Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Innozide 20 mg/12.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg enalapril maleate and 12.5 mg hydrochlorothiazide.

Excipients: Contains 141.00 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Round, fluted, yellow tablets with MSD 718 on one side and scored on the other

The scoreline allows breaking for ease of swallowing only.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of hypertension where a further reduction in blood pressure is required following the use of 20 mg enalapril.

Management of hypertension in patients who have been stabilised on the individual components.

4.2 Posology and method of administration

For oral administration.

The dosage of 'Innozide' should be determined primarily by the experience with the enalapril maleate component.

The maximum recommended daily dose is two tablets.

Adults
Essential hypertension
The dosage is one tablet, taken once daily. If necessary, the dosage may be increased by a small increment of either constituent.

Dosage in renal insufficiency
Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. moderate or severe renal insufficiency).

In patients with creatinine clearance of >30 and <80 ml/min, 'Innozide' should be used only after titration of the individual components.
Use in the elderly
In clinical studies the efficacy and tolerability of enalapril maleate and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients.

Paediatric use
Safety and effectiveness in children have not been established.

Prior diuretic therapy

Symptomatic hypotension may occur following the initial dose of Innozide; this is more likely in patients who are volume- or salt-depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Innozide. *(please refer to section 4.4)*

4.3 Contraindications

- Hypersensitivity to enalapril maleate, hydrochlorothiazide, or any of the excipients of 'Innozide'.
- Severe renal impairment (creatinine clearance ≤ 30 mL/min).
- Anuria.

- History of angioneurotic oedema associated with previous ACE-inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Hypersensitivity to sulfonamide-derived drugs.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe hepatic impairment.
- The concomitant use of 'Innozide' 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).
- Concomitant use with sacubitril/valsartan therapy. Innozide must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

'Innozide' is contraindicated in patients with anuria or aortic stenosis, hypertrophic cardiomyopathy or hyperkalaemia.

'Innozide' is contraindicated in patients with stenosis of the renal arteries.

'Innozide' is contraindicated in acute hypertension.

The use of 'Innozide' is not indicated in patients with congestive heart failure, due to lack of clinical data with this fixed combination. This fact has no bearing on the use in heart failure of the individual components which are effective treatment either alone or concomitantly, when titrated appropriately.

4.4 Special warnings and precautions for use

Enalapril Maleate-Hydrochlorothiazide

Hypotension and Electrolyte Fluid Imbalance

Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving 'Innozide', symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g., by diuretic therapy, dietary salt restriction, diarrhoea or vomiting (see sections 4.5 and 4.8).Diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with 'Innozide'. Regular determination of serum electrolytes should be performed at appropriate intervals in such patients. Special attention should be paid to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. In hypertensive patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

Renal Function Impairment

'Innozide' should not be administered to patients with renal insufficiency (creatinine clearance < 80 mL/min. and > 30 mL/min.) until titration of enalapril has shown the need for the dose present in this formulation (see section 4.2).

Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when enalapril has been given concurrently with a diuretic (see Special warnings and precautions for use, Enalapril Maleate,

Renal Function Impairment; Hydrochlorothiazide, Renal Function Impairment in section 4.4). If this occurs, therapy with 'Innozide' should be discontinued. This situation should raise the possibility of underlying renal artery stenosis (see Special warnings and precautions for use, Enalapril Maleate, Renovascular Hypertension in section 4.4).

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.

Hyperkalaemia
The combination of enalapril and a low-dose diuretic cannot exclude the possibility of a hyperkalaemia to occur (see Special warnings and precautions for use, Enalapril Maleate, Hyperkalaemia in section 4.4).

Lithium
The combination of lithium with enalapril and diuretic agents is generally not recommended (see section 4.5).

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

Enalapril Maleate
Aortic Stenosis/Hypertrophic Cardiomyopathy
As with all vasodilators, ACE inhibitors should be given with caution in patients with left ventricular valvular outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal Function Impairment
Renal failure has been reported in association with enalapril and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with therapy with enalapril is usually reversible (see section 4.2 and Special warnings and precautions for use, Enalapril Maleate-Hydrochlorothiazide, Renal Function Impairment; Hydrochlorothiazide, Renal Function Impairment in section 4.4).

Renovascular Hypertension
There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision and monitoring of renal function.

Kidney Transplantation
There is no experience regarding the administration of enalapril in patients with a recent kidney transplantation. Treatment with enalapril is therefore not recommended.

Haemodialysis Patients
The use of enalapril is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE

inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see Special warnings and precautions for use, Hydrochlorothiazide, Hepatic Disease in section 4.4).

Neutropenia/Agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hyperkalaemia
ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect 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, hyperkalaemia 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).

Diabetic Patients
Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see Special warnings and precautions for use, Hydrochlorothiazide, Metabolic and Endocrine Effects in section 4.4 and section 4.5).

Hypersensitivity/Angioneurotic Oedema
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril maleate. This may occur at any time during treatment. In such cases, 'Innozide' should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy which may include subcutaneous epinephrine solution 1:1,000 (0.3 mL to 0.5 mL) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. However, in general it appears that Blacks have an increased risk for angioedema.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

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 'Innozide'. Treatment with 'Innozide' 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.

Anaphylactoid Reactions during Hymenoptera Desensitisation
Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation.

Anaphylactoid Reactions during LDL-Apheresis
Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulphate have experienced life-threatening anaphylactic reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

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.

Surgery/Anaesthesia
Enalapril blocks angiotensin II formation and therefore impairs the ability of patients undergoing major surgery or anaesthesia with agents that produce hypotension to compensate via the renin-angiotensin system. Hypotension which occurs due to this mechanism can be corrected by volume expansion (see section 4.5).

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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 (see sections 4.3 and 4.6).

Ethnic Differences
As with other angiotensin converting enzyme inhibitors, enalapril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Hydrochlorothiazide
Renal function Impairment
Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 mL/min. or below (i.e., moderate or severe renal insufficiency) (see section 4.2 and Special warnings and precautions for use, Enalapril Maleate-Hydrochlorothiazide, Renal Function Impairment; Enalapril Maleate, Renal Function Impairment in section 4.4).

Hepatic Disease
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see Special warnings and precautions for use, Enalapril Maleate, Hepatic Failure in section 4.4).

Metabolic and Endocrine Effects
Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see Special warnings and precautions for use, Enalapril Maleate, Diabetic Patients in section 4.4).

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy; however, at the 12.5 mg dose of hydrochlorothiazide, minimal or no effect was reported. In addition, in clinical studies with 6 mg of hydrochlorothiazide no clinically significant effect on glucose, cholesterol, triglycerides, sodium, magnesium or potassium was reported.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. This effect on hyperuricaemia appears to be dose-related and is not clinically significant at the 6 mg dose of hydrochlorothiazide. In addition, enalapril may increase urinary uric acid and thus attenuate the hyperuricaemic effect of hydrochlorothiazide.

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides (including hydrochlorothiazide) can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are xerostomia, thirst, weakness, lethargy, somnolence, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Although hypokalaemia may develop during use of thiazide diuretics, concurrent therapy with enalapril may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients with inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).

Hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does usually not require treatment.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of latent hyperparathyroidism. Thiazides should be discontinued before testing parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Eye disorders
Choroidal effusion, acute myopia and secondary angle-closure glaucoma:
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Acute Respiratory Toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Innozide should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Anti-doping test
Hydrochlorothiazide contained in this medicinal product can produce a positive analytic result in an anti-doping test.

Hypersensitivity
In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interactions

Enalapril Maleate-Hydrochlorothiazide

Antacids*:* induce decreased bioavailability of ACE inhibitors.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Clinical trial data have 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).

Other Antihypertensive Agents
Concomitant use of these agents may increase the hypotensive effects of enalapril and hydrochlorothiazide. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors.

Use of 'Innozide' with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non-Steroidal Anti-Inflammatory Drugs
Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor or may decrease the diuretic, natriuretic and antihypertensive effects of diuretics.

NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or ACE inhibitors exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function (such as the elderly or patients who are volume-depleted, including those on diuretic therapy).

Enalapril Maleate

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

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).

Ganglionic-blocking agents or adrenergic-blocking agents, combined with enalapril, should only be administered under careful observation of the patient.

Potassium-sparing Diuretics, Potassium Supplements, or other drugs that may increase serum potassium
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with 'Innozide'. 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 'Innozide' 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 'Innozide' 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.

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

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

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril (see sections 4.2 and 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic or by increasing volume or salt intake.

Tricyclic Antidepressants/Antipsychotics/Anaesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors (see section 4.5).

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (see sections 4.4 and 4.8).
Alcohol
Alcohol enhances the hypotensive effect of ACE inhibitors (see section 4.5).

Acetyl Salicylic Acid, Thrombolytics and b-blockers
Enalapril can be safely administered concomitantly with acetyl salicylic acid (at cardiologic doses), thrombolytics and b-blockers.

Gold
Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including enalapril.

Hydrochlorothiazide

Nondepolarizing Muscle Relaxants
Thiazides may increase the responsiveness to tubocurarine.

Alcohol, Barbiturates, or Opioid Analgesics

Potentiation of orthostatic hypotension may occur (see section 4.5).

Antidiabetic Drugs (Oral Agents and Insulin)

Dosage adjustment of the antidiabetic drug may be required (see sections 4.4 and 4.8).

Cholestyramine and Colestipol Resins
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Increasing the QT Interval (e.g., quinidine, procainamide, amiodarone, sotalol)
Increased risk of torsades de pointes.

Digitalis Glycosides
Hypokalaemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalaemia.

Kaliuretic Diuretics (e.g., Furosemide), Carbenoxolone, or Laxative Abuse
Hydrochlorothiazide may increase the loss of potassium and/or magnesium.

Pressor Amines (e.g., Noradrenaline)
The effect of pressor amines may be decreased (see section 4.5).

Cytostatics (e.g., Cyclophosphamide, Methotrexate)
Thiazides may reduce the renal excretion of cytotoxic drugs and potentiate their myelosuppressive effects.

4.6 Fertility, pregnancy and lactation

Pregnancy
ACE-inhibitors*:*
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated 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.
Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (see section 5.3).
Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development. Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide:
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation
Enalapril:
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of 'Innozide' in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of 'Innozide' in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

Hydrochlorothiazide:
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of 'Innozide' during breast-feeding is not recommended. If 'Innozide' is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur. (See section 4.8)

4.8 Undesirable effects

Side effects reported with 'Innozide', enalapril alone or hydrochlorothiazide alone either during clinical studies or after the drug was marketed include:
[Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).]

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Not known: Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)

Blood and Lymphatic System Disorders:
uncommon: anaemia (including aplastic and haemolytic)
rare: neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, leukopenia, pancytopenia, lymphadenopathy, autoimmune diseases

Endocrine disorders:
not known: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and Nutrition Disorders:
common: hypokalaemia, increase of cholesterol, increase of triglycerides, hyperuricaemia
uncommon: hypoglycaemia (see section 4.4), hypomagnesaemia, gout**
rare: increase in blood glucose
very rare: hypercalcaemia (see section 4.4)

Nervous System and Psychiatric Disorders:
common: headache, depression, syncope, taste alteration
uncommon: confusion, somnolence, insomnia, nervousness, paresthesia, vertigo, decreased libido**
rare: dream abnormality, sleep disorders, paresis (due to hypokalaemia)

Eye Disorders:
very common: blurred vision
Not known: choroidal effusion

Ear and Labyrinth Disorders:
uncommon: tinnitus

Cardiac and Vascular Disorders:
very common: dizziness
common: hypotension, orthostatic hypotension, rhythm disturbances, angina pectoris, tachycardia
uncommon: flushing, palpitations, myocardial infarction or cerebrovascular accident*, possibly secondary to excessive hypotension in high risk patients (see section 4.4)
rare: Raynaud's phenomenon

Respiratory, Thoracic and Mediastinal Disorders:
very common: cough
common: dyspnoea
uncommon: rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma
rare: pulmonary infiltrates, respiratory disorders (including pneumonitis and pulmonary oedema), rhinitis, allergic alveolitis/eosinophilic pneumonia
very rare: Acute respiratory distress syndrome (ARDS) (see section 4.4)

Gastrointestinal Disorders:
very common: nausea
common: diarrhoea, abdominal pain
uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer, flatulence**

rare: stomatitis/aphthous ulcerations, glossitis
very rare:intestinal angioedema

Hepatobiliary Disorders:
rare: hepatic failure, hepatic necrosis (may be fatal), hepatitis – either hepatocellular or cholestatic, jaundice, cholecystitis (in particular in patients with pre-existing cholelithiasis)

Skin and Subcutaneous Tissue Disorders:
common: rash (exanthema)
hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see section 4.4).
uncommon: diaphoresis, pruritus, urticaria, alopecia
rare: erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, purpura, cutaneous lupus erythematosus, erythroderma, pemphigus

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Musculoskeletal, Connective Tissue and Bone Disorders:
common: muscle cramps***
uncommon: arthralgia**

Renal and Urinary Disorders:
uncommon: renal dysfunction, renal failure, proteinuria
rare: oliguria, interstitial nephritis

Reproductive System and Breast Disorders:
uncommon: impotence
rare: gynecomastia

General Disorders and Administration Site Conditions:
very common: asthenia
common: chest pain, fatigue
uncommon: malaise, fever

Investigations:
common: hyperkalemia, increases in serum creatinine
uncommon: increases in blood urea, hyponatremia
rare: elevations of liver enzymes, elevations of serum bilirubin

* Incidence rates were comparable to those in the placebo and active control groups in the clinical trials.
** only seen with doses of hydrochlorothiazide 12.5 mg and 25 mg
*** The frequency of muscle cramps as common pertains to doses of hydrochlorothiazide 12.5 mg and 25 mg, whereas, the frequency of the event is uncommon as it pertains to 6 mg doses of hydrochlorothiazide.

Description of selected adverse reactions
Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed (see sections 4.4 and 5.1).

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 the HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

No specific information is available on the treatment of overdosage with 'Innozide'. Treatment is symptomatic and supportive. Therapy with 'Innozide' should be discontinued and the patient observed closely. Suggested measures include induction of

emesis, administration of activated charcoal, and administration of a laxative if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Enalapril Maleate
The most prominent features of overdosage reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdosage of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Serum enalaprilat levels 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril maleate, respectively.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating enalapril maleate (e.g., emesis, gastric lavage, administration of absorbents, and sodium sulphate). Enalaprilat may be removed from the general circulation by hemodialysis. (See section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.
Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: enalapril and diuretics, ATC code C09 BA02.

Enalapril maleate
Angiotensin-converting enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE, which leads to increased plasma renin activity (due to removal of negative feedback on renin release), and decreased aldosterone secretion.

ACE is identical to kininase II. Thus enalapril may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of enalapril remains to be elucidated. While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, which plays a major role in the regulation of blood pressure, enalapril is antihypertensive even in patients with low-renin hypertension.

Enalapril maleate - hydrochlorothiazide
Hydrochlorothiazide is a diuretic and antihypertensive agent which increases plasma renin activity. Although enalapril alone is antihypertensive even in patients with low-renin hypertension, concomitant administration of hydrochlorothiazide in these patients leads to greater reduction of blood pressure.

Dual Blockade
Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), 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.

Non-melanoma skin cancer
Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95%CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95%CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Enalapril maleate - hydrochlorothiazide
Concomitant multiple doses of enalapril maleate and hydrochlorothiazide have little or no effect on the bioavailability of these drugs. The combination tablet is bioequivalent to concomitant administration of the separate entities.

Absorption
Oral enalapril maleate is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril maleate is approximately 60%.

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin-converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril maleate. Excretion of enalapril is primarily renal.

The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to ACE.

In subjects with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of administration of enalapril maleate. The effective half-life for accumulation of enalaprilat following multiple doses of oral maleate is 11 hours. The absorption of oral enalapril maleate is not influenced by the presence of food in the gastro-intestinal tract. The extent of absorption and hydrolysis of enalapril are similar for the various doses in the recommended therapeutic range.

Distribution
Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Enalapril crosses the placental barrier. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Biotransformation
Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney.

Elimination
Excretion of enalapril is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril.

The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril maleate is 11 hours. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Characteristics in patients
Enalaprilat may be removed from the general circulation by haemodialysis.

Lactation:
After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7 micogram/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7 microgram/L (range 1.2 to 2.3µg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breastfed infant would be about 0.16% of the maternal weight-adjusted dosage. A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 microgram/L 4 hours after a dose and peak enalaprilat levels of 0.75 microgram/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44 microgram/L and 0.63 microgram/L of milk respectively. Enalaprilat milk levels were undetectable (<0.2 microgram/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined.

5.3 Preclinical safety data

No relevant information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate
Lactose monohydrate
Maize starch
Yellow iron oxide (E172)
Pre-gelatinised starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Blister: Do not store above 25°C. Store in the original package.
Bottle:Do not store above 25°C. Keep the container tightly closed.

6.5 Nature and contents of container

Blister packs consisting of a nylon/aluminium/PVC base and aluminium/PVC lid containing 2, 4, 6 or 28 tablets.

Amber glass bottles and HDPE bottles containing 2, 4 or 6 tablets closed by either metal screw caps or clic-loc caps. Each bottle contains a desiccant.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Organon Pharma (Ireland) Limited
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D01 V4A3
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8 MARKETING AUTHORISATION NUMBER

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