# SUMMARY OF PRODUCT CHARACTERISTICS

## Safetelmi 20, 40 & 80

## (Telmisartan Tablets USP 20 mg, 40 mg & 80 mg)

## 1. NAME OF THE MEDICINAL PRODUCT

Safetelmi 20/40/80 (Telmisartan Tablets USP 20 mg/40 mg/80 mg)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains telmisartan USP 20 mg or 40 mg or 80 mg

For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

White to off white colored round shaped smooth flat bevel edged plain both sides uncoated 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, 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:*

**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.

**Hepatic impairment:** In patients with mild to moderate hepatic impairment, the posology should not exceed 40 mg once daily.

*Elderly*

No dose adjustment is necessary for elderly patients.

*Paediatric population*

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

**Method of administration**

Telmisartan tablets are for once-daily oral administration and should be taken with liquid, with or without food.

*Precautions to be taken before handling or administering the medicinal product.*

Telmisartan should be kept in the sealed blister due to the hygroscopic property of the tablets. Tablets should be taken out of the blister shortly before administration.

**4.3 Contraindications**

* Hypersensitivity to the active substance or to any of the excipients.

* Second and third trimesters of pregnancy.

* 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 antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancyis 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*
As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia, 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 administering telmisartan with other blockers of the renin-angiotensin-aldosterone system) is there fore not recommended. Close monitoring of renal function is advisable if co-administration is considered necessary.

### *Other conditions with stimulation of the renin-angiotensin-aldosterone system*
In patients whose vascular tone and renal function depend predominantly on the activityof therenin-angiotensin-aldosterone system (e.g.patients with severe congestive heart failure orunderlying renal disease, including renal artery stenosis), treatment with medicinal products thataffect 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 medicinalproducts acting through inhibition of the renin-angiotensin system. Therefore, the use oftelmisartan 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

mitralstenosis, or obstructive hypertrophic cardiomyopathy.

*Diabetic patients treated with insulin or antidiabetics*

In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in thesepatients an approptiate blood glucose monitoring should be considered; a dose adjustment ofinsulin or antidiabetics may be required, when indicated.

*Hyperkalaemia*

The use of medicinal products that affect the renin-angiotensin-aldosterone system may causehyperkalaemia.

In the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantlytreated with other medicinal products that may increase potassium levels, and/or in patients withintercurrent 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 ofmedicinal 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.

- Intercurrentevents, in particular dehydratation, acute cardiac decompensation, metabolicacidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectiousdiseases), cellular lysis (e.g.acute limb ischemia, rhabdomyolysis, extend trauma).

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

*Sorbitol*

This medicinal product contains sorbitol (E420). Patients with rare hereditary problems of fructoseintolerance should not take Telmisartan.

*Ethnic differences*

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

*Other*

As with any antihypertensive agent, excessive reduction of blood pressure in patients withischaemic

cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarctionor 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. 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 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 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 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.

*Corticosteroids (systemic route):*

Reduction of the antihypertensive effect.

**4.6 Fertility, pregnancy & lactation**

*Pregnancy*

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

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACEinhibitors during the first trimester of pregnancy has not been conclusive; however a smallincrease 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, ifappropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters isknown to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossificationretardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to angiotensin II receptor antagonists have occurred from the second trimester ofpregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken angiotensin II receptor antagonists should be closely observedfor hypotension.

### Breast-feeding

Because no information is available regarding the use of Telmisartan during breast-feeding, Telmisartanis not recommended and alternative treatments with better established safety profiles duringbreast-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.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

a. Summary of the safety profile

Serious adverse drug reactions include anaphylactic reaction and angioedema which may occur rarely (less than 1 cases per 1,000 patients), and acute renal failure.

The overall incidence of adverse events reported with telmisartan (41.4 %) was usually comparable to placebo (41.4% vs 43.9 %) in controlled trials in patients treated for hypertension. 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 controlled 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 21,642 patients treated with telmisartan for the reduction of cardiovascular morbidity for up to six years.

b. 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 outcome1

### *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

### *Eye disorders*

Rare: Visual disturbance

### *Ear and labyrinth disorders*

Uncommon: Vertigo

### *Cardiac disorders*

Uncommon: Bradycardia

Rare: Tachycardia

### *Vascular disorders*

Uncommon: Hypotension2, orthostatic hypotension

### *Respiratory, thoracic and mediastinal disorders*

Uncommon: Dyspnoea

### *Gastrointestinal disorders*

Uncommon: Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting

Rare: Dry mouth, stomach discomfort

*Hepato-biliary disorders*

Rare: Hepatic function abnormal/liver disorder3

*Skin and subcutaneous tissue disorders*

Uncommon: Pruritus, hyperhidrosis, rash

Rare: Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption

*Muscoloskeletal 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

*Description of selected adverse reactions*

1. 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.

2. Hypotension

This adverse drug 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.

3. 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.

**4.9 Overdose**

Thereis 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

*Pharmacotherapeuticgroup:* Angiotensin II Antagonists, plain, ATC Code: C09CA07.

*Mechanismofaction*

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 receptorsubtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibitany partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. Thebinding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 andother less characterised AT receptors. The functional role of these receptors is not known, nor is theeffect 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 plasmarenin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininaseII), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiatebradykinin-mediated adverse effects.

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

*Clinical efficacy and safety*

*Treatment of essential hypertension*

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

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

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure

withoutaffecting pulse rate. The contribution of the medicinal product's diuretic and natriuretic effect to itshypotensive activity has still to be defined. The antihypertensive efficacy of telmisartan iscomparable 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 ofseveraldayswithoutevidenceofreboundhypertension.

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

*Cardiovascularprevention*

**ONTARGET** (ONgoing Telmisartan Alone and in Combination with Ramipril Global EndpointTrial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramiprilon cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronaryartery disease, stroke, TIA, peripheral arterial disease, or type 2 diabetes mellitus accompanied byevidence of end-organ damage (e.g. Retinopathy, left ventricular hypertrophy, macro- ormicroalbuminuria), 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 ofcardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization forcongestive 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 mortalityrate 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 endpointof 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 (TheHeart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs.Placebo.

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

fatalmyocardial 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% CI0.81-1.05, p = 0.22)]. There was evidence for a benefit of telmisartan compared to placebo in thepre-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 cardiovascularmortality (hazard ratio 1.03, 95% CI 0.85 - 1.24).

Cough and angioedema were less frequently reported in patients treated with telmisartan than inpatients 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 syncopein the combination arm. Therefore the use of a combination of telmisartan and ramipril is notrecommended in this population.

In the "Prevention Regimen For Effectively avoiding Second Strokes" (PRoFESS) trial in patients50 years and older, who recently experienced stroke, an increased incidence of sepsis was noted fortelmisartan 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)]. Theobserved increased occurrence rate of sepsis associated with the use of telmisartan may be either achance finding or related to a mechanism not currently known.

**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 ($AUC_{0-\infty}$) 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. 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.

## 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 (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.

Afte 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

Differences in plasma concentrations were observed, with Cmax 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.

## 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 receptor antagonists, do not appear to have clinical significance.

No clear evidence of a teratogenic effect was observed, however at toxic levels of telmisartan an effect on the postnatal development of the off springs such as lower body weight and delayed eye opening, was observed.

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

# 6. PHARMACEUTICAL PARTICULARS

## 6.1. LIST OF EXCIPIENTS:

Microcrystalline cellulose, croscarmellose sodium (Ac-Di-Sol), meglumine, poloxamer 188 NF, povidone, isopropyl alcohol & magnesium stearate.

## 6.2. INCOMPATIBILITIES:

Not applicable

## 6.3. SHELF LIFE:

36 months.

## 6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store above 30°C.

## 6.5. NATURE AND CONTENTS OF CONTAINER:

10 tablets of Telmisartan Tablets USP 20 mg/40 mg/80 mg are packed in Aluminium base foil on one side and Aluminium lidding foil on another side in the form of Aluminium-Aluminium blister pack and such 1 or 3 packs are further packed in pre-printed carton along with instructions for use.

## 6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND HANDLING:

Telmisartan should be kept in the sealed blister due to the hygroscopic property of the tablets. Tablets should be taken out of the blister shortly before administration.

**7.MARKETING AUTHORISATION HOLDER:**

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