Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trinomia 100 mg/40 mg/5 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg of acetylsalicylic acid, 40 mg of atorvastatin (as 43.38 mg of atorvastatin calcium trihydrate) and 5 mg of ramipril.

Excipient(s) with known effect: Contains 79.40 mg of lactose monohydrate and 0.48 mg of soya lecithin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

Size 0 hard shell gelatine capsules (approx. length: 21.7 mm) with opaque orange-coloured cap and opaque white-coloured body, imprinted with "AAR 100/40/5" containing two 50 mg acetylsalicylic white or nearly white film-coated tablets engraved "AS", two 20 mg atorvastatin pink film-coated tablets engraved "AT" and one 5 mg ramipril pale yellow film-coated tablet engraved "R5".

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Trinomia is indicated for the secondary prevention of cardiovascular accidents as substitution therapy in adult patients adequatelly controlled with the monocomponents given concomitantly at equivalent therapeutical doses.

4.2 Posology and method of administration

Posology
Adults

Patients who are currently controlled with equivalent therapeutical doses of acetylsalicylic acid, atorvastatin and ramipril can be directly switched to Trinomia capsules.

The initiation of treatment should take place under medical supervision (see section 4.4).

For cardiovascular prevention, the target maintenance dose of Ramipril is 10 mg once daily.

Paediatric population

Trinomia is contraindicated in children and adolescents below 18 years of age (see section 4.3).

Special populations

- Patients with renal impairment:Daily dose in patients with renal impairment should be based on creatinine clearance (see section 5.2):
  - if creatinine clearance is ≥ 60 ml/min, the maximal daily dose of ramipril is 10 mg;
  - if creatinine clearance is between 30-60 ml/min, the maximal daily dose of ramipril is 5 mg;

In patients in hemodialysis and/or with severe renal impairment (creatinine clearance < 30 ml/min) Trinomia is contraindicated (see section 4.3).

- Patients with hepatic impairment:Trinomia should be administered with caution in case of hepatic impairment (see sections 4.4 and 5.2). Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, withdrawal of Trinomia is recommended (see section 4.8).

In addition, the maximum daily dose of ramipril in this patients is 2.5 mg and treatment must be initiated only under close medical supervision.

In patients with severe or active hepatic impairment Trinomia is contraindicated (see section 4.3).

- Elderly
In very old and frail patients, treatment should be started with caution because of greater chance of undesirable effects.

Co-administration with other medicines

In patients taking hepatitis C antiviral agents elbasvir/grazoprevir concomitantly with atorvastatin, the dose of atorvastatin should not exceed 20 mg/day (see sections 4.4 and 4.5).

Method of administration
Trinomia hard capsules are for oral use.

Trinomia should be taken orally as a single capsule per day, preferably after a meal.

Trinomia has to be swallowed with liquid. It must not be chewed nor crushed before swallowing. The capsule must not be opened. The closure system guarantees the pharmacological properties of the active drugs.

Avoid grapefruit juice when taking Trinomia.

4.3 Contraindications

- Hypersensitivity to the active substances, to any of the excipients listed in section 6.1, to other salicylates, to nonsteroidal anti-inflammatory drugs (NSAIDs), to any other ACE (Angiotensin Converting Enzyme) inhibitors or to tartrazine.

- Hypersensitity to soya or peanut.

- In case of history of previous asthma attacks or other allergic reactions to salicylic acid or other non-steroidal analgesics / anti-imflamatories.

- Active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages.

- Haemophilia and other bleeding disorders.

- Severe kidney and liver impairment (see section 4.2).

- Patients in hemodialysis (see section 4.2).

- Severe heart failure.

- Concomitant treatment with methotrexate at a dosage of 15 mg or more per week (see section 4.5).

- Concomitant use of Trinomia with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

- Patients with nasal polyps associated to ashma induced or exacerbated by acetylsalicylic acid.

- Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see section 4.4).

- During pregnancy, lactation and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

- Due to the risk of rhabdomyolysis concomitant treatment with tipranavir or ritonavir (see section 4.4 and 4.5).

- Due to the risk of rhabdomyolysis concomitant treatment with ciclosporin (see section 4.4 and 4.5).

- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or Angiotensin II receptor antagonists (AIIRAs).

- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5).

- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney.

- Ramipril must not be used in patients with hypotensive or haemodinamically unstable states.

- Children and adolescents below 18 years of age. Risk of Reye syndrome exists in case fo children under 16 years with fever, flu or chicken pox.

- Patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir.

- Concomitant use with sacubitril/valsartan therapy. Trinomia must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Trinomia should only be used as a substitution therapy in patients adequatelly controlled with the monocomponents given concomitantly at equivalent therapeutical doses.

Warnings for special populations:

Particularly careful medical supervision is required in case of:

- hypersensitivity to other analgesics/ antiinflammatory/ antipyretic/ antirheumatics or other allergens (see section 4.3).

- other known allergies (e.g. skin reactions, pruritus, urticaria), bronchial asthma, hay fever, swollen nasal mucous membranes (adenoid hyperplasia) and other chronic respiratory diseases (see section 4.3).

- patients with a history of gastric or enteric ulcers, or of gastrointestinal bleeding (see section 4.3).

- patients with reduced liver and / or renal function (see section 4.2).

- patients at particular risk of hypotension: In patients with strongly activated renin-angiotensin-aldosterone system, transient or persistent heart failure post MI, patients at risk of cardiac or cerebral ischemia, in case of acute hypotension medical supervision including blood pressure monitoring is necessary to reduce the risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition (section 4.3).

- deterioration of cardiovascular circulation (renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or serious haemorrhagic events).

- patients with glucose 6 phosphate dehydrogenase deficiency.

- patients at risk for elevated levels of uric acid.

- patients who consume substantial quantities of alcohol and/or have a history of liver disease.

- diagnosed pregnancy , the treatment should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

- ACE inhibitors cause higher rate of angioedema in black patients than in non black patients.

As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black people possibly because of a higher prevalence of hypertension with low renin level in the black hypertensive population

Monitoring during the treatment is required in case of:

- concomitant treatment with nonsteroidal anti inflammatory drugs (NSAIDs), corticosteroids, selective serotonin re-uptake inhibitors (SSRIs), antiplatelet drugs, anticoagulants

- concomitant treatment with ibuprofen

- Patients who develop any signs or symptoms suggestive of liver injury

- Surgery: Therapy with Trinomia should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes. In case of smaller interventions such as tooth extractions, Trinomia can contribute to the prolongation of bleeding time.

- Particularly careful monitoring is required in patients with renal impairment (see section 4.2). There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant.

- Serum potassium:ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. Theeffect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5). Other situations that may increase the risk of hyperkalaemia are: age >70 years, uncontrolled diabetes mellitus, dehydration, acute cardiac decompensation or metabolic acidosis.

Warning for specific side-effects:
- *Liver effects:*
Liver function tests should be performed before the initiation of treatment with atorvastatin and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of Trinomia is recommended (see section 4.8).

Trinomia should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

- *Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)*
In a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment.

- *Skeletal muscle effects:*
Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

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

Before the treatment:
Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin treatment in the following situations:

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed.
- In elderly (age > 70 years-old), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.
- Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2).

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.

If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

Creatine kinase measurement:
Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the results.

Whilst on treatment:
- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.
- If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to 5 x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered with close monitoring.
- Trinomia must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

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

Concomitant treatment with other medicinal products
Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elvasvir/grazoprevir), erythromycin, niacin or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

Trinomia 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). The patient 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 Trinomia and fusidic acid should only be considered on a case by case basis and under close medical supervision.

- *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 dyspnoea, 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 of diabetes (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.

- *Angioedema:*
Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8).
In case of angioedema, Trinomia must be discontinued.

Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of the symptoms.

Intestinal angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of Trimomia. Treatment with Trinomia must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

- *Dual blockade of the renin-angiotensin-aldosterone system (RAAS)*
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

- *Anaphylactic reactions during desensitization:*
The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. A temporary discontinuation of Trinomia should be considered prior to desensitization.

- *Neutropenia/agranulocytosis*
Neutropenia/agranulocytosis, thrombocytopenia and anaemia, have been rarely seen and bone marrow depression has been reported. It is recommended to monitor the white blood cell. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or

scleroderma), and those treated with other medicinal products that can cause changes in the blood picture (see sections 4.5 and 4.8).

- *Cough*

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Trinomia contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

4.5 Interaction with other medicinal products and other forms of interaction

Acetylsalicylic acid: pharmacodynamic & pharmacokinetic interactions:
- Effect of co-administered medicinal products on Acetylsalicylic acid

Other platelet aggregation inhibitors: Platelet aggregation inhibitors such as: ticlopidine and clopidogrel can lead to increased clotting time.

Other non-steroidal analgesics / anti-imflamatories and antirheumatics: These drugs increase the risk of gastrointestinal bleeding and ulcers.

Systemic glucocorticoids (with the exception of hydrocortisone as replacement therapy in Addison's disease): Systemic glucocorticoids increase the risk of gastroenteric ulcers and bleeding.

Diuretics: NSAIDs can cause acute renal failure, especially in dehydrated patients. In case of a concomitant use of Trinomia and diuretics it is recommended to monitor the right hydration of the patients.

Alcohol: Alcohol increases the risk of gastroenteric ulcers and bleeding.

Selective serotonin reuptake inhibitors (SSRIs): SSRIs increase the risk of bleeding, in particular of gastrointestinal bleeding due to their synergistic effects.

Uricosuric agents: the concomitant treatment with Trinomia reduce the effect of uricosuric agents and increase plasma levels of acetylsalicylic acid by reducing its excretion.

Metamizole: Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose aspirin for cardioprotection.

- Effect of Acetylsalicylic acid on co-administered medicinal products

Anticoagulant and thrombolytic therapy: Acetylsalicylic acid may increase the risk of bleeding if taken before or concomitantly with anticoagulant and thrombolytic therapy. Therefore, patients requiring anticoagulant and thrombolytic therapy have to be watched for signs of external or internal bleeding.

Digoxin: NSAIDs increase plasma levels of digoxin. Monitoring of digoxin plasma levels is recommended during the concomitant treatment or withdrawal of Trinomia.

Antidiabetic agents including insulin: The concomitant administration of Trinomia and antidiabetic agents including insulin increase the hypoglycaemic effect of these medicinal products. Blood glucose monitoring is recommended. (see subsection *Pharmacodynamic and pharmacokinetic Interactions of ramipril: Precautions for use* below).

Methotrexate: salicylates may displace methotrexate from plasma binding proteins and decrease its renal clearance, leading to toxic methotrexate plasma concentrations. Concomitant treatment with methotrexate at a dosage of 15 mg or more per week is contraindicated (see section 4.3). In case of a dosage of methotrexate lower of 15 mg per week, monitoring of renal function and hemogram should be performed, especially at the beginning of the treatment.

Valproic acid: salicylates may displace valproic acid from plasma binding proteins and decrease its metabolism increasing valproic acid plasma concentrations.

Ibuprofen: There is no conclusive evidence regarding the potential of interaction when acetylsalicylic acid is used concomitantly with long-term ibuprofen, although some experimental data showed a decreased effect on platelet aggregation (see Section 5.1).

Antiacids: Antiacids can increase renal elimination of salicylates by alkalinization of urine.

ACE inhibitors: Although it has been reported that acetylsalicylic acid may decrease the beneficial effect of ACE inhibitors by reducing the synthesis of vasodilatory prostaglandins, several studies have found that a negative interaction with ACE inhibitors is present with high doses of aspirin (*ie* ≥ 325 mg), but not with low doses of aspirin (*ie* ≤ 100 mg).

Ciclosporine: NSAIDs may increase nephrotoxicity of ciclosporine due to effects mediated by renal prostaglandins. It is recommended to carefully monitor renal function, especially in elderly patients.

Vancomycin: Acetylsalicylic acid may increase the risk of ototoxicity of vancomycin.

Interferon α: Acetylsalicylic acid reduce the activity of interferon α.

Lithium: NSAIDs reduce lithium elimination, increasing plasmatic levels of lithium that can reach toxic values. It is not recommended the concomitant use of lithium with AINEs. If this combination is needed, plasmatic concentratin of lithium should be carefully monitored during beginning, adjustment and withdrawal of treatment.

Barbiturates: Acetylsalicylic acid increase plasmatic levels of barbiturates.

Zidovudine: Acetylsalicylic acid may increase plasmatic levels of zidovudine because it inhibit competetively glucuronidation or directly inhibiting hepatic microsomal metabolism.

Phenytoin: Acetylsalicylic acid may increase plasmatic levels of phenytoin.

Laboratory tests: Acetylsalicylic acid may alter the following analytical tests:
- Blood: increase (biologic) of transaminases (ALT and AST), alkaline phosphatase, ammonia, bilirubin, cholesterol, creatine kinase, digoxin, free thyroxine, lactate dehydrogenase (LDH), thyroxine binding globulin, triglycerides, uric acid and valproic acid; increase (analytical interference) of glucose, paracetamol and total proteins; reduction (biologic) of free thyroxine.glucose, phenytoin, TSH, TSH-RH, thyroxine, triglycerides, triiodothyronine, uric acid and creatin clearance; reduction (analytical interference) of transaminases (ALT), albumin, alkaline phosphatase, cholesterol, creatine kinas, lactate dehydrogenase (LDH) and total proteins.
- Urine: Reduction (biologic) of estriol; reduction (analytical interference) of 5-hidroxyindolacetic acid, 4-hydroxy-3-methoxymandelic acid, total estrogens and glucose.

Atorvastatin: pharmacodynamic & pharmacokinetic interactions
- Effect of co-administered medicinal products on atorvastatin
Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2). Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates, fusidic acid and ezetimibe (see section 4.3 and 4.4).

CYP3A4 inhibitors:
Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, some antivirals used in the treatement of HCV (e.g. elbasvir/grazoprevir) and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided lower

starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1).. An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

CYP3A4 inducers
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transport inhibitors
Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended (see Table 1).

Gemfibrozil / fibric acid derivatives
The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, patients should be appropriately monitored (see section 4.4).

Ezetimibe
The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.

Colestipol
Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was coadministered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either medicinal product was given alone.

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, atorvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4.

Colchicine
Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

- *Effect of atorvastatin on co-administered medicinal products*

Digoxin
When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.

Oral contraceptives

Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyloestradiol.

Warfarin

In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If Trinomia is discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin

Co-administered medicinal product and dosing regimen	**Atorvastatin**		
	Dose (mg)	**Change in AUC[&]**	**Clinical Recommendation[#]**
Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (days 14 to 21)	40 mg on day 1, 10 mg on day 20	↑ 9.4 fold	Trinomia is contraindicated in this cases.
Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.9 fold	
Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	↑ 8.7 fold	
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	↑ 5.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients would be recommended.
Clarithromycin 500 mg BID, 9 days	80 mg OD for 8 days	↑ 4.4 fold	
Saquinavir 400 mg BID/ Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 5-18, 30 min after atorvastatin dosing	40 mg OD for 4 days	↑ 3.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Darunavir 300 mg BID/Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	↑ 3.3 fold	
Itraconazole 200 mg OD, 4	40 mg SD	↑ 3.3 fold	

days			
Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	↑ 2.5 fold	
Fosamprenavir 1400 mg BID, 14 days	10 mg OD for 4 days	↑ 2.3 fold	
Nelfinavir 1250 mg BID, 14 days	10 mg OD for 28 days	↑ 1.7 fold^	No specific recommendation.
Grapefruit Juice, 240 mL OD *	40 mg, SD	↑ 37%	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg, SD	↑ 51%	After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33%^	Lower maximum dose and clinical monitoring of these patients is recommended.
Amlodipine 10 mg, single dose	80 mg, SD	↑ 18%	No specific recommendation.
Cimetidine 300 mg QID, 2 weeks	10 mg OD for 4 weeks	↓ less than 1%	No specific recommendation.
Antiacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 2 weeks	10 mg OD for 4 weeks	↓ 35%^	No specific recommendation.
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	↓ 41%	No specific recommendation.
Rifampin 600 mg OD, 7 days (co-administered)	40 mg SD	↑ 30%	If co-administration cannot be avoided, simultaneous coadministration of atorvastatin with rifampin is recommended, with clinical monitoring.
Rifampin 600 mg OD, 5 days (doses separated)	40 mg SD	↓ 80%	
Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40 mg SD	↑ 3%	Lower starting dose and clinical monitoring of these patients is recommended.
Boceprevir 800 mg TID, 7 days	40 mg SD	↑ 2.3 fold	Lower starting dose and clinical monitoring of these patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with boceprevir.
Glecaprevir 400 mg OD/ Pibrentasvir 120 mg OD, 7	10 mg OD for 7 days	↑ 8.3 fold	Co-administration with products containing glecaprevir or pibrentasvir is contraindicated (see section 4.3).

days			
Elbasvir 50 mg OD/ Grazoprevir 200 mg OD, 13 days	10 mg SD	↑ 1.95 fold	The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with products containing elbasvir or grazoprevir.

& Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).
# See sections 4.3, 4.4 and 4.5 for clinical significance.
* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolized by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites).
^ Total atorvastatin equivalent activity
Increase is indicated as "↑", decrease as "↓"
OD = once daily; SD = single dose; BID = twice daily; TID = three times daily; QID = four times daily

Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products

Atorvastatin and doping regimen	**Co-administered medicinal product**		
	Medicinal product/Dose (mg)	**Change in AUC&**	**Clinical Recommendation**
80 mg OD for 10 days	Digoxin 0.25 mg OD, 20 days	↑ 15%	Patients taking digoxin should be monitored appropriately.
40 mg OD for 22 days	Oral contraceptive OD, 2 months - norethindrone 1 mg -ethinyl estradiol 35 microgram	 ↑ 28% ↑ 19%	No specific recommendation.
80 mg OD for 15 days	* Phenazone, 600 mg SD	↑ 3.0%	No specific recommendation.
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No specific recommendation
10 mg, OD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 27%	No specific recommendation
10 mg OD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No specific recommendation

& Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change)
* Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.
Increase is indicated as "↑", decrease as "↓"
OD = once daily; SD = single dose

Ramipril: pharmacodynamic & pharmacokinetic interactions

Contra-indicated combinations
Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

- Medicines increasing the risk of angioedema: Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Precautions for use
- Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes: Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with ramipril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may

lead to significant increases in serum potassium. Care should also be taken when ramipril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of ramipril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

- Heparin: Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

- Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anaesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin): Potentiation of the risk of hypotension is to be anticipated.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

- Vasopressor sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine) that may reduce the antihypertensive effect of ramipril: Blood pressure monitoring is recommended.

- Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell count: Increased likelihood of haematological reactions (see section 4.4).

- Lithium salts: Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium level must be monitored.

- Antidiabetic agents including insulin: Hypoglycaemic reactions may occur. Blood glucose monitoring is recommended.

- Medicines increasing the risk of angioedema: Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

- Ciclosoporin: Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of child-bearing potential should use appropriate contraceptive measures during treatment (see section 4.3).

Pregnancy
Trinomia is contraindicated during pregnancy (see section 4.3).

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor/ Angiotensin II Receptor Antagonist (AIIRA) therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).

During first and second trimester of pregnancy, acetylsalicylic acid should be taken only in cases strictly needed.

Inhibition of prostaglandin synthesis may have negative effects on the pregnancy and/or the embryonic/foetal development. Data from epidemiological studies show increased risk of foetal death as well as cardiac defects and gastroschisis after administration of prostaglandin synthesis inhibitors in the early pregnancy. It is assumed that the risk increases in relation to dosage strength and treatment duration.

Previous experience with daily doses of 50–150 mg acetylsalicylic acid administered to pregnant women in the second and third trimester did not show inhibition of labour, increased tendency for bleeding, or premature occlusion of the *ductus arteriosus*.

There are no enough data that can endorse or discard the association of acetylsalicylic acid with an increased risk of miscarriage. In addition, there are no data that demonstrated the association of acetylsalicylic acid with malformation, although it cannot be excluded an increased risk of gastroschisis.

In a meta-analysis that includes 6 cohort studies, 1 controlled randomised study and 15 case-control studies (Kozer et al, 2002) about the relationship between malformations and the treatment with acetylsalicylic acid durint first trimester of pregnancy, it was not showed a significant increase in malformations risk (odds ratio= 1.33 OR IC 95%: 0.94 – 1.89). The most important cohort study included approximately 15000 prengant women that had taken acetylsalicylic acid during the first trimester of pregnancy.

Studies in animals have shown reproductive toxicity regarding the active substances acetylsalicylic acid, atorvastatin and ramipril (see section 5.3).

In case of women planning to become pregnant or pregnant women in first or second trimester taken acetylsalicylic acid, the duration of treatment should be as shorter as possible.

During third trimester of pregnancy, due to the use of prostaglandin synthesis inhibitors, the foetus may be exposed to:
- Cardiopulmonary toxicity (premature closure of ductus arteriosus and pulmonary hypertension)
- Renal insufficiency, that can result in kidney failure and oligohidroamniosis.

The mother and the foetus, at the end of the pregnancy, may be exposed to:
- Possible prolongation of bleeding time, an atiaggregant effect that may occur even at lower doses.
- Inhibition of uterine contractions resulting in a delay or extension of time of labor.

Atorvastatin safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Animal studies have shown toxicity to reproduction (see section 5.3).

Maternal treatment with atorvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

For these reasons, Trinomia must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Trinomia must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (see sections 4.3 and 4.4.)

Lactation
Small quantities of acetylsalicylic acid and its metabolites pass into the breast milk. It is not known whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk (see section 5.3). Moreover, insufficient information is available regarding the use of ramipril during breastfeeding (see section 5.2).

Because of the potential for serious adverse reactions, women taking Trinomia must not breast-feed their infants. Trinomia is contraindicated during breastfeeding (see section 4.3).

Fertility
In animal studies atorvastatin had no effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Both acetylsalicylic acid and atorvastatin have no or negligible influence on the ability to drive and use machines.

Due to the ramipril component, some adverse effects (e.g. symptoms of a reduction in blood pressure such as dizziness) may impair the patient's ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery).

This can happen especially when changing over from other preparations and when increasing the dose. Therefore when taking Trinomia it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

Summary of the safety profile
Trinomia should only be used as a substitution therapy in patients adequately controlled with the monocomponents given concomitantly at equivalent therapeutical doses.

The most common undesirable effects associated with aspirin treatment are gastrointestinal complaints. Ulceration and bleeding are uncommon (less than 1 case per 100). Gastrointestinal tract perforation is very rare (less than 1 case per 10.000). Immediately inform your physician when you notice black stools or blood in your vomit (signs of severe gastric bleeding).

Known adverse effects with ramipril therapy include persistent dry cough and reactions due to hypotension. Uncommon (less than 1 case per 100) adverse effects associated with ramipril therapy included angioedema, renal and hepatic impairments. Neutropenia, agranulocitosis rarely occur (less than 1 case per 1.000).

Myalgia (muscle pain, muscle spasms, joint swelling) is a common adverse effect with statins treatment. Myopathy and rhabdomyolysis are rare (less than 1 case per 1.000). Monitoring of CK is to be considered as part of evaluation of patients with CK levels significantly elevated at baseline (> 5 times ULN).

In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 atorvastatin vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving atorvastastin These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on atorvastatin. These elevations were dose related and were reversible in all patients.

Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% atorvastatin-treated patients (see section 4.4).

The following adverse events have been reported with some statins:
- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m2, raised triglycerides, history of hypertension).

Tabulated summary of adverse reactions

Table 3: Tabulated summary of adverse reactions
very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000) , not known (cannot be estimated from the available data)

MedDRA System Organ class	Undesirable Effects	Frequency		
		Ramipril	Atorvastatin	ASA
Blood and lymphatic	Eosinophilia.	Uncommon		

system disorders	White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count decreased, haemoglobin decreased, platelet count decreased (thrombocytopenia).	Rare		
	Severe haemorrhages that can be life-threatening in some cases, for example cerebral haemorrhage, have been reported, especially in patients with uncontrolled hypertension and/or concurrenttreatment with anticoagulants.			Rare
	Bleeding such as nose bleed, bleeding gums, bleeding skin or bleeding in the urogenital tract are observed, with a possible prolongation of the clotting time (see section 4.4). This effect may last for 4 to 8 days after ingestion.			Rare
	Trombocytopenia.		Rare	
	Bone marrow failure, pancytopenia, haemolytic anaemia.	Not known		
Gastrointestinal disorders	Gastrointestinal complaints such as heartburn, nausea, vomiting, stomach ache and diarrhoea.			Very common
	Minor blood loss from the gastrointestinal tract (micro-bleeding).			Very common
	Dyspepsia, nausea, diarrhoea.	Common	Common	
	Vomiting	Common	Uncommon	
	Digestive disturbances, abdominal discomfort,	Common		
	Gastrointestinal inflammation.	Common		Uncommon
	Constipation.	Uncommon	Common	
	Flatulence.		Common	
	Gastrointestinal ulcers.			Uncommon
	Gastrointestinal bleeding.			Uncommon
	Iron deficiency anaemia due to occult blood losses from the gastrointestinal tract after long-term use.			Uncommon
	Abdominal pain upper and lower, eructation, pancreatitis.		Uncommon	
	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, dry mouth	Uncommon		
	Glossitis.	Rare		
	Perforation of a gastrointestinal ulcer. Immediately inform your physician when you notice black stools or blood in your vomit (signs of severe gastric bleeding).			Very rare
	Aphtous stomatitis.	Not known		
Respiratory, thoracic and mediastinal disorders	Paroxysmal bronchospasm, serious dyspnoea, rhinitis, nasal congestion.			Common
	Pharyngolaryngeal pain, epistaxis.		Common	
	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea.	Common		
	Bronchospasm including asthma aggravated, nasal congestion.	Uncommon		
Infections and infestations	Nasopharyngitis.		Common	
Nervous system disorders	Headache.	Common	Common	
	Dizziness.	Common	Uncommon	
	Vertigo, ageusia.	Uncommon		
	Paraesthesia, dysgeusia	Uncommon	Uncommon	
	Hypoesthesia, amnesia.		Uncommon	
	Peripheral neuropathy.		Rare	
	Tremor, balance disorder.	Rare		
	Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia.	Not known		
	Headache, dizziness, impaired hearing or buzzing in the ears (tinnitus) and mental confusion.			Not applicable (can be symptoms

				of overdose. See section 4.9)
	Myasthenia gravis.		Not known	
Skin and subcutaneous tissue disorders	Rash in particular maculo-papular.	Common		
	Cutaneous reactions.			Uncommon
	Urticaria, skin rash, pruritus, alopecia.		Uncommon	
	Angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome, pruritus, hyperhidrosis.	Uncommon		
	Angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.		Rare	
	Exfoliative dermatitis, urticaria, onycholysis.	Rare		
	Photosensitivity reaction.	Very rare		
	Erythema multiforme	Not known		Very rare
	Toxic epidermal necrolysis, Stevens-Johnson syndrome	Not known		
	Pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia	Not known		
Immune system disorders	Allergic reactions.		Common	
	Hypersensitive reactions of the skin, respiratory tract, the gastrointestinal tract, and the cardiovascular system, especially in asthma patients (with these possible symptoms: reduction of blood pressure, dyspnoea, rhinitis, nasal congestion, anaphylactic shock, Quincke's oedema).			Rare
	Anaphylaxis.		Very rare	
	Anaphylactic or anaphylactoid reactions, antinuclear antibody increased.	Not known		
Hepatobiliary disorders	Hepatitis.		Uncommon	
	Hepatic enzymes and/or bilirubin conjugated increased.	Uncommon		
	Cholestasis.		Rare	
	Jaundice cholestatic, hepatocellular damage.	Rare		
	Hepatic failure.		Very rare	
	Elevated values in blood liver tests.			Very rare
	Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional).	Not known		
Renal and urinary disorders	Renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased.	Uncommon		
	Renal impairment			Very rare
Metabolism and nutrition disorders	Hyperglycaemia.		Common	
	Blood potassium increased.	Common		
	Hypoglycaemia.		Uncommon	Very rare
	Weight gain.		Uncommon	
	Anorexia.	Uncommon	Uncommon	
	Decreased appetite.	Uncommon		
	At low doses, acetylsalicylic acid reduces the excretion of uric acid. In susceptible patients, this may cause attacks of gout.			Very rare
	Blood sodium decreased.	Not known		
Psychiatric disorders	Nightmare, insomnia.		Uncommon	
	Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence.	Uncommon		
	Confusional state.	Rare		
	Disturbance in attention.	Not known		
Eye disorders	Blurred vision.	Uncommon	Uncommon	
	Visual disturbance.	Uncommon	Rare	
	Conjunctivitis.	Rare		

	Ocular myasthenia.		Not known	
Ear and labyrinth disorders	Tinnitus.	Rare	Uncommon	
	Hearing impaired.	Rare		
	Hearing loss.		Very rare	
Musculoskeletal and connective tissue disorders	Myalgia, muscle spasms.	Common	Common	
	Pain in extremity, joint swelling, back pain.		Common	
	Arthralgia.	Uncommon	Common	
	Neck pain, muscle fatigue.		Uncommon	
	Myopathy, myositis, rhabdomyolysis, muscle rupture, tendonopathy, sometimes complicated by rupture.		Rare	
	Immune-mediated necrotizing myopathy (see section 4.4)		Not known	
	Lupus-like syndrome		Very rare	
Reproductive system and breast disorders	Transient erectile impotence, libido decreased.	Uncommon		
	Gynaecomastia.	Not known	Very rare	
General disorders and administration site conditions	Chest pain, fatigue.	Common	Uncommon	
	Pyrexia	Uncommon	Uncommon	
	Malaise, peripheral oedema.		Uncommon	
	Asthenia	Rare	Uncommon	
Investigations	Liver function test abnormal, blood creatine kinase increased.		Common	
	White blood cells urine positive		Uncommon	
Cardiac disorders	Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral	Uncommon		
Vascular disorders	Hypotension, orthostatic blood pressure decreased, syncope.	Common		
	Flushing.	Uncommon		
	Vascular stenosis, hypoperfusion, vasculitis.	Rare		
	Raynaud's phenomenon.	Not known		

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Acetylsalicylic acid

In chronic overdose of acetylsalicylic acid, symptoms of the central nervous system predominate such as drowsiness, dizziness, confusion or nausea (salicylism). Acute acetylsalicylic intoxication, on the other hand, is a severe disruption of the acid-base equilibrium. Even within the range of therapeutic doses, increased breathing leads to respiratory alkalosis, which is compensated by increased renal excretion of hydrogen carbonate to maintain normal blood pH. Under toxic doses, the compensation is no longer sufficient and the blood pH decreases as well as the concentration of hydrogen carbonate. At times, pCO_2 in the plasma may be normal. The condition appears to be metabolic acidosis, though it is a combination of respiratory and metabolic acidosis. The causes for this are: limitation of breathing by toxic doses, accumulation of acid, in part due to decreased elimination by the kidneys (sulfuric and phosphoric acid, as well as salicylic acid, lactic acid, acetoacetic acid and others), due to a severe disruption of carbohydrate metabolism. Additionally, an electrolyte imbalance and major losses of potassium are observed.

Symptoms of acute intoxication

In addition to acid-base imbalances, electrolyte imbalances (e.g. loss of potassium), hypoglycemia, skin rashes and gastrointestinal bleeding, symptoms such as hyperventilation, tinnitus, nausea, vomiting, disruption of vision and hearing, headaches, dizziness and disorientation are observed as well. Severe intoxication (above 400 microgram/ml) may result in deliria, tremor, respiratory distress, sweating, dehydration, hyperthermia and coma. For lethal intoxications, death is usually caused by failure of respiratory function.

Therapy of intoxication

The scope of therapeutic options for poisoning with acetylsalicylic acid is determined by the severity, stage, and the clinical symptoms of the intoxication. They correspond to the standard procedures to decrease absorption of the substance, balancing hydration and electrolytes, as well as controlling the disrupted thermal regulation and respiratory function. Therapy is dominated by treatments that accelerate elimination and normalize the acid-base and electrolyte balance. In addition to infusions of sodium bicarbonate and potassium chloride, diuretics are also administered. The pH value of the urine should be basic to increase the degree of ionization of the salicylic acid and as a result to decrease tubular reabsorption. Control of the blood chemistry (pH value, pCO_2, bicarbonate, potassium etc.) is highly recommended. Severe cases may require hemodialysis.

In case of a suspected overdose, the patient should be kept under observation during 24 hours because appearance of symptoms and salycilates plasmatic levels may take several hours.

Atorvastatin
Specific treatment is not available for atorvastatin overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

Ramipril
Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure. The patient should be closely monitored and the treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. Ramiprilat, the active metabolite of ramipril is poorly removed from the general circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA Reductase inhibitors,other combinations.
ATC code: C10BX06

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Trinomia in all subsets of the paediatric population in the prevention of ischaemic heart disease (see section 4.2 for information on paediatric use).

Acetylsalicylic acid
Acetylsalicylic acid irreversibly inhibits platelet aggregation. This effect on platelets is due to cyclooxygenase acetylation. This irreversibly inhibits synthesis of thromboxane A_2 (a platelet aggregation promoting and vasoconstricting prostaglandin) in the platelets. This effect is permanent and usually lasts for the entire 8-day life span of a platelet.

Paradoxically, acetylsalicylic acid also inhibits the synthesis of prostacyclin (a platelet aggregation inhibiting prostaglandin but with vasodilatory effects) in the endothelial cells of the blood vessels. This effect is temporary. As soon as the acetylsalicylic acid has been eliminated form the blood, the nucleated endothelial cells synthesize prostacyclin again. As a result, a single, low daily dose of acetylsalicylic acid (< 100 mg/day) results in inhibition of thromboxane A_2 in the platelets without considerably affecting prostacyclin synthesis.

Acetylsalicylic acid also belongs to the group of acid-forming non-steroidal anti-imflamatories with analgesic, antipyretic and anti-imflamatory properties. The mechanism for their action consists of the irreversible inhibition of the cyclooxygenase enzymes that are involved in prostaglandin synthesis. At higher doses, acetylsalicylic acid is used for treatment of mild to moderate pain, elevated body temperature, and for the treatment of acute and chronic inflammatory diseases such as rheumatoid arthritis.

Experimental data showed that ibuprofen may inhibit platelet aggregation of acetylsalicylic acid at lower dosages when concomitantly administered. In a study comparing the effect of the administration of a single dose of ibuprofen 400 mg 8 hours before or 30 minutes before administration of 81 mg of acetylsalicylic acid (in an immediate release tablet), it was observed a reduction of the effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation was observed. However these data is limited because there is uncertainty about the extrapolation of these data to clinical practice.

Therefore there are no relevant conclusion about the regular use of ibruprofen and there are also no relevant clinical effect that may be considred associated with the occasional use of ibuprofen.

Atorvastatin
Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.

Atorvastatin has been shown to reduce concentrations of total-C (30% - 46%), LDL-C (41% - 61%), apolipoprotein B (34% - 50%), and triglycerides (14% - 33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.

Clinical efficacy and safety
Prevention of cardiovascular disease
The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomized, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40–79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤ 6.5 mmol/l (251 mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥ 55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C > 6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.

Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	**Relative Risk Reduction (%)**	**No. of Events (Atorvastatin vs Placebo)**	**Absolute Risk Reduction[1] (%)**	**p-value**
Fatal CHD plus non-fatal MI	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular events and revascularization procedures	20%	389 vs. 483	1.9%	0.0008
Total coronary events	29%	178 vs 247	1.4%	0.0006

[1]Based on difference in crude events rates occurring over a median follow-up of 3.3 years.
CHD = coronary heart disease; MI = myocardial infarction.

Total mortality and cardiovascular mortality were not significantly reduced (185 vs. 212 events, p=0.17 and 74 vs. 82 events, p=0.51). In the subgroup analyses by gender (81% males, 19% females), a beneficial effect of atorvastatin was seen in males but could not be established in females possibly due to the low event rate in the female subgroup. Overall and cardiovascular mortality were numerically higher in the female patients (38 vs. 30 and 17 vs. 12), but this was not statistically significant. There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD plus non-fatal MI) was significantly reduced by atorvastatin in patients treated with amlodipine (HR 0.47 (0.32-0.69), p=0.00008), but not in those treated with atenolol (HR 0.83 (0.59-1.17), p=0.287).

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomized, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤ 4.14 mmol/l (160 mg/dl) and TG ≤ 6.78 mmol/l (600 mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

Patients were treated with either atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410) for a median follow-up of 3.9 years.

The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37%	83 vs. 127	3.2%	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs 64	1.9%	0.0070
Strokes (Fatal and non-fatal)	48%	21 vs. 39	1.3%	0.0163

[1] Based on difference in crude events rates occurring over a median follow-up of 3.9 years.
AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.
There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level. A favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group, p=0.0592).

Ramipril
Mechanism of action
Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.

Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

Pharmacodynamic effects
Antihypertensive properties:
Administration of ramipril causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow and glomerular filtration rate. Administration of ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.

In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral administration. The peak effect of a single dose is usually reached 3 to 6 hours after oral administration. The antihypertensive effect of a single dose usually lasts for 24 hours.

The maximum antihypertensive effect of continued treatment with ramipril is generally apparent after 3 to 4 weeks. It has been shown that the antihypertensive effect is sustained under long term therapy lasting 2 years.

Abrupt discontinuation of ramipril does not produce a rapid and excessive rebound increase in blood pressure.

Heart failure:
In addition to conventional therapy with diuretics and optional cardiac glycosides, ramipril has been shown to be effective in patients with functional classes II-IV of the New-York Heart Association. The drug had beneficial effects on cardiac haemodynamics (decreased left and right ventricular filling pressures, reduced total peripheral vascular resistance, increased cardiac output and improved cardiac index). It also reduced neuroendocrine activation.

Clinical efficacy and safety

Cardiovascular prevention/Nephroprotection:

A preventive placebo-controlled study (the HOPE-study), was carried out in which ramipril was added to standard therapy in more than 9,200 patients. Patients with increased risk of cardiovascular disease following either atherothrombotic cardiovascular disease (history of coronary heart disease, stroke or peripheral vascular disease) or diabetes mellitus with at least one additional risk factor (documented microalbuminuria, hypertension, elevated total cholesterol level, low high-density lipoprotein cholesterol level or cigarette smoking) were included in the study.

The study showed that ramipril statistically significantly decreases the incidence of myocardial infarction, death from cardiovascular causes and stroke, alone and combined (primary combined events).

Table 4: The HOPE study: Main results

	Ramipril %	Placebo %	relative risk (95% confidence interval)	p-value
All patients	**n=4,645**	**N=4,652**		
Primary combined events	**14.0**	**17.8**	**0.78 (0.70-0.86)**	**<0.001**
Myocardial infarction	*9.9*	*12.3*	*0.80 (0.70-0.90)*	*<0.001*
Death from cardiovascular events	*6.1*	*8.1*	*0.74 (0.64-0.87)*	*<0.001*
Stroke	*3.4*	*4.9*	*0.68 (0.56-0.84)*	*<0.001*
Secondary endpoints				
Death from any cause	*10.4*	*12.2*	*0.84 (0.75-0.95)*	*0.005*
Need for Revascularisation	*16.0*	*18.3*	*0.85 (0.77-0.94)*	*0.002*
Hospitalisation for unstable angina	*12.1*	*12.3*	*0.98 (0.87-1.10)*	*NS*
Hospitalisation for heart failure	*3.2*	*3.5*	*0.88 (0.70-1.10)*	*0.25*
Complications related to diabetes	*6.4*	*7.6*	*0.84 (0.72-0.98)*	*0.03*

The MICRO-HOPE study, a predefined substudy from HOPE, investigated the effect of the addition of ramipril 10 mg to the current medical regimen versus placebo in 3,577 patients at least ≥ 55 years old (with no upper limit of age), with a majority of type 2 diabetes (and at least another CV risk factor), normotensive or hypertensive.

The primary analysis showed that 117 (6.5 %) participants on ramipril and 149 (8.4 %) on placebo developed overt nephropathy, which corresponds to a RRR 24 %; 95 % CI [3-40], p = 0.027.

The REIN study, a multicenter randomized, double-blind parallel group, placebo-controlled study aimed at assessing the effect of treatment with ramipril on the rate of decline of glomerular function rate (GFR) in 352 normotensive or hypertensive patients (18-70 years old) suffering from mild (i.e. mean urinary protein excretion > 1 and < 3 g/24 h) or severe proteinuria (≥ 3 g/24 h) due to chronic non-diabetic nephropathy. Both subpopulations were prospectively stratified.

The main analysis of patients with the most severe proteinuria (stratum prematurely disrupted due to benefit in ramipril group) showed that the mean rate of GFR decline per month was lower with ramipril than with placebo; -0.54 (0.66) vs. -0.88 (1.03) ml/min/month, p = 0.038. The intergroup difference was thus 0.34 [0.03-0.65] per month, and around 4 ml/min/year; 23.1 % of the patients in the ramipril group reached the combined secondary endpoint of doubling of baseline serum creatinine concentration and/or end-stage renal disease (ESRD) (need for dialysis or renal transplantation) vs. 45.5 % in the placebo group (p = 0.02).

Secondary prevention after acute myocardial infarction:

The AIRE study included more than 2,000 patients with transient/persistent clinical signs of heart failure after documented myocardial infarction. The ramipril treatment was started 3 to 10 days after the acute myocardial infarction. The study showed that after an average follow-up time of 15 months the mortality in ramipril-treated patients was 16.9 % and in the placebo treated patients was 22.6 %. This means an absolute mortality reduction of 5.7 % and a relative risk reduction of 27 % (95 % CI [11-40 %]).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Acetylsalicylic acid
Acetylsalicylic acid is metabolized into its main active metabolite, salicylic acid before, during and after absorption. The metabolites are predominantly eliminated by the kidneys. In addition to salicylic acid, the main metabolites of acetylsalicylic acid are the glycine conjugate of salicylic acid (salicyluric acid), the glucuronide ether and ester of salicylic acid (salicyl phenolic and salicyl acyl glucuronide), as well as gentisic acid formed by oxidation of salicylic acid, and its glycine conjugate.

The absorption of acetylsalicylic acid after oral administration is fast and complete, depending on the galenic formulation. Hydrolysis of the acetyl residue from acetylsalicylic acid in fact takes place to some extent during passage through the gastrointestinal mucosa. Maximal plasma levels are reached after 10 - 20 minutes (acetylsalicylic acid) or after 0.3 - 2 hours, respectively (total salicylate).

After single dose administration, food has no effect on total drug exposure but delays time to maximum concentration (tmax) of acetylsalicylic acid by 1.1 hours and reduces Cmax by approximately 42%.

The elimination kinetics of salicylic acid largely depend on the dosage, since the capacity to metabolize salicylic acid is limited (elimination half-life fluctuates between 2 and 30 hours).

The elimination half-life of acetylsalicylic acid is only a few minutes; the elimination half-life of salicylic acid is 2 hours after administration of a 0.5 g dose of acetylsalicylic acid, 4 hours after administration of 1 g, and increases to 20 h after a single dose of 5 g.

Plasma protein binding in human subjects is concentration-dependent; values ranging from 49 % to more than 70 % (acetylsalicylic acid) and 66 % to 98 % (salicylic acid, respectively) have been reported. Salicylic acid is measurable in liquor and synovial fluid after administration of acetylsalicylic acid. Salicylic acid passes through the placenta and is transferred into breast milk.

Atorvastatin
Absorption:
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (Cmax) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.
After single dose administration, food has no effect on total drug exposure but delays time to maximum concentration (tmax) of atorvastatin by 1.7 hours and reduces Cmax by approximately 47%.

Distribution:

Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins.

Biotransformation:
Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination:
Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin.

Special populations:
Elderly: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

Paediatric: In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage ≥ 2 (N=24) paediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolemia and baseline LDL-C ≥ 4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film-coated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for Cmax and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.

Hepatic insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in Cmax and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

SLOC1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

Ramipril
Absorption:
Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract: peak plasma concentrations of ramipril are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56% and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite ramiprilat after oral administration of 2.5 and 5 mg ramipril is 45 %.

After single dose administration, food decreases mean AUC by 26% and delays time to maximum concentration (tmax) of ramipril by 1.2 hours and reduces Cmax by approximately 69%. The effect of food on rampiril AUC and Cmax are not considered clinically relevant.

Peak plasma concentrations of ramiprilat, the sole active metabolite of ramipril are reached 2-4 hours after ramipril intake. Steady state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

Distribution:
The serum protein binding of ramipril is about 73 % and that of ramiprilat about 56 %.

Metabolism:
Ramipril is almost completely metabolised to ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat.

Elimination:
Excretion of the metabolites is primarily renal.

Plasma concentrations of ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations.

After multiple once-daily doses of ramipril, the effective half-life of ramiprilat concentrations was 13-17 hours for the 5-10 mg doses and longer for the lower 1.25-2.5 mg doses. This difference is related to the saturable capacity of the enzyme to bind ramiprilat.

A single oral dose of ramipril produced an undetectable level of ramipril and its metabolite in breast milk. However the effect of multiple doses is not known.

Patients with renal impairment (see section 4.2): Renal excretion of ramiprilat is reduced in patients with impaired renal function, and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in subjects with normal renal function.

Patients with hepatic impairment (see section 4.2): In patients with impaired liver function, the metabolism of ramipril to ramiprilat was delayed, due to diminished activity of hepatic esterases, and plasma ramipril levels in these patients were increased. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function.

5.3 Preclinical safety data

No nonclinical safety studies have been conducted with the active substances in combination.

Acetylsalicylic acid
The preclinical safety profile of acetylsalicylic acid is well documented. In animal studies, salicylates have not been shown to cause any organ damage except for kidney damage at high doses.

Acetylsalicylic acid has been extensively examined in vitro and in vivo for possible mutagenic effects. In their entirety, the results do not indicate any suspicion of any mutagenic effects. The same is true for studies investigating the possibility of any carcinogenic effects.

In animal studies, teratogenic effects of salicylates have been reported for several species. Impaired implantation, embryo- and fetotoxic effects and impaired learning ability in prenatally exposed offspring have been described.

Atorvastatin
Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females.

There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental

transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

Ramipril
Oral administration of ramipril has been found to be devoid of acute toxicity in rodents and dogs. Studies involving chronic oral administration have been conducted in rats, dogs and monkeys. Indications of plasma electrolyte shifts and changes in blood picture have been found in the 3 species.

As an expression of the pharmacodynamic activity of ramipril, pronounced enlargement of the juxtaglomerular apparatus has been noted in the dog and monkey from daily doses of 250 mg/kg/d. Rats, dogs and monkeys tolerated daily doses of 2, 2.5 and 8 mg/kg/d respectively without harmful effects. It was observed irreversible damage in kidney of young rats administered with a single dose of ramipril.

Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties. Fertility was not impaired either in male or in female rats. The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight or higher.

Extensive mutagenicity testing using several test systems has yielded no indication that ramipril possesses mutagenic or genotoxic properties. Long-term carcinogenicity studies in mice and rats provided no evidence for a carcinogenic effect.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Microcrystalline cellulose
Talc
Sodium starch glycolate (type A)
Lactose monohydrate
Pregelatinised starch (maize)
Calcium carbonate
Hydroxypropylcellulose
Polysorbate 80
Crospovidone (type A)
Silica colloidal anhydrous
Magnesium stearate
Hypromellose
Sodium stearyl fumarate

Film-coating
Polyvinyl alcohol
Titanium dioxide (E171)
Talc
Lecithin (soya)
Xanthan gum
Hypromellose
Triethyl citrate
Povidone
Yellow iron oxide (E172)
Red iron oxide (E172)

Capsule shell
Gelatin
Titanium dioxide
Yellow iron oxide (E172)
Red iron oxide (E172)
Shellac
Black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Blister (OPA/Aluminium/PVC//Aluminium):7, 14, 28, 56, 84 or 98 hard capsules in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ferrer Internacional, S.A
Gran Via Carlos III, 94,
08028-Barcelona
Spain

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