For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

TELDAY R 5
(Telmisartan and Ramipril Tablets)

COMPOSITION
Each film coated tablet coated tablet contains:
Telmisartan I.P. 40mg
Ramipril I.P. 5mg
Colours: Ferric Oxide Red USPNF and Titanium Dioxide I.P.

DOSAGE FORM
Film coated tablets.

INDICATIONS
Telday R 5 is indicated for the treatment of mild to moderate hypertension in adults.

POSOLOGY AND METHOD OF ADMINISTRATION
The recommended dose of Telmisartan and Ramipril fixed dose combination tablets is one tablet once a day orally with liquid, with or without food or as recommended by physician.

Telmisartan
Posology
Treatment of essential hypertension
The usually effective dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, the dose of telmisartan can be increased to a maximum of 80 mg once daily. Alternatively, telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide, which has been shown to have an additive blood pressure lowering effect with telmisartan. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment.

Cardiovascular prevention
The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of telmisartan are effective in reducing cardiovascular morbidity.
When initiating telmisartan therapy for the reduction of cardiovascular morbidity, close monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Special populations
Patients with renal impairment
Limited experience is available in patients with severe renal impairment or haemodialysis. A lower starting dose of 20 mg is recommended in these patients
No posology adjustment is required for patients with mild to moderate renal impairment.

Patients with hepatic impairment
Telmisartan is contraindicated in patients with severe hepatic impairment
In patients with mild to moderate hepatic impairment, the posology should not exceed 40 mg once daily.

Elderly patients
No dose adjustment is necessary for elderly patients.

Paediatric population
The safety and efficacy of telmisartan in children and adolescents aged below 18 years have not been established.

Ramipril
Posology
It is recommended that Ramipril is taken each day at the same time of the day.
Ramipril can be taken before, with or after meals, because food intake does not modify its bioavailability.
Ramipril has to be swallowed with liquid. It must not be chewed or crushed.
Adults
Diuretic-Treated patients
Hypotension may occur following initiation of therapy with Ramipril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with ramipril.
In hypertensive patients in whom the diuretic is not discontinued, therapy with Ramipril should be initiated with a 1.25 mg dose. Renal function and serum potassium should be monitored. The subsequent dose of ramipril should be adjusted according to blood pressure target.
Hypertension
The dose should be individualised according to the patient profile and blood pressure control.
Ramipril may be used in monotherapy or in combination with other classes of antihypertensive medicinal products.
Starting dose
Ramipril should be started gradually with an initial recommended dose of 2.5 mg daily.
Patients with a strongly activated renin-angiotensin-aldosterone system may experience an excessive drop in blood pressure following the initial dose. A starting dose of 1.25 mg is recommended in such patients and the initiation of treatment should take place under medical supervision
Titration and maintenance dose
The dose can be doubled at interval of two to four weeks to progressively achieve target blood pressure; the maximum permitted dose of Ramipril is 10 mg daily. Usually the dose is administered once daily.
Cardiovascular prevention
Starting dose
The recommended initial dose is 2.5 mg of Ramipril once daily.
Titration and maintenance dose
Depending on the patient's tolerability to the active substance, the dose should be gradually increased. It is recommended to double the dose after one or two weeks of treatment and - after another two to three weeks - to increase it up to the target maintenance dose of 10 mg Ramipril once daily.
Special populations
Patients with renal impairment
Daily dose in patients with renal impairment should be based on creatinine clearance: -
- if creatinine clearance is $\geq$ 60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 10 mg;

- if creatinine clearance is between 30-60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 5 mg;
- if creatinine clearance is between 10-30 ml/min, the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg;
- in haemodialysed hypertensive patients: ramipril is slightly dialysable; the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg; the medicinal product should be administered few hours after haemodialysis is performed.

Patients with hepatic impairment
In patients with hepatic impairment, treatment with Ramipril must be initiated only under close medical supervision and the maximum daily dose is 2.5 mg ramipril.

Elderly
Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of undesirable effects especially in very old and frail patients. A reduced initial dose of 1.25 mg ramipril should be considered.

Paediatric population
The safety and efficacy of ramipril in children has not yet been established.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or any other ACE (Angiotensin Converting Enzyme) inhibitors or to any of the excipients
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs)
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
- Second and third trimesters of pregnancy
- must not be used in patients with hypotensive or haemodynamically unstable states
- Biliary obstructive disorders
- Severe hepatic impairment
- The concomitant use with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2)

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Telmisartan

Pregnancy
Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist 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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hepatic impairment
Telmisartan is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan. Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation
When Telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Telmisartan in patients with recent kidney transplantation.

Intravascular hypovolaemia
Symptomatic hypotension, especially after the first dose of Telmisartan, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, or vomiting. Such conditions should be corrected before the administration of Telmisartan. Volume and/or sodium depletion should be corrected prior to administration of Telmisartan.

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.

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.

Other conditions with stimulation of the renin-angiotensin-aldosterone system
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as telmisartan has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Diabetic patients treated with insulin or antidiabetics
In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia. In the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events, hyperkalaemia may be fatal.

Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated.

The main risk factors for hyperkalaemia to be considered are:

- Diabetes mellitus, renal impairment, age (>70 years)
- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.
- Intercurrent events, in particular dehydratation, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extend trauma).

Close monitoring of serum potassium in at risk patients is recommended.

Ethnic differences

As observed for angiotensin converting enzyme inhibitors, telmisartan and the other angiotensin II receptor antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Other

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Ramipril
Special populations
Pregnancy
ACE inhibitors such as ramipril or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/AIIRAs 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/AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Patients at particular risk of hypotension
• *Patients with strongly activated renin-angiotensin-aldosterone system*
Patients with strongly activated renin-angiotensin-aldosterone system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase.

Significant activation of renin-angiotensin-aldosterone system is to be anticipated and medical supervision including blood pressure monitoring is necessary, for example in:
- patients with severe hypertension
- patients with decompensated congestive heart failure
- patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve)

- patients with unilateral renal artery stenosis with a second functional kidney
- patients in whom fluid or salt depletion exists or may develop (including patients with diuretics)
- patients with liver cirrhosis and/or ascites
- patients undergoing major surgery or during anaesthesia with agents that produce hypotension.
Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload).
• *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.
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.
• *Transient or persistent heart failure post MI*
• *Patients at risk of cardiac or cerebral ischemia in case of acute hypotension*
The initial phase of treatment requires special medical supervision.
• *Older people*

Surgery
It is recommended that treatment with angiotensin converting enzyme inhibitors such as ramipril should be discontinued where possible one day before surgery.

Monitoring of renal function
Renal function should be assessed before and during treatment and dose adjusted especially in the initial weeks of treatment. Particularly careful monitoring is required in patients with renal impairment. There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant.

Angioedema
Angioedema has been reported in patients treated with ACE inhibitors including ramipril. This risk may be increased in patients taking concomitant medications such as mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, everolimus, sirolimus), vildagliptin or racecadotril.

In case of angioedema, ramipril 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. These patients presented with abdominal pain (with or without nausea or vomiting).

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 ramipril should be considered prior to desensitization.

Electrolyte Monitoring: Hyperkalaemia
Hyperkalaemia has been observed in some patients treated with ACE inhibitors including ramipril. Patients at risk for development of hyperkalaemia include those with renal insufficiency, age (> 70 years), uncontrolled diabetes mellitus, or those using potassium salts, potassium retaining diuretics and other plasma potassium increasing active substances, or conditions such as dehydration, acute cardiac decompensation, metabolic acidosis. If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Electrolyte Monitoring: Hyponatraemia
Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatraemia has been observed in some patients treated with ramipril. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatraemia.

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, as well as thrombocytopenia and anaemia, have been rarely seen and bone marrow depression has also been reported. It is recommended to monitor the white blood cell count to permit detection of a possible leucopoenia. 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 all those treated with other medicinal products that can cause changes in the blood picture.

Ethnic differences
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 than in non-black patients, possibly because of a higher prevalence of hypertension with low renin level in the black hypertensive population.

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.

DRUG-INTERACTION
Telmisartan
Digoxin
When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia. The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including

selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).

The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.

Concomitant use not recommended
Potassium sparing diuretics or potassium supplements
Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution
Non-steroidal anti-inflammatory medicinal products
NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC_{0-24} and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume depletion and in a risk of hypotension when initiating therapy with telmisartan.

To be taken into account with concomitant use
Other antihypertensive agents

The blood pressure lowering effect of telmisartan can be increased by concomitant use of other antihypertensive medicinal products.

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.

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics or antidepressants.

Corticosteroids (systemic route)
Reduction of the antihypertensive effect.

Ramipril
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.

Contraindicated 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. If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Precautions for use
Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, trimethoprim and in fixed dose combination with sulfamethoxazole, tacrolimus, ciclosporin):
Hyperkalaemia may occur, therefore close monitoring of serum potassium is required.
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
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.
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.

Non-steroidal anti-inflammatory drugs and acetylsalicylic acid:
Reduction of the antihypertensive effect of Ramipril is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and to an increase in kalaemia.

mTOR inhibitors or DPP-IV inhibitors:
An increased risk of angioedema is possible in patients taking concomitant medications such as mTOR inhibitors (e.g. temsirolimus, everolimus, sirolimus) or vildagliptin. Caution should be used when starting therapy.

Racecadotril:
A potential increased risk of angioedema has been reported for a concomitant use of ACE inhibitors and NEP inhibitor such as racecadotril.

FERTILITY, PREGNANCY AND LACTATION
Telmisartan
Pregnancy

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy

There are no adequate data from the use of Telmisartan in pregnant women. Studies in animals have shown reproductive toxicity.

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. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of drugs. Unless continued angiotensin II receptor antagonist 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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist therapy 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).
Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension.

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

Fertility
In preclinical studies, no effects of Telmisartan on male and female fertility were observed.

Ramipril

Pregnancy

Ramipril is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy.

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 foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Should exposure to ACE inhibitors 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.

Breast-feeding

Because insufficient information is available regarding the use of ramipril during breastfeeding, Ramipril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Effects on ability to drive and use machines

When driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy such as Telmisartan.

UNDESIRABLE EFFECTS

Telmisartan

Summary of the safety profile

Serious adverse drug reactions include anaphylactic reaction and angioedema which may occur rarely ($\geq 1/10,000$ to $<1/1,000$), and acute renal failure.

The overall incidence of adverse reactions reported with telmisartan was usually comparable to placebo (41.4 % vs 43.9 %) in controlled trials in patients treated for hypertension. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients. The safety profile of telmisartan in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

The adverse reactions listed below have been accumulated from controlled clinical trials in patients treated for hypertension and from post-marketing reports. The listing also takes into account serious adverse reactions and adverse reactions leading to discontinuation reported in three clinical long-term studies including 21642 patients treated with telmisartan for the reduction of cardiovascular morbidity for up to six years.

Tabulated summary of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: 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).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations

Uncommon:	Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis
Rare:	Sepsis including fatal outcome[1]

Blood and the lymphatic system disorders

Uncommon:	Anaemia
Rare:	Eosinophilia, thrombocytopenia

Immune system disorders

Rare:	Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders

Uncommon:	Hyperkalaemia
Rare:	Hypoglycaemia (in diabetic patients)

Psychiatric disorders

Uncommon:	Insomnia, depression
Rare:	Anxiety

Nervous system disorders

Uncommon:	Syncope
Rare:	Somnolence

Eye disorders

Rare:	Visual disturbance

Ear and labyrinth disorders

Uncommon:	Vertigo

Cardiac disorders

Uncommon:	Bradycardia
Rare:	Tachycardia

Vascular disorders

Uncommon:	Hypotension[2], orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon:	Dyspnoea, cough

| Very rare: | Interstitial lung disease[4] |

Gastrointestinal disorders

| Uncommon: | Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting |
| Rare: | Dry mouth, stomach discomfort, dysgeusia |

Hepato-biliary disorders

| Rare: | Hepatic function abnormal/liver disorder[3] |

Skin and subcutaneous tissue disorders

| Uncommon: | Pruritus, hyperhidrosis, rash |
| Rare: | Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption |

Musculoskeletal and connective tissue disorders

| Uncommon: | Back pain (e.g. sciatica), muscle spasms, myalgia |
| Rare: | Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms) |

Renal and urinary disorders

| Uncommon: | Renal impairment including acute renal failure |

General disorders and administration site conditions

| Uncommon: | Chest pain, asthenia (weakness) |
| Rare: | Influenza-like illness |

Investigations

| Uncommon: | Blood creatinine increased |
| Rare: | Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased |

1, 2, 3, 4: for further descriptions, please see sub-section *"Description of selected adverse reactions"*

Description of selected adverse reactions

Sepsis

In the PRoFESS trial, an increased incidence of sepsis was observed with telmisartan compared with placebo. The event may be a chance finding or related to a mechanism currently not known

Hypotension

This adverse reaction was reported as common in patients with controlled blood pressure who were treated with telmisartan for the reduction of cardiovascular morbidity on top of standard care.

Hepatic function abnormal / liver disorder

Most cases of hepatic function abnormal / liver disorder from post-marketing experience occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

Interstitial lung disease

Cases of interstitial lung disease have been reported from post-marketing experience in temporal association with the intake of telmisartan. However, a causal relationship has not been established.

Ramipril

Summary of safety profile

The safety profile of ramipril includes persistent dry cough and reactions due to hypotension. Serious adverse reactions include angioedema, hyperkalaemia, renal or hepatic impairment, pancreatitis, severe skin reactions and neutropenia/agranulocytosis.

Tabulated list of adverse reactions

Adverse reactions frequency is defined using the following convention:

Very common ($\geq$ 1/10); common ($\geq$ 1/100 to < 1/10); uncommon ($\geq$ 1/1,000 to < 1/100); rare ($\geq$ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders		Eosinophilia	White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count decreased, haemoglobin decreased, platelet count decreased		Bone marrow failure, pancytopenia, haemolytic anaemia
Immune system disorders					Anaphylactic or anaphylactoid reactions, antinuclear antibody increased
Endocrine disorders					Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders	Blood potassium increased	Anorexia, decreased appetite,			Blood sodium decreased
Metabolism and nutrition disorders	Blood potassium increased	Anorexia, decreased appetite,			Blood sodium decreased
Psychiatric disorders		Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence	Confusional state		Disturbance in attention
Nervous system disorders	Headache, dizziness	Vertigo, paraesthesia, ageusia, dysgeusia,	Tremor, balance disorder		Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia
Eye disorders		Visual disturbance including blurred vision	Conjunctivitis		
Ear and labyrinth disorders			Hearing impaired, tinnitus		
Cardiac disorders		Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral			
Vascular disorders	Hypotension, orthostatic blood pressure	Flushing	Vascular stenosis, hypoperfusion, vasculitis		Raynaud's phenomenon

	decreased, syncope				
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Bronchospasm including asthma aggravated, nasal congestion			
Gastrointestinal disorders	Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth	Glossitis		Aphtous stomatitis
Hepatobiliary disorders		Hepatic enzymes and/or bilirubin conjugated increased,	Jaundice cholestatic, hepatocellular damage		Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional).
Skin and subcutaneous tissue disorders	Rash in particular maculo-papular	Angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosis	Exfoliative dermatitis, urticaria, onycholysis,	Photosensitivity reaction	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or

					lichenoid exanthema or enanthema, alopecia
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia	Arthralgia			
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			
Reproductive system and breast disorders		Transient erectile impotence, libido decreased			Gynaecomastia
General disorders and administration site conditions	Chest pain, fatigue	Pyrexia	Asthenia		

Paediatric population

The safety of ramipril was monitored in 325 children and adolescents, aged 2-16 years old, during 2 clinical trials. Whilst the nature and severity of the adverse events are similar to that of the adults, the frequency of the following is higher in the children:

Tachycardia, nasal congestion and rhinitis, "common" (ie, $\geq 1/100$ to $< 1/10$) in paediatric, and "uncommon" (i.e. $\geq 1/1,000$ to $< 1/100$) in adult population.

Conjunctivitis "common" (ie, $\geq 1/100$ to $< 1/10$) in paediatric and "rare" (i.e. $\geq 1/10,000$ to $< 1/1,000$) in adult population.

Tremor and urticaria "uncommon" (.ie. $\geq 1/1,000$ to $< 1/100$) in paediatric population and "rare" (i.e. $\geq 1/10,000$ to $< 1/1,000$) in adult population.

The overall safety profile for ramipril in paediatric patients does not differ significantly from the safety profile in adults.

OVERDOSE
Telmisartan
There is limited information available with regard to overdose in humans.

Symptoms: The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Treatment: Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdosage. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacement given quickly.

Ramipril

Symptoms

Symptoms associated with overdose of ACE inhibitors may include excessive peripheral vasodilation (with marked hypotension, shock), bradycardia, electrolyte disturbances and renal failure.

Management

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.

PHARMACOLOGICAL PROPERTIES
Telmisartan
Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II Antagonists, plain ATC Code: C09CA07.

Mechanism of action

Telmisartan is an orally active and specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore, it is not expected to potentiate bradykinin-mediated adverse effects.

In human, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

Clinical efficacy and safety
Treatment of essential hypertension

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 8 weeks after the start of treatment and is sustained during long-term therapy.

The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies. There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure (SBP). In this respect data concerning diastolic blood pressure (DBP) are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The contribution of the medicinal product's diuretic and natriuretic effect to its hypotensive activity has still to be defined. The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes of antihypertensive medicinal products (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril).

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

Cardiovascular prevention
ONTARGET (**ON**going **T**elmisartan **A**lone and in Combination with **Ramipril G**lobal **E**ndpoint **T**rial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, TIA, peripheral arterial disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which is a population at risk for cardiovascular events.

Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years.

Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7 %) and ramipril (16.5 %) groups. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13). The all-cause mortality rate was 11.6 % and 11.8 % among telmisartan and ramipril treated patients, respectively.

Telmisartan was found to be similarly effective to ramipril in the pre-specified secondary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.99 (97.5 % CI 0.90 - 1.08), p (non-inferiority) = 0.0004], the primary endpoint in the reference study HOPE (The **H**eart **O**utcomes **P**revention **E**valuation Study), which had investigated the effect of ramipril vs. placebo.

TRANSCEND randomized ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to telmisartan 80 mg (n=2954) or placebo (n=2972), both given on top of standard care. The mean duration of follow up was 4 years and 8 months. No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death,

non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found [15.7 % in the telmisartan and 17.0 % in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p = 0.22)]. There was evidence for a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95 % CI 0.76 - 1.00, p = 0.048)]. There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95 % CI 0.85 - 1.24).

Cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. CV mortality and all-cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

In the "Prevention Regimen For Effectively avoiding Second Strokes" (PRoFESS) trial in patients 50 years and older, who recently experienced stroke, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70 % vs. 0.49 % [RR 1.43 (95 % confidence interval 1.00 - 2.06)]; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33 %) vs. patients taking placebo (0.16 %) [RR 2.07 (95 % confidence interval 1.14 - 3.76)]. The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known.
Paediatric population
The safety and efficacy of Telmisartan in children and adolescents aged below 18 years have not been established.

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. For more detailed information see above under the heading "Cardiovascular prevention". 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.

The blood pressure lowering effects of two doses of telmisartan were assessed in 76 hypertensive, largely overweight patients aged 6 to < 18 years (body weight ≥ 20 kg and ≤ 120 kg, mean 74.6 kg), after taking telmisartan 1 mg/kg (n =29 treated) or 2 mg/kg (n = 31 treated) over a four-week treatment period. By inclusion the presence of secondary hypertension was not investigated. In some of the investigated patients the doses used were higher than those recommended in the treatment of hypertension in the adult population, reaching a daily dose comparable to 160 mg, which was tested in adults. After adjustment for age group effects mean SBP changes from baseline (primary objective) were -14.5 (1.7) mm Hg in the telmisartan 2 mg/kg group, -9.7 (1.7) mm Hg in the telmisartan 1 mg/kg group, and -6.0 (2.4) in the placebo group. The adjusted DBP changes from baseline were -8.4 (1.5) mm Hg, -4.5 (1.6) mm Hg and -3.5 (2.1) mm Hg respectively. The change was dose dependent. The safety data from this study in patients aged 6 to < 18 years appeared generally similar to that observed in adults. The safety of long term treatment of telmisartan in children and adolescents was not evaluated.
An increase in eosinophils reported in this patient population has not been recorded in adults. Its clinical significance and relevance is unknown.
These clinical data do not allow to make conclusions on the efficacy and safety of telmisartan in hypertensive paediatric population.

Ramipril
Pharmacodynamic properties
Pharmacotherapeutic group: ACE Inhibitors, plain, ATC code C09AA05.
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).

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 causes	*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).

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.

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 %]).

Paediatric Population

In a randomized, double-blind, placebo-controlled clinical study involving 244 paediatric patients with hypertension (73% primary hypertension), aged 6-16 years, patients received either low dose, medium dose or high dose of ramipril to achieve plasma concentrations of ramiprilat corresponding to the adult dose range of 1.25mg, 5mg and 20mg on the basis of body weight. At the end of 4 weeks, ramipril was ineffective in the endpoint of lowering systolic blood pressure but lowered diastolic blood pressure at the highest dose. Both medium and high

doses of Ramipril showed significant reduction of both systolic and diastolic blood pressure in children with confirmed hypertension.

This effect was not seen in a 4 week dose-escalation, randomized, double-blind withdrawal study in 218 paediatric patients aged 6-16 years (75% primary hypertension), where both diastolic and systolic blood pressures demonstrated a modest rebound but not a statistically significant return to the baseline, in all three dose levels tested [low dose (0.625mg – 2.5mg), medium dose (2.5mg – 10mg) or high dose (5mg – 20mg)] ramipril based on weight. Ramipril did not have a linear dose response in the paediatric population studied.

Pharmacokinetic properties
Telmisartan
Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Linearity/non-linearity

The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. C_{max} and to a lesser extent AUC increase disproportionately at doses above 40 mg.

Distribution

Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{dss}) is approximately 500 l.

Biotransformation

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Elimination

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cl_{tot}) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Special Populations
Paediatric population

The pharmacokinetics of two doses of telmisartan were assessed as a secondary objective in hypertensive patients (n = 57) aged 6 to < 18 years after taking telmisartan 1 mg/kg or 2 mg/kg over a four-week treatment period. Pharmacokinetic objectives included the determination of the steady-state of telmisartan in children and adolescents, and investigation of age related differences. Although the study was too small for a meaningful assessment of the pharmacokinetics of children under 12 years of age, the results are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for C_{max}.

Gender
Differences in plasma concentrations were observed, with C_{max} and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.
Elderly
The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.
Renal impairment
In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient patients and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.
Hepatic impairment
Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100 %. The elimination half-life is not changed in patients with hepatic impairment.

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 mg and 5 mg ramipril is 45 %.
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 %.
Biotransformation
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.

Patients with renal impairment
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
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.

Lactation
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.

Paediatric Population
The pharmacokinetic profile of ramipril was studied in 30 paediatric hypertensive patients, aged 2-16 years, weighing ≥ 10kg. After doses of 0.05 to 0.2mg/kg, ramipril was rapidly and extensively metabolized to ramiprilat. Peak plasma concentrations of ramiprilat occurred within 2-3 hours. Ramiprilat clearance highly correlated with the log of body weight (p<0.01) as well as dose (p<0.001). Clearance and volume of distribution increased with increasing children age for each dose group. The dose of 0.05mg/kg in children achieved exposure levels comparable to those in adults treated with ramipril 5mg. The dose of 0.2mg/kg in children resulted in exposure levels higher than the maximum recommended dose of 10mg per day in adults.

PRECLINICAL SAFETY DATA
Telmisartan
In preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral saline supplementation.
In both species, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance.
No clear evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the offsprings such as lower body weight and delayed eye opening was observed.
There was no evidence of mutagenicity and relevant clastogenic activity in *in vitro* studies and no evidence of carcinogenicity in rats and mice.

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.

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.

Irreversible kidney damage has been observed in very young rats given a single dose of ramipril.

EXPIRY DATE
Do not use later than the date of expiry.

PACKAGING INFORMATIOND
Telday R 5 is available in strips of 10 tablets.

STORAGE AND HANDLING INSTRUCTIONS
Store below 25°C, protected from light and moisture. Keep out of reach of children.

MARKETED BY

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IN/TELDAY R 5,40mg/Apr-17/07/PI