-HDL C/HDL-C, ApoB, ApoB/ApoA-1. These changes were each in the direction of improved lipid responses and were sustained over 2 years.

No effect on growth, weight, BMI or sexual maturation was detected after 24 months of treatment (see section 4.4).

Rosuvastatin was studied in a randomised, double-blind, placebo-controlled, multi-centre, cross-over study with 20 mg once daily versus placebo in 14 children and adolescents (aged from 6 to 17 years) with homozygous familial hypercholesterolaemia. The study included an active 4-week dietary lead-in phase during which patients were treated with rosuvastatin 10 mg, a cross-over phase that consisted of a 6-week treatment period with rosuvastatin 20 mg preceded or followed by a 6-week placebo treatment period, and a 12-week maintenance phase during which all patients were treated with rosuvastatin 20 mg. Patients who entered the study on ezetimibe or apheresis therapy continued the treatment throughout the entire study.

A statistically significant (p=0.005) reduction in LDL-C (22.3%, 85.4 mg/dL or 2.2 mmol/L) was observed following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. Statistically significant reductions in Total-C (20.1%, p=0.003), non-HDL-C (22.9%, p=0.003), and ApoB (17.1%, p=0.024) were observed. Reductions were also seen in TG, LDL-C/HDL-C, Total-C/HDL-C, non-HDL-C/HDL-C, and ApoB/ApoA-1 following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. The reduction in LDL-C after 6 weeks of treatment with rosuvastatin 20 mg following 6 weeks of treatment with placebo was maintained over 12 weeks of continuous therapy. One patient had a further reduction in LDL-C (8.0%), Total-C (6.7%) and non-HDL-C (7.4%) following 6 weeks of treatment with 40 mg after up-titration.

During an extended open-label treatment in 9 of these patients with 20 mg rosuvastatin for up to 90 weeks, the LDL-C reduction was maintained in the range of -12.1% to -21.3%.
In the 7 evaluable children and adolescent patients (aged from 8 to 17 years) from the force-titration open label study with homozygous familial hypercholesterolaemia (see above), the percent reduction in LDL-C (21.0%), Total-C (19.2%), and non-HDL-C (21.0%) from baseline following 6 weeks of treatment with rosuvastatin 20 mg was consistent with that observed in the aforementioned study in children and adolescents with homozygous familial hypercholesterolaemia.

Ezetimibe

Primary Hypercholesterolaemia
In a double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolaemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.6 to 4.1 mmol/L [100 to 160 mg/dL], depending on baseline characteristics) were randomised to receive either ezetimibe 10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82%), significantly more patients randomised to ezetimibe achieved their LDL-C goal at study endpoint compared to patients randomised to placebo, 72% and 19%, respectively. The corresponding LDL-C reductions were significantly different (25% and 4% for ezetimibe versus placebo, respectively). In addition, ezetimibe, added to on- going statin therapy, significantly decreased total-C, Apo B, TG and increased HDL-C, compared with placebo. Ezetimibe or placebo added to statin therapy reduced median C-reactive

protein by 10% or 0% from baseline, respectively

In two, double-blind, randomised placebo-controlled, 12-week studies in 1,719 patients with primary hypercholesterolaemia, ezetimibe 10 mg significantly lowered total-C (13%), LDL-C (19%), Apo B (14%), and TG (8%) and increased HDL-C (3%) compared to placebo. In addition, ezetimibe had no effect on the plasma concentrations of fat-soluble vitamins A, D, and E, no effect on prothrombin time, and, like other lipid-lowering agents, did not impair adrenocortical steroid hormone production.

In a multicenter, double-blind, controlled clinical study (ENHANCE), 720 patients with heterozygous familial hypercholesterolaemia were randomised to receive ezetimibe 10 mg in combination with simvastatin 80 mg (n = 357) or simvastatin 80 mg (n = 363) for 2 years. The primary objective of the study was to investigate the effect of the ezetimibe/simvastatin combination therapy on carotid artery intima-media thickness (IMT) compared to simvastatin monotherapy. The impact of this surrogate marker on cardiovascular morbidity and mortality is still not demonstrated.
The primary endpoint, the change in the mean IMT of all six carotid segments, did not differ significantly (p = 0.29) between the two treatment groups as measured by B-mode ultrasound. With ezetimibe 10 mg in combination with simvastatin 80 mg or simvastatin 80 mg alone, intima-medial thickening increased by 0.0111 mm and 0.0058 mm, respectively, over the study's 2 year duration (baseline mean carotid IMT 0.68 mm and 0.69 mm respectively.
Ezetimibe 10 mg in combination with simvastatin 80 mg lowered LDL-C, total-C, Apo B, and TG significantly more than simvastatin 80 mg. The percent increase in HDL-C was similar for the two treatment groups. The adverse reactions reported for ezetimibe 10 mg in combination with simvastatin 80 mg were consistent with its known safety profile.

Paediatric population
In a multicentre, double-blind, controlled study, 138 patients (59 boys and 79 girls), 6 to 10 years of age (mean age 8.3 years) with heterozygous familial or non-familial hypercholesterolaemia (HeFH) with baseline LDL-C levels between 3.74 and 9.92 mmol/L were randomised to either Ezetimibe 10 mg or placebo for 12 weeks.
At week 12, Ezetimibe significantly reduced total-C (-21% vs. 0%), LDL-C (-28% vs. -1%), Apo-B (-22% vs. -1%), and non-HDL-C (-26% vs. 0%) compared to placebo. Results for the two treatment groups were similar for TG and HDL-C (-6% vs. +8%, and +2% vs. +1%, respectively).
In a multicentre, double-blind, controlled study, 142 boys (Tanner Stage II and above) and 106 postmenarchal girls, 10 to 17 years of age (mean age 14.2 years) with heterozygous familial hypercholesterolaemia (HeFH) with baseline LDL-C levels between 4.1 and 10.4 mmol/L were randomised to either Ezetimibe 10 mg co-administered with simvastatin (10, 20 or 40 mg) or simvastatin (10, 20 or 40 mg) alone for 6 weeks, co-administered Ezetimibe and 40 mg simvastatin or 40 mg simvastatin alone for the next 27 weeks, and open-label co-administered Ezetimibe and simvastatin
(10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.

At Week 6, Ezetimibe co-administered with simvastatin (all doses) significantly reduced total-C (38% vs 26%), LDL-C (49% vs 34%), Apo B (39% vs 27%), and non-HDL-C (47% vs 33%) compared to simvastatin (all doses) alone. Results for the two treatment groups were similar for TG and HDL-C (-17% vs -12% and +7% vs +6%, respectively). At Week 33, results were consistent with those at Week 6 and significantly more patients receiving Ezetimibe and 40 mg simvastatin (62%) attained the NCEP AAP ideal goal (< 2.8 mmol/L [110 mg/dL]) for LDL-C compared to those receiving 40 mg simvastatin (25%). At Week 53, the end of the open-label extension, the effects on lipid parameters were maintained.

The safety and efficacy of Ezetimibe co-administered with doses of simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age. The safety and efficacy of Ezetimibe co-administered with simvastatin have not been studied in paediatric patients < 10 years of age.
The long-term efficacy of therapy with Ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Prevention of Cardiovascular Events
The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a multicenter, 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/dL (≤ 3.2 mmol/L) at the time of presentation with ACS if they had not been taking lipid-lowering therapy, or ≤ 100 mg/dL (≤ 2.6 mmol/L) 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.

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/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). 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/dL (1.4 mmol/L) for the ezetimibe/simvastatin group and 69.9 mg/dL (1.8 mmol/L) for the simvastatin monotherapy group. Lipid values were generally obtained for patients who remained on study therapy.

The primary endpoint was a composite consisting of cardiovascular death, major coronary events (MCE; defined as non-fatal myocardial infarction, documented unstable angina that required hospitalisation, or any coronary revascularisation procedure occurring at least 30 days after randomised treatment assignment) and non-fatal stroke. The study demonstrated that treatment with ezetimibe when added to simvastatin provided incremental benefit in reducing the primary composite endpoint of cardiovascular death, MCE, and non-fatal stroke compared with simvastatin alone (relative risk reduction of 6.4%, p = 0.016). The primary endpoint occurred in 2,572 of 9,067 patients (7-year Kaplan-Meier [KM] rate 32.72%) in the ezetimibe/simvastatin group and 2,742 of 9,077 patients (7-year KM rate 34.67%) in the simvastatin alone group. (See Figure 1 and Table 3.) This incremental benefit is expected to be similar with co-administration of other statins shown to be effective in reducing the risk of cardiovascular events. Total mortality was unchanged in this high risk group (see Table 3).
There was an overall benefit for all strokes; however there was a small non-significant increase in haemorrhagic stroke in the ezetimibe-simvastatin group compared with simvastatin alone (see Table 3). The risk of haemorrhagic stroke for ezetimibe co-administered with higher potency statins in long-term outcome studies has not been evaluated.
The treatment effect of ezetimibe/simvastatin was generally consistent with the overall results across many subgroups, including sex, age, race, medical history of diabetes mellitus, baseline lipid levels, prior statin therapy, prior stroke, and hypertension.

Figure 1: Effect of Ezetimibe/Simvastatin on the Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke

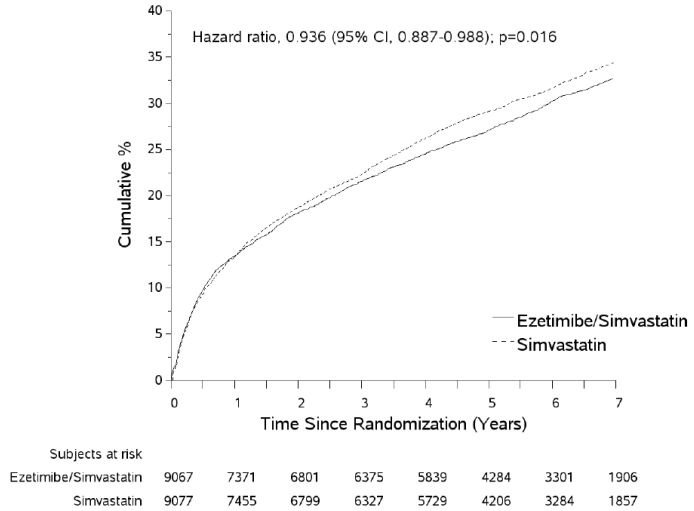

Table 3
Major Cardiovascular Events by Treatment Group in All Randomised Patients in IMPROVE-IT

Outcome	**Ezetimibe/Simvastatin 10/40 mg[a] (n=9,067)**		**Simvastatin 40 mg[b] (n=9,077)**		**Hazard Ratio (95% CI)**	**p-value**
	n	K-M % [c]	n	K-M % [c]		
Primary Composite Efficacy Endpoint (CV death, Major Coronary Events and non-fatal stroke)	2,572	32.72%	2,742	34.67%	0.936 (0.887, 0.988)	0.016
Secondary Composite Efficacy Endpoints						
CHD death, non-fatal MI, urgent coronary revascularisation after 30 days	1,322	17.52%	1,448	18.88%	0.912 (0.847, 0.983)	0.016
MCE, non-fatal stroke, death (all causes)	3,089	38.65%	3,246	40.25%	0.948 (0.903, 0.996)	0.035
CV death, non-fatal MI, unstable angina requiring hospitalisation, any revascularisation, non-fatal stroke	2,716	34.49%	2,869	36.20%	0.945 (0.897, 0.996)	0.035
Components of Primary Composite Endpoint and Select Efficacy Endpoints (first occurrences of specified event at any time)						
Cardiovascular death	537	6.89%	538	6.84%	1.000 (0.887, 1.127)	0.997
Major Coronary Event:						

Non-fatal MI	945	12.77%	1083	14.41%	0.871 (0.798, 0.950)	0.002
Unstable angina requiring hospitalisation	156	2.06%	148	1.92%	1.059 (0.846, 1.326)	0.618
Coronary revascularisation after 30 days	1,690	21.84%	1,793	23.36%	0.947 (0.886, 1.012)	0.107
Non-fatal stroke	245	3.49%	305	4.24%	0.802 (0.678, 0.949)	0.010
All MI (fatal and non-fatal)	977	13.13%	1,118	14.82%	0.872 (0.800, 0.950)	0.002
All stroke (fatal and non-fatal)	296	4.16%	345	4.77%	0.857 (0.734, 1.001)	0.052
Non-haemorrhagic stroke [d]	242	3.48%	305	4.23%	0.793 (0.670, 0.939)	0.007
Haemorrhagic stroke	59	0.77%	43	0.59%	1.377 (0.930, 2.040)	0.110
Death from any cause	1,215	15.36%	1,231	15.28%	0.989 (0.914, 1.070)	0.782

[a] 6% were uptitrated to ezetimibe/simvastatin 10/80 mg.
[b] 27% were uptitrated to simvastatin 80 mg.
[c] Kaplan-Meier estimate at 7 years.
[d] includes ischemic stroke or stroke of undetermined type.

Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)
The Study of Heart and Renal Protection (SHARP) was a multi-national, randomised, placebo-controlled, double-blind study conducted in 9,438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. A total of 4,650 patients were allocated to a fixed dose combination of ezetimibe 10 mg with simvastatin 20 mg and 4,620 to placebo, and followed for a median of 4.9 years. Patients had a mean age of 62 and 63% were male, 72% Caucasian, 23% diabetic and, for those not on dialysis, the mean estimated glomerular filtration rate (eGFR) was 26.5 mL/min/1.73 m2. There were no lipid entry criteria. Mean LDL-C at baseline was 108 mg/dL. After one year, including patients no longer taking study medication, LDL-C was reduced 26 % relative to placebo by simvastatin 20 mg alone and 38% by ezetimibe 10 mg combined with simvastatin 20 mg.

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 ezetimibe combined with simvastatin (n = 4,193) or placebo (n = 4,191) groups. Secondary analyses included the same composite analyzed for the full cohort randomised (at study baseline or at year 1) to ezetimibe combined with simvastatin (n = 4,650) or placebo (n = 4,620) as well as the components of this composite.

The primary endpoint analysis showed that ezetimibe combined with simvastatin significantly reduced the risk of major vascular events (749 patients with events in the placebo group vs. 639 in the ezetimibe combined with simvastatin group) with a relative risk reduction of 16% (p = 0.001).

Nevertheless, this study design did not allow for a separate contribution of the monocomponent ezetimibe to efficacy to significantly reduce the risk of major vascular events in patients with CKD.

The individual components of MVE in all randomised patients are presented in Table 4. ezetimibe combined with simvastatin significantly reduced the risk of stroke and any revascularisation, with non-significant numerical differences favouring ezetimibe combined with simvastatin for non-fatal MI and cardiac death.

Table 4
Major Vascular Events by Treatment Group in all randomised patients in SHARP[a]

Outcome	Ezetimibe 10 mg combined with simvastatin 20 mg (n = 4,650)	Placebo (n = 4,620)	Risk Ratio (95% CI)	P-value
Major Vascular Events	701 (15.1%)	814 (17.6%)	0.85 (0.77-0.94)	0.001
Non-fatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	0.12
Cardiac Death	253 (5.4%)	272 (5.9%)	0.93 (0.78-1.10)	0.38
Any Stroke	171 (3.7%)	210 (4.5%)	0.81 (0.66-0.99)	0.038
Non-haemorrhagic Stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011
Haemorrhagic Stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any Revascularisation	284 (6.1%)	352 (7.6%)	0.79 (0.68-0.93)	0.004
Major Atherosclerotic Events (MAE)[b]	526 (11.3%)	619 (13.4%)	0.83 (0.74-0.94)	0.002

[a]Intention-to-treat analysis on all SHARP patients randomised to ezetimibe combined with simvastatin or placebo either at baseline or year 1
[b] MAE; defined as the composite of non-fatal myocardial infarction, coronary death, non-haemorrhagic stroke, or any revascularisation

The absolute reduction in LDL cholesterol achieved with ezetimibe combined with simvastatin was lower among patients with a lower baseline LDL-C (< 2.5 mmol/L) and patients on dialysis at baseline than the other patients, and the corresponding risk reductions in these two groups were attenuated.

Rosuvastatin + Ezetimibe

Primary hypercholesterolemia

A 6-week, randomized, double-blind, parallel-group, clinical trial evaluated the safety and efficacy of ezetimibe (10 mg) added to stable rosuvastatin therapy versus up-titration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg (n=440). Pooled data demonstrated that ezetimibe added to stable rosuvastatin 5 mg or 10 mg reduced LDL cholesterol by 21%. In contrast, doubling rosuvastatin to 10 mg or 20 mg reduced LDL cholesterol by 5.7% (between-group difference of 15.2%, p <0.001). Individually, ezetimibe plus rosuvastatin 5 mg reduced LDL cholesterol more than did rosuvastatin 10 mg (12.3% difference, p<0.001),

and ezetimibe plus rosuvastatin 10 mg reduced LDL cholesterol more than did rosuvastatin 20 mg (17.5% difference, p<0.001).

A 6-week, randomized study was designed to investigate the efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg in patients at high risk of coronary heart disease (n=469). Significantly more patients receiving Ezehron Duo than rosuvastatin alone achieved their ATP III LDL cholesterol goal (<100 mg/dl, 94.0% vs 79.1%, p <0.001). Rosuvastatin 40 mg was effective at improving the atherogenic lipid profile in this high-risk population.

A randomized, open-label, 12-week study investigated the level of LDL reduction in each treatment arm (rosuvastatin 10 mg plus ezetimibe 10 mg, rosuvastatin 20 mg/ezetimibe 10 mg, simvastatin 40/ezetimibe 10 mg, simvastatin 80/ezetimibe 10 mg). The reduction from baseline with the low dose rosuvastatin combination***s*** was 59.7%, significantly superior to the low dose simvastatin combinations, 55.2% (p<0.05). Treatment with the high-dose rosuvastatin combo reduced LDL cholesterol 63.5% compared with a reduction of 57.4% with the high-dose simvastatin combination (p<0.001).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing rosuvastatin and the reference medicinal product containing ezetimibe, in all subsets of the paediatric population in the treatment of elevated cholesterol (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Rosuvastatin and ezetimibe therapy
Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2 fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

Rosuvastatin
Absorption: Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%.

Distribution: Rosuvastatin is taken up extensively by the liver, which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Biotransformation: Rosuvastatin undergoes limited metabolism (approximately 10%). *In vitro* metabolism studies using human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl- and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Elimination: Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine.
Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is

approximately 50 litres/hour (coefficient of variation 21.7%).
As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

Linearity*:* Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Special populations
Age and sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers (see "Paediatric population" below).

Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians; Asian-Indians show an approximate 1.3-fold elevation in median AUC and C_{max}.
A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal insufficiency: In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (Cr_{Cl} □30 ml/min) had a 3-fold increase in plasma concentration and a 9- fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were 50% greater compared to healthy volunteers.

Hepatic insufficiency: In a study with subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores.
There is no experience in subjects with Child-Pugh scores above 9.

*Genetic polymorphisms***:** Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with a higher rosuvastatin exposure (AUC) compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes. This specific genotyping is not established in clinical practice, but for patients who are known to have these types of polymorphisms, a lower daily dose of Ezehron Duo is recommended.

Paediatric population: Two pharmacokinetic studies with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolaemia 10-17 or 6-17 years of age (total of 214 patients) demonstrated that exposure in paediatric patients appears comparable to or lower than that in adult patients. Rosuvastatin exposure was predictable with respect to dose and time over a 2-year period.

Ezetimibe
Absorption: After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically-active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (Cmax) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe.

The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.
Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe. Ezetimibe can be administered with or without food.

Distribution: Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

Biotransformation*:* Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Elimination: Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Special populations
Age and sex: Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe. Therefore, no dosage adjustment is necessary in the elderly. Plasma concentrations for total ezetimibe are slightly higher (approximately 20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe.
Therefore, no dosage adjustment is necessary on the basis of gender.

Renal insufficiency: After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 ml/min/1.73m2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.
An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Hepatic insufficiency: After a single 10 mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score >9) hepatic insufficiency, Ezehron Duo are not recommended in these patients (see section 4.4).

Paediatric population: The pharmacokinetics of ezetimibe are similar between children ≥6 years and adults. Pharmacokinetic data in the paediatric population <6 years of age are not available. Clinical experience in paediatric and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

5.3 Preclinical safety data

In co-administration studies with ezetimibe and statins the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in co-administration therapy. No such interactions occurred in the clinical studies. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for statins and 500 to 2,000 times the AUC level for the active metabolites).
In a series of *in vivo* and *in vitro* assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential. Long-term carcinogenicity tests on ezetimibe were negative.
The co-administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed.

Rosuvastatin: Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been evaluated. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels were as follows: in repeated-dose toxicity studies histopathologic liver changes likely due to the pharmacologic action of rosuvastatin were observed in mouse, rat, and to a lesser extent with effects in the gall bladder in dogs, but not in monkeys. In addition, testicular toxicity was observed in monkeys and dogs at higher dosages. Reproductive toxicity was evident in rats, with reduced litter sizes, litter weight and pup survival observed at maternally toxic doses, where systemic exposures were several times above the therapeutic exposure level.

Ezetimibe: Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (≥0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a one-year study on dogs given doses of up to 300mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.
Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1,000 mg/kg/day. The co-administration of ezetimibe with lovastatin resulted in embryolethal effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactose monohydrate,
- Microcrystalline Cellulose,
- Croscarmellose Sodium,
- Crospovidone, type A
- Povidone K-30
- Sodium laurel sulfate and Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store in the original package in order to protect from light. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Packs of 7, 10, 14, 28, 30, 56, 60, 84, 90, 98 and 100 tablets in blister (PA/AL/PVC // Al). Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Adamed Sp. z o.o.
Pieńków 149,
05-152 Czosnów
Poland

8. MARKETING AUTHORISATION NUMBER(S)

Ezehron Duo 5 mg/10 mg, tablet: MA948/00401
Ezehron Duo 10 mg/10 mg, tablet: MA948/00402
Ezehron Duo 20 mg/10 mg, tablet: MA948/00403

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th February 2018

Date of renewal: 22nd October 2025

10. DATE OF REVISION OF THE TEXT

February 2025