Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dinortes 20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of telmisartan.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round bevelled tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension:
Treatment of essential hypertension in adults

Cardiovascular prevention:
Reduction of cardiovascular morbidity in patients with:

i) manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or
ii) type 2 diabetes mellitus with documented target organ damage.

4.2 Posology and method of administration

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, telmisartan dose can be increased to a maximum of 80 mg once daily. Alternatively, telmisartan may be used in combination with thiazidetype 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 (see section 5.1).

Cardiovascular prevention:

The recommended dose is 80 mg once daily. It is known whether doses lower than 80 mg of telmisartan are effective in reducing cardiovascular morbidity.
When initiating telmisartan therapy for the reduction of cardiovascular mobidity, close monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Dinortes may be taken with or without food.

Renal impairment: no posology adjustment is required for patients with mild to moderate 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 (see section 4.4).

Hepatic impairment: in patients with mild to moderate hepatic impairment the posology should not exceed 40 mg once daily (see section 4.4).

Elderly
No dosing adjustment is necessary for elderly patients.

Paediatric patients
Dinortes is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients (see section 6.1)
• Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
• Biliary obstructive disorders
• Severe hepatic impairment

4.4 Special warnings and precautions for use

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 anti-hypertensive 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 (see sections 4.3 and 4.6).

Hepatic impairment:
Dinortes is not be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment (see section 4.3) since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan. Dinortes 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 transplant:
When Dinortes 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 Dinortes in patients with recent kidney transplantation.

Intravascular hypovolaemia:
Symptomatic hypotension, especially after the first dose of Dinortes, 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 Dinortes. Volume and/or sodium depletion should be corrected prior to administration of Dinortes.

Dual blockade of the renin-angiotensin-aldosterone system: As a consequence of inhibiting the reninangiotensin-aldosterone system, hypotension and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system.

Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACEinhibitor to an angiotensin II receptor antagonist) is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

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 reninangiotensin-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 (see section 4.8).

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.

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 class of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptors 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 (see section 4.5).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia (see section 4.4).

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 significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia 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 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 nonselective NSAIDs) may reduce the antihypertensive effect of angiotensin II 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 AUC0-24 and Cmax 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.

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.

Corticosteroïds (systemic route):
Reduction of the antihypertensive effect.

4.6 Fertility, pregnancy and lactation

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Pregnancy (see section 4.3 and 4.4):
There are no adequate data from the use of Micardis in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
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. 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 anti-hypertensive 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.
Angiotensin II receptor antagonist therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also section 5.3).
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 (see also sections 4.3 and 4.4).

Lactation (see section 4.3):
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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

4.8 Undesirable effects

The overall incidence of adverse events reported with telmisartan (41.4%) was usually comparable to placebo (43.9%) in placebo controlled trials. The incidence of adverse events 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 drug reactions listed below have been accumulated from all clinical trials in patients treated for hypertension and from post marketing reports. The listing also takes into account serious adverse events and adverse events 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

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000 <1/100); rare (≥ 1/10,000 <1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

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

Infections and infestations:
Uncommon (≥1/1,000 to <1/100): Upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis
Not known (can not be estimated from the available data): Sepsis including fatal outcome[1]

Blood and the lymphatic system disorders
Uncommon (≥1/1,000 to < 1/100): Anaemia
Rare(≥1/10,000 to <1/1,000): Thrombocytopenia
Not known (can not be estimated from the available data): Eosinophilia

Immune system disorders
Rare (≥1/10,000 to <1/1,000: Hypersensitivity
Not known (can not be estimated from the available data): Anaphylactic reaction

Metabolism and nutrition disorders
Uncommon (≥1/1,000 to <1/100): Hyperkalaemia

Psychiatric disorders:
Uncommon (≥1/1,000 to < 1/100): Depression, insomnia
Rare (≥1/10,000 to <1/1,000: Anxiety.

Nervous system disorders
Uncommon (≥1/1,000 to <1/100): Syncope.

Eye disorders:
Rare (≥1/10,000 to <1/1,000): Abnormal vision

Ear and labyrinth disorders:
Uncommon (≥1/1,000 to <1/100): Vertigo

Cardiac disorders
Uncommon (≥1/1,000 to <1/100): Bradycardia
Rare (≥1/10,000 to <1/1,000): Tachycardia

Vascular disorders
Uncommon (≥1/1,000 to <1/100): Hypotension[2], orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon (≥1/1,000 to <1/100): Dyspnoea

Gastrointestinal disorders:
Uncommon (≥1/1,000 to <1/100): Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting
Rare (≥1/10,000 to <1/1,000): Stomach upset, dry mouth
Hepato-biliary disorders
Rare (≥1/10,000 to <1/1,000) : Hepatic function abnormal/liver disorder

Skin and subcutaneous tissue disorders:
Uncommon (≥1/1,000 to <1/100): Hyperhidrosis, pruritus, rash.
Rare (≥1/10,000 to <1/1,000): Erythema, angioedema,, drug eruption, toxic skin eruption, eczema.
Not known (can not be estimated from the available data): Urticaria.

Musculoskeletal and connective tissue disorders:

Uncommon (≥1/1,000 to <1/100): Myalgia, back pain(e.g. sciatica), muscle cramps
Rare (≥1/10,000 to <1/1,000): Arthralgia, , pain in extremity.
Not known (can not be estimated from the available data) :Tendonitis

Renal and urinary disorders
Uncommon (≥1/1,000 to <1/100) : Renal impairment including acute renal failure

General disorders and administration site conditions
Uncommon (≥1/1,000 to <1/100): Chest pain, asthenia (weakness).
Rare (≥1/10,000 to <1/1,000): Influenza-like illness

Investigations
Uncommon (≥1/1,000 to <1/100): Blood creatinine increased.
Rare (≥1/10,000 to <1/1,000): Blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased, haemoglobin decreased.

[1]In the PRoFEESS 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 know (see section 5.1).

[2]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.

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Angiotensin II Antagonists, ATC Code: C09CA07.

Mechanism of action:
Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist.
Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 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 bradykininmediated 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 hyertension:

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4-8 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 **C**ombination with **R**amipril **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 mellitys 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 comibination of temisartan 80 mg plus ramipril 10 mg (n=8502), and followed for a mean observation time of 4.5 years.

Telmisartan showec 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 temisartan vs. ramipril was 1.01 (97.5 % Cl 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 **S**tudy), which had investigated the effect or 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 or 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 ration 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 ramipirl or telmisartan alone. CV mortality and all cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence or 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 year and older, who recently experience stroke, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70% vs. 0.49% [RR1.43 (95% confidence interval 1.00-2.06]; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33%) vs. patients raking 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.

Beneficial effects of telmisartan on mortality and cardiovascular morbidity are currently unknown.

5.2 Pharmacokinetic properties

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 (AUC0-∞) 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. Cmax 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 (Vdss) is approximately 500 l.

Metabolism:
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 (Cmax) 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 (Cltot) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Special Populations

Gender effects:
Differences in plasma concentrations were observed, with Cmax and AUC being approximately 3-and 2-fold higher, respectively, in females compared to males.

Elderly patients:
The pharmacokinetics of telmisartan do not differ in young and elderly patients.

Patients with renal impairment:
In patients with mild to moderate and severe renal impairment patients 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.

Patients with 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.

5.3 Preclinical safety data

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 antagonists, do not appear to have clinical significance.

There is no evidence of teratogenic effect but animal studies indicated some hazardous potential of telmisartan to the postnatal development of the offspring: lower body weight, delayed eye opening, higher mortality.

There was no evidence of mutagenicity and relevant clastogenic activity in *in vitro* studies and no evidence of carcinogenicity in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Meglumine
Sodium hydroxide
Mannitol
Magnesium stearate
Crospovidone

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Aluminium/aluminium blisters:
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The outer containers are carton boxes.

Dinortes 20/40/80 mg tablets are supplied in blisters (Aluminium/Aluminium) containing 14, 28, 30, 56, 84, 90, 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 1239/16/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th November 2010

10 DATE OF REVISION OF THE TEXT