SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tanatril 20 mg tablets
Imidapril 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg imidapril hydrochloride

Excipient with known effect:
Each tablet contains 90 mg lactose monohydrate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets

Off-white oblong biconvex tablets with a plane edge, scored on both sides.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicine is indicated for the treatment of essential hypertension in adults.
(See sections 4.3, 4.4, 4.5 and 5.1).

4.2 Posology and method of administration

Posology- *Adults*

Treatment should be initiated with a daily dose of 5 mg.

If optimum control of blood pressure has not been achieved after at least 3 weeks of treatment, the daily dose should be increased to 10 mg, the dose that has been determined to be most effective.

However, for a small number of patients it may be necessary to increase the daily dose to 20 mg (the recommended maximum dose) or preferably, to consider combination therapy with a diuretic.
It has not been assessed whether hypertensive patients would benefit from a combination of imidapril with other antihypertensive therapies.

- *Elderly* (65 years or older)

The initial dose is 2.5 mg once a day. The dose should be titrated according to the blood pressure response. The recommended maximum dose is 10 mg once a day.

- *Renal impairment*

Imidapril and its pharmacologically active metabolite, imidaprilat, are predominantly excreted via the kidney.
Renal function should be evaluated before commencing therapy with imidapril in patients suspected of renal impairment.

- Creatinine clearance between 30 ml/min and 80 ml/min (see section 4.4):

Reduced doses are required for these patients and therefore it is recommended that treatment be initiated with 2.5 mg.
- Creatinine clearance between 10 ml/min and 29 ml/min (see section 4.4):

Because of limited experience which has shown an increase in the AUC of imidaprilat (see section 5.2), imidapril should not be administered to these patients.

- Creatinine clearance below 10 ml/min (renal failure with or without haemodialysis):

The drug is contraindicated in these patients (see section 4.3).

- *Hepatic impairment*

The recommended starting dose in patients with hepatic impairment is 2.5 mg once a day. Imidapril should be used with caution in patients with hepatic impairment.

- *Patients at increased risk for first dose hypotension*

First dose hypotension may occur in high-risk patients (see section 4.4). Initiation of therapy requires, if possible, correction in salt and/or body fluids deficiencies, and discontinuation of an existing diuretic therapy for two to three days before ACE inhibition. If this is not

possible, initial dose should be imidapril 2.5 mg. In hypertensive patients with concomitant cardiac failure symptomatic hypotension has been observed after treatment with ACE inhibitors.
In these patients the initial dose should be 2.5 mg imidapril once a day under close medical supervision. Patients at high risk for severe acute first dose hypotension should be monitored medically, preferably in hospital, for up to 6-8 hours after administration of the first dose of imidapril and whenever the dose of imidapril or a concomitant diuretic is increased. The initial dose should be 2.5 mg. This also applies to patients with angina pectoris and cerebrovascular disease. These patients are at increased risk to experience myocardial infarction or cerebrovascular accident following excessive hypotension.

- *Paediatric population*
The safety and efficacy of this medicine in children have not been established. No data are available.

Method of administration

Oral use.

It is recommended that the tablets be taken at about the same time of day about 15 minutes before meals, conditions under which efficacy has been demonstrated.

4.3 Contraindications

- Hypersensitivity to the active substance or to any other ACE inhibitor or to any of the excipients listed in section 6.1.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary/idiopathic angioedema.
- Second and third trimesters of pregnancy (see section 4.6).
- Renal failure with or without haemodialysis (creatinine clearance < 10 ml/min). - The concomitant use of this medicine with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan.

4.4 Special warnings and precautions for use

- Hypotension

Imidapril like other ACE inhibitors may cause a profound fall in blood pressure especially after the first dose. Symptomatic hypotension is

rare in uncomplicated hypertensive patients. It is more likely to occur in patients who have been volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting.
It has been reported mainly in patients with severe cardiac failure with or without associated renal insufficiency. This is more likely in patients on high doses of loop diuretics, or those with hyponatraemia or functional renal impairment. In these patients treatment should be started under very close medical supervision, preferably in a hospital, with imidapril 2.5 mg and careful dose titration. If possible, diuretic treatment should be discontinued temporarily. Such considerations apply also to patients with ischaemic heart- or cerebrovascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident.
If the patient develops hypotension, they should be placed in a supine position. Volume repletion with intravenous normal saline may be required. The appearance of hypotension after the initial dose does not preclude subsequent careful dose titration with imidapril after effective management.

- Aortic or mitral valve stenosis/Hypertrophic cardiomyopathy

As with others ACE inhibitors, imidapril should be used with caution in patients with an obstruction in the outflow tract of the left ventricle.

- Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported rarely in patients receiving ACE inhibitors, including imidapril. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Imidapril 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 imidapril is used in such patients, it is advised that white blood cell count and differential counts should be performed prior to therapy, every 2 weeks during the first 3 months of imidapril therapy, and periodically thereafter. During treatment all patients should be instructed to report any sign of infection (e.g. sore throat, fever) when a differential white blood cell count should be performed.
Imidapril and other concomitant medication should be withdrawn if neutropenia (neutrophils less than $1000/mm^3$) is detected or suspected. In most patients neutrophil counts rapidly return to normal upon discontinuing imidapril.

- Patients with renal insufficiency

Changes in renal function may be anticipated in susceptible individuals due to the inhibition of the renin-angiotensin-aldosterone system. Therefore imidapril like other ACE inhibitors should be used with caution in patients with renal insufficiency. Reduced doses are required for patients with creatinine clearance between 30ml/min to 80ml/min (see section 4.2).
Imidapril should not be administered in patients with creatinine clearance less than 30 ml/min because of limited experience in these patients (see sections 4.2 and 5.2).
Close monitoring of renal function during therapy should be performed as deemed appropriate.
Renal failure has been reported in association with ACE inhibitors, mainly in patients with severe cardiac failure or underlying renal disease, including renal artery stenosis. Some patients, with no apparent pre-existing renal disease, may develop increases in blood urea and creatinine concentrations when a diuretic is given concomitantly. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required. It is recommended that the renal function be monitored during the first weeks of therapy.

- Patients with 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 with low doses, careful titration, and monitoring of renal function.

- Patients on haemodialysis

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes 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.

- Kidney transplantation

There is no experience regarding the administration of imidapril in patients with a recent kidney transplantation

- Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including imidapril. This may occur at any time during the treatment. In such cases, imidapril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where

swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. If the tongue, glottis or larynx are involved and airway obstruction is likely, appropriate therapy should be administered which may include an injection of epinephrine 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.
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).
Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors (see section 4.8).

- Patients on LDL lipid apheresis

Patients treated with an ACE inhibitor undergoing LDL lipid apheresis with dextrane sulfate may experience anaphylactoid reactions similar to those seen in patients under-going haemodialysis with high-flux membranes (see above). For these patients, it is recommended that an agent from a different class of antihypertensive drugs is used.

- Anaphylactoid reactions during desensitisation:

Sustained life-threatening anaphylactoid reactions have been rarely reported for patients undergoing desensitising treatment with hymenoptera venom while receiving another ACE inhibitor. In the same patients, these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon inadvertent rechallenge. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.

- Patients with hepatic insufficiency

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.

- Cough

During treatment with imidapril a dry and non-productive cough may occur which disappears after discontinuation.

- Surgery/Anaesthesia

No data are available on the use of imidapril under conditions of surgery or anaesthesia. However, imidapril, like other ACE inhibitors, may cause hypotension or even hypotensive shock in patients undergoing major surgery or during anaesthesia through the enhancement of other hypotensive potentials. If it is not possible to withhold imidapril volume management should be handled with care.

- Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including imidapril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of imidapril and any of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

- Proteinuria

Proteinuria was rarely seen with imidapril. It may occur particularly in patients with existing renal function impairment but was also seen on relatively high doses of other ACE inhibitors.

- Diabetic patients:

The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor.

- Elderly

Some elderly, especially very old patients, may be more responsive to imidapril than younger patients. For elderly patients aged 65 years or older, the initial daily dose should be imidapril 2.5 mg. Evaluation of the renal function at the beginning of the treatment is recommended.

- Paediatric population

Imidapril should not be administered to children until safety and efficacy have been established.

- Ethnic differences

ACE-inhibitors are 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.

- Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

Potassium sparing diuretics alone or in combination or potassium supplements:

Imidapril, like other ACE inhibitors, attenuates diuretic induced potassium loss. Potassium sparing diuretics, e.g. spironolactone, triamterene or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium(potentially lethal), especially in conjunction with renal impairment (additive hyperkalemic effects). ACE inhibitors must not be associated with hyperkalemic substances, except in hypokalaemia. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.

Non-potassium-sparing diuretics:

Risk of sudden hypotension and/or acute renal impairment on initiation of treatment with an ACE inhibitor in patients with pre-existing salt/volume depletion.
In arterial hypertension, when prior diuretic therapy can have caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE inhibitor, in which case a non-potassium-sparing diuretic can be thereafter reintroduced, or the ACE inhibitor must be initiated with a low dosage and progressively increase.
The renal function (creatinine levels) should be monitored during the first few weeks of ACE inhibitor therapy.

Lithium:

Increased lithium concentration, potentially to toxic levels (decreased renal lithium excretion).
Use of imidapril 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 (NSAIDs):

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (ie acetylsalicylic acid at anti-

inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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.

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of imidapril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosteronesystem (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).

Antidiabetic agents (insulin, hypoglycaemic sulphonamides):

The use of ACE inhibitors may increase the hypoglycaemic effect in diabetic patients treated with insulin or hypoglycaemia sulphonamides. Hypoglycaemic episodes appear to be rare (improved glucose tolerance which could lead to reduced need for insulin).
Self-monitoring of glycaemia should be reinforced.

Acetylsalicylic acid, thrombolytics, beta-blockers:

Imidapril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, and beta-blockers.

Tricyclic antidepressants, neuroleptics:

Increased antihypertensive effect and risk of orthostatic hypotension (additive effect).

Rifampicin:

The administration of rifampicin reduced the plasma level of imidaprilat, the active metabolite of imidapril. The antihypertensive effect of imidapril might therefore be reduced.

Antacids:

May induce decreased bioavailability of imidapril.

Sympathomimetics:

May reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored to confirm that the desired effect is obtained.

NEP inhibitors

As the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema, sacubitril/valsartan must not be started until 36 hours after taking the last dose of imidapril therapy. Imidapril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan. Concomitant use of other NEP inhibitors (e.g. racecadotril) and imidapril may also increase the risk of angioedema. A careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors in patients on imidapril.

mTOR inhibitors & vildagliptin

Concomitant use of ACE inhibitors with 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). Caution should be used when starting mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in patients on imidapril.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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 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.
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.).
Should exposure to ACE inhibitor 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).

Breast-feeding

Because no information is available regarding the use of imidapril during breastfeeding, imidapril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

This medicine has minor influence on the ability to drive and use machines.
It should be taken into account that occasionally dizziness or weariness may occur.
No studies on the effects on the ability to drive have been performed.

4.8 Undesirable effects

a. Summary of the safety profile

The incidence of adverse events in hypertensive patients on imidapril was 34% with 36% for placebo. Cough, dizziness, fatigue/somnolence,

dyspepsia and vomiting occurred more frequently in the imidapril group.
The undesirable effects that have been observed and reported during treatment with imidapril in pre-approval studies are presented in the table below with the following frequencies: Very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

b. Tabulated list of adverse reactions

Pyschiatric disorders	
Rare	Insomnia
Nervous system disorders	
Uncommon	Headache, dizziness
Rare	Dysgeusia, dizziness postural
Ear and labyrinth disorders	
Rare	Tinnitus
Cardiac disorders	
Rare	Palpitations
Vascular disorders	
Uncommon	Hypotension*
Respiratory, thoracic and mediastinal disorders	
Common	Cough*
Not known	Oropharyngeal discomfort
Gastrointestinal disorders	
Rare	Nausea*, vomiting*, diarrhoea*, abdominal pain*
Skin and subcutaneous tissue disorders	
Uncommon	Rash, pruritus
Renal and urinary disorders	
Rare	Renal impairment, proteinuria
General disorders and administration site conditions	
Rare	Oedema, fatigue
Investigations	

Rare	Alanine aminotransferase increased, blood creatinine increased*, blood urea increased, aspartate aminotransferase increased, red blood cell count decreased, blood lactate dehydrogenase increased, white blood cell count decreased, haemoglobin decreased

* See also below section c.

c. Description of selected adverse reactions and class-related adverse reactions

The following adverse reactions have been observed in association with imidapril or with other ACE inhibitors. Please also refer to section 4.4 to avoid these reactions:

Blood and lymphatic system disorders:

Neutropenia/agranulocytosis, thrombocytopenia, pancytopenia and anaemia have been reported rarely in patients receiving ACE inhibitors (see section 4.4). In patients with a congenital deficiency concerning G-6-PDH individual cases of haemolytic anaemia have been reported under other ACE inhibitors.

Nervous system disorders:

Dizziness, weariness, somnolence and fatigue have been reported. Rarely depression, sleep disorders, paresthesias, impotence, disorder of balance, confusion, tinnitus, blurred vision, headache and taste disturbance may occur with ACE inhibitors.

Cardiac disorders:

Severe hypotension may occur after initiation of therapy or increase of dose in certain risk groups. Symptoms like feeling of weakness, impaired vision, rarely with disturbance of consciousness (syncope) can occur in association with hypotension. Individual cases of tachycardia, palpitations, arrhythmias, angina pectoris, myocardial infarction, transient ischemic attacks and cerebral haemorrhage have been reported for ACE inhibitors in association with hypotension.

Respiratory, thoracic and mediastinal disorders:

ACE inhibitors have been documented to induce cough in a substantial number of patients. Rarely dyspnoea, sinusitis, rhinitis, glossitis, bronchitis, bronchiospasm and angioedema involving the upper airways, and very rarely allergic alveolits/eosinophilic pneumonia may occur with ACE inhibitors.

Gastrointestinal disorders:

Diarrhoea, nausea, vomiting, gastritis, abdominal pain, constipation, dry mouth, cholestatic icterus, hepatitis, pancreatitis and ileus may occur with ACE-inhibitors.

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. Symptoms are abdominal pain with or without nausea or vomiting.

Hepatobiliary disorders:

Patients receiving ACE inhibitors have developed jaundice or had marked elevations of hepatic enzymes.

Skin and subcutaneous tissue disorders:

Occasionally allergic and hypersensitivity reactions such as rash, pruritus, exanthema and urticaria can occur. ACE inhibitors have been associated with the onset of angioedema involving the face and oropharyngeal tissues.
Cases of erythema multiforme, Steven-Johnson syndrome, toxic epidermic necrolysis, psoriasis-like efflorescences, alopecia and dermatitis exfoliative, photosensitivity reaction were reported for ACE inhibitors. Cutaneous symptoms can be accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased ANA titers.

Renal and urinary disorders:

Renal insufficiency may rarely occur or be intensified. Acute renal failure has been reported for other ACE inhibitors.

Investigations:

Decreases in haemoglobin, haematocrit, platelets and white cell count as well as elevation of liver enzymes gamma-glutamyltransferase increased, blood alkaline phosphatase increased, serum bilirubin and creatine phosphokinase (CPK) have been reported in a few patients. Elevation of serum potassium may occur since imidapril leads to a decrease in aldosterone secretion. Increases in blood urea and plasma creatinine, reversible on discontinuation, may occur, especially in the presence of renal insufficiency.
Metabolism and nutrition disorders:

Hyperkalaemia

Ear and labyrinth disorders:

Vertigo

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 Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure.

Management
After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently. Therapeutic measures depend on the nature and severity of the symptoms. Measurements to prevent absorption and hasten elimination such as gastric lavage, administration of adsorbents and sodium sulfate within 30 minutes after intake should be applied if ingestion is recent.
If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly. Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered. Imidapril and imidaprilat may be removed from the circulation by haemodialysis. The use of highflux polyacrylonitrile membranes should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors.

ATC Code: C09A A16,

Mechanism of action

The hypotensive effect of imidapril in hypertension appears to result primarily from the suppression of the plasma renin-angiotensin-aldosterone system. Renin is an endogenous enzyme synthesised by the kidneys and released into the circulation where it converts angiotensinogen to angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme, a peptidylpeptidase, to angiotensin II. Angiotensin II is a potent vasoconstrictor responsible for arterial vasoconstriction and increased blood pressure, as well as for stimulation of the adrenal gland to secrete aldosterone. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to reduced aldosterone secretion.

Although the latter decrease is small, small increases in serum potassium concentrations may occur, along with sodium and fluid loss. The cessation of the negative feedback of angiotensin II on the renin secretion results in an increase of the plasma renin activity.

Another function of the converting enzyme is to degrade the potent vasodepressive kinin peptide bradykinin to inactive metabolites. Therefore inhibition of ACE results in an increased activity of circulating and local kallikrein-kinin system which may contribute to peripheral vasodilation by activating the prostaglandin system. Possibly this mechanism is involved in the hypotensive effect of ACE inhibitors and is responsible for certain side effects.

Pharmacodynamic effects

Administration of imidapril to hypertensive patients results in a reduction of sitting, supine and standing blood pressure to about the same extent with no compensatory in-crease of the heart rate. The peak hypotensive effect was observed 6-8 hours after drug intake.

Achievement of optimal blood pressure reduction may require several weeks of therapy in some patients. The antihypertensive effects are maintained during long term treatment. Abrupt withdrawal of therapy has not been associated with a rapid increase in blood pressure.

There is an increase in renal blood flow and glomerular filtration rate is usually unchanged.

Clinical efficacy and safety

ACE inhibitors are effective even in patients with low-renin hypertension. Although antihypertensive effects have been found in the races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to ACE inhibitor monotherapy than non-black patients. This difference disappears when a diuretic is added.

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

Absorption

Following oral administration imidapril is rapidly absorbed from the gastrointestinal tract and reaches its maximum plasma concentration within 2 hours. Plasma concentrations decline monophasically with a half-life of about 2 hours. Its absorption is about 70%. A fat-rich meal significantly reduces the absorption of imidapril.

Pharmacokinetic parameters after repeated oral administration of 10 mg of this product to healthy adults once daily for 7 days

Pharmacokinetic parameters	Imidapril		Imidaprilat	
	Initial administration	Repeated administration	Initial administration	Repeated administration
C_{max}（ng/mL）	28.9	27.1	7.8	20.3
T_{max}（h）	2.0	2.3	9.3	7.0
$t_{1/2}$（h）	1.7	1.6	14.8	7.6
AUC_{0-24h}（ng·h/mL）	113.3	113.6	107.8	246.6

Distribution

The protein binding of imidapril and imidaprilat is moderate (85% and 53%, respectively).

Biotransformation, Elimination

Imidapril is mainly hydrolysed to its pharmacologically active metabolite, imidaprilat. Maximum plasma concentrations of imidaprilat are reached within 7 hours. Plasma concentrations of imidaprilat decline biphasically with an initial halflife of about 7-9 hours and a terminal half-life of more than 24 hours. The absolute bioavailability of imidaprilat is about 42 %. After oral administration of the radiolabelled compound about 40% of total radioactivity is excreted in urine and about 50% in the faeces. Linearity

Oral absorption of imidapril after single oral dosing appeared linear from at least 10 mg up to 240 mg imidapril based on plasma and urinary excretion data.

Renal impairment

After multiple dosing steady state concentrations of imidaprilat are reached after the first administration of imidapril after about 5 days. Increased plasma levels and AUC values of imidapril and imidaprilat were observed in patients with renal impairment. There was a twofold increase in the AUC of imidaprilat in patients with a creatinine

clearance 30-80 ml/min and an almost tenfold increase in patients with a creatinine clearance 10-29 ml/min. The experience in all grades of renal impairment is very limited. There is no experience with the 20 mg dose in renal impairment.

Hepatic impairment

In patients with hepatic impairment the AUC of imidapril and imidaprilat were slightly higher than in normal subjects while the t_{max} for both was similar in the two groups. Furthermore the $t_{1/2}$ of imidaprilat, but not that of imidapril, was significantly increased in the hepatically impaired patients.

5.3 Preclinical safety data

There were no specific effects from either short studies (including mutagenicity studies) or long-term toxicity studies (including carcinogenicity studies) which provide any additional relevant data to that available from the use in man.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

In animal reproduction studies imidapril did not show clear evidence of foetotoxicity though prenatal growth retardation and reduced body weight gain were seen in rat pups at 1500 mg/kg. Male and female fertility in rats was not impaired.
Teratogenicity studies in rats and rabbits did not reveal any teratogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate, anhydrous

Maize starch, pregelatinised

Lactose monohydrate

Croscarmellose sodium

Glycerol distearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Aluminium/aluminium blister: Do not store above 30°C.

PVC/PVdC/aluminium blister: Do not store above 25°C.

6.5 Nature and contents of container

Aluminium/aluminium or PVC/PVdC/aluminium – Blister with 5, 7, 10 and 14 tablets.
Packs with 7, 10, 14, 15, 20, 28, 30, 50, 56, 84, 90, 100, and 1000 tablets Not all packaging material or pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 48259/0072

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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