SUMMARY OF PRODUCT CHARECTERISTICS OF TELMISARTAN TABLETS USP 40mg

1. Name of the medicinal product:

Telmisartan Tablets USP 40mg

2. Qualitative and quantitative composition

Each Uncoated Tablet contains:

Telmisartan USP ------ 40 mg

S. No.	Name of the Ingredient	Specification	Qty/Tablet (mg)	Functional category
Dry mixing				
1	Mannitol (PearlitolSD-200)	BP	137.000	Disintegrant
2	Sodium Starch Glycolate (Type A)	BP	9.500	Disintegrant
Drug Solution				
3	Telmisartan	USP	40.000	Active
4	Meglumine	BP	16.000	Conjunction
5	Sodium Hydroxide (Pellets)	BP	3.500	Solvents
6	Purified Water #	USP	92.500	Aqueous Solvent
Binder:				
7	Povidone (K-30) BP	BP	2.500	Lubricant
8	Purified Water #	USP	7.500	aqueous Solvent
Pre -Lubrication:				
9	Mannitol (PearlitolSD-200)	BP	18.000	Diluent
10	Sodium Starch Glycolate (Type A)	BP	9.500	Disintegrant
Lubrication:				
11	Magnesium Stearate	BP	4.000	Lubricant
Total Core Tablet Weight:			**240.000**	

Not present in finished Product.

3. Pharmaceutical form

White to off white colour, oval shaped, biconvex uncoated tablets with score line on one side and plain on other side.

4. Clinical particular

4.1 Therapeutic indications:

Hypertension

Treatment of essential hypertension in adults.

Cardiovascular prevention

Reduction of cardiovascular morbidity in adults with:

• Manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or

• Type 2 diabetes mellitus with documented target organ damage

4.2 Posology and method of administration

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.

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.

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

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.

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 trimester of pregnancy
- Biliary obstructive disorders.

• Severe hepatic impairment.

• The concomitant use of telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)

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 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.

Sorbitol

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

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

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 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 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.

4.6 Pregnancy and lactation

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.

4.7 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

4.8 Undesirable effects

Summary of the safety profile

Serious adverse drug reactions include anaphylactic reaction and angioedema which may occur rarely (≥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 21,642 patients treated with telmisartan for the reduction of cardiovascular morbidity for up to six years.

Tabulated list 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
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

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.

4.9 Overdose

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

5. Pharmacological properties

5.1 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 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 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 (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) 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 Heart Outcomes Prevention Evaluation 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.

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.

Paediatric population

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

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.

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. 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 (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.

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).

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 Cmax.

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 does 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.

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 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.

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol, Sodium Starch Glycolate (Type A), Meglumine , Sodium Hydroxide , Povidone (K-30) and Magnesium Stearate

6.2 Incompatibilities : Not applicable.

6.3 Shelf life: 2 years

6.4 Special precautions for storage: Store in the original package below 30°C keep out of reach of children

6.5 Nature and contents of container

Alu/Alu Blister pack: 3 x 10 Tablets

6.6 Special precautions for disposal and other handling No special requirements.

7. Marketing authorisation holder

Prisma Pharma FZE.

P.O. Box 17269,

Jebel Ali Free Zone,

Dubai, U.A.E.

Email: info@prismapharma.com

8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text

05.12.2019

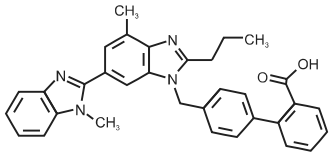
1.3.3 Package leaflet/insert

Enclosed

HYTAN® 40/80 TABLETS

(Telmisartan Tablets USP 40/80 mg)

Composition:
Hyten 40: Each uncoated tablet contains: Telmisartan USP 40 mg
Hyten 80: Each uncoated tablet contains: Telmisartan USP 80 mg
Description: Telmisartan is a non-peptide angiotensin II receptor (type AT1) antagonist. Telmisartan is chemically described as 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid. Its empirical formula is C33H30N4O2, its molecular weight is 514.63, and its structural formula is:



Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base.Telmisartan is available as tablets for oral administration, containing 20 mg, 40 mg or 80 mg of telmisartan. The tablets contain the following inactive ingredients: sodium hydroxide, meglumine, povidone, sorbitol, and magnesium stearate.Telmisartan tablets are hygroscopic and require protection from moisture

Mechanism of Action: Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis. There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT1 receptor than for the AT2 receptor. Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure

Pharmacokinetics: Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5 to 1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10 to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing

Distribution: Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α1 - acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding

Metabolism and Elimination: Following either intravenous or oral administration of 14C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively). Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine

Indications:

Hypertension

Treatment of essential hypertension in adults

Cardiovascular prevention

Reduction of cardiovascular morbidity in adults with:

Manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or

Type 2 diabetes mellitus with documented target organ damage

Dosage and administration

Hypertension
Dosage must be individualized. The usual starting dose of Telmisartan tablets is 40 mg once a day. Blood pressure response is dose-related over the range of 20 to 80 mg Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. When additional blood pressure reduction beyond that achieved with 80 mgTelmisartan is required, a diuretic may be added

No initial dosage adjustment is necessary for elderly patients or patients with renal impairment, including those on hemodialysis. Patients on dialysis may develop orthostatic hypotension; their blood pressure should be closely monitored

Telmisartan tablets may be administered with other antihypertensive agents

Telmisartan tablets may be administered with or without food

Cardiovascular Risk Reduction

The recommended dose ofTelmisartan tablets is 80 mg once a day and can be administered with or without food. It is not known whether doses lower than 80 mg of telmisartan are effective in reducing the risk of cardiovascular morbidity and mortality

When initiatingTelmisartan therapy for cardiovascular risk reduction, monitoring of blood pressure is recommended, and if appropriate, adjustment of medications that lower blood pressure may be necessary

Contraindications
Telmisartan is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan or any other component of this product

Dosage forms and Strengths
40 mg, White to off white colour, oval shaped, biconvex uncoated tablets with score line on one side and plain on other side
80 mg, White to off white colour, oval shaped, biconvex uncoated tablets with score line on one side and plain on other side

warnings and precautions

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

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

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

Interaction with other medicinal products and other forms of interaction

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

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including TELMISARTAN . Therefore, monitor serum lithium levels during concomitant use

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):
In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy

Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state Cmax and AUC of ramipril 2.3- and 2.1-fold, respectively, and Cmax and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, Cmax and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Concomitant use ofTelmisartan and ramipril is not recommended. Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects s in vitro on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19

Use in specific population
Pregnancy Teratogenic Effects, Pregnancy Categories C (first trimester) and D (second and third trimesters)

Nursing Mothers It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother

Pediatric Use Safety and effectiveness in pediatric patients have not been established

Geriatric Use
Of the total number of patients receivingTelmisartan in hypertension clinical studies, 551 (19%) were 65 to 74 years of age and 130 (4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out

Hepatic Insufficiency Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency

Adverse Reactions: Summary of the safety profile:Serious adverse drug reactions include anaphylactic reaction and angioedema which may occur rarely (≥ 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 21,642 patients treated with telmisartan for the reduction of cardiovascular morbidity for up to six years. Tabulated list 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,**2)Immune system disorders:** Rare: Anaphylactic reaction, hypersensitivity,3)**Metabolism and nutrition disorders:** Uncommon: Hyperkalaemia, Rare: Hypoglycaemia (in diabetic patients),4) **Psychiatric disorders**: Uncommon: Insomnia, depression, Rare: Anxiety. 5)**Nervous system disorders:** Uncommon: Syncope, Rare: Somnolence,6) **Eye disorders:** Rare: Visual disturbance,7)**Ear and labyrinth disorders:** Uncommon: Vertigo,8) **Cardiac disorders:** Uncommon: Bradycardia, Rare: Tachycardia,9) **Vascular disorders:** Uncommon: Hypotension, orthostatic hypotension,10) **Respiratory, thoracic and mediastinal disorders:** Uncommon: Dyspnoea, cough, Very rare: Interstitial lung disease,11) **Gastrointestinal disorders:** Uncommon: Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, Rare: Dry mouth, stomach discomfort, dysgeusia,12) **Hepato-biliary disorders**- Rare: Hepatic function abnormal(liver disorder,13) **Skin and subcutaneous tissue disorders:** Uncommon: Pruritus, hyperhidrosis, rash, Rare: Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption,14) **Muscoloskeletal and connective tissue disorders**- Uncommon: Back pain (e.g. sciatica), muscle spasms, myalgia, Rare: Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms),15) Renal and urinary disorders- Uncommon: Renal impairment including acute renal failure,16) General disorders and administration site conditions- Uncommon: Chest pain, asthenia (weakness), Rare: Influenza-like illness,17) Investigations- Uncommon: Blood creatinine increased, Rare: Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

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 establiished

Overdosage
Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage withTelmisartan tablets would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis

Special precautions for storage: Store in the original package below 30°C. Keep out of reach of Children.

Presentation: Alu-Alu blister of 3 x 10 Tablets

Alu/Alu Blister pack: 3 x 10 Tablets

PRISMA®
A RAY OF HOPE

Manufactured for:
Prisma Pharma FZE
P. O. Box 17269
Jebel Ali Free Zone
Dubai, U.A.E.

Manufactured by:
Bafna Pharmaceuticals Ltd.
147, Madhavaram Redhills High Rd
Grantlyon Village
Chennai - 600052, India

HYTAN - Registered Trademark of Prisma Holdings Ltd, Mauritius
® - Registered Trademark

BFT 446 LF

Length (210mm) x Height (297mm)

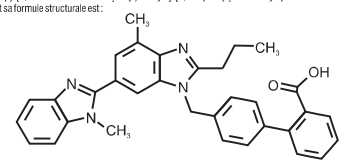
HYTAN®-40/80 COMPRIMÉS

(Comprimés de Telmisartan USP 40/80 mg)

Composition:

Hyten 40: Chaque comprimé non enrobé contient : Telmisartan USP 40 mg Hyten 80 : Chaque comprimé non enrobé contient : Telmisartan USP 80 mg

Description: Letelmisartan est un antagoniste non peptidique des récepteurs de l'angiotensine II (type AT1). Le telmisartan est décrit chimiquement comme l'acide 4'-[(1,4'-diméthyl-2'-propyl[2,6-bi-1H-benzimidazol]-1'-yl)méthyle]-[1,1'-biphényl]-2-carboxylique. Sa formule empirique est C33H30N4O2, son poids moléculaire est 514,63 et sa formule structurale est :



Le telmisartan est un solide blanc à légèrement jaunâtre. Il est pratiquement insoluble dans l'eau et dans un intervalle pH de 3 à 9, peu soluble dans les acides forts (sauf dans l'acide chlorhydrique) et soluble dans les bases fortes. le telmisartan est disponible en comprimés pour administration orale, contenant 20 mg, 40 mg ou 80 mg de telmisartan. Les comprimés contiennent les ingrédients inactifs suivants : hydroxyde de sodium, méglumine, povidone, sorbitol et stéarate de magnésium. Les comprimés de telmisartan sont hygroscopiques et nécessitent une protection contre l'humidité

Mécanisme d'action: L'angiotensine II est formée à partir de l'angiotensine I dans une réaction catalysée par une enzyme de conversion de l'angiotensine (ACE, kininase II). L'angiotensine II est le principal agent vasopresseur du système rénine-angiotensine, avec des effets qui comprennent la vasoconstriction, la stimulation de la synthèse et la libération de l'aldostérone, la stimulation cardiaque et la réabsorption rénale du sodium. Le telmisartan bloque les effets vasoconstricteurs et sécréteurs d'aldostérone de l'angiotensine II en bloquant sélectivement la liaison de l'angiotensine II au récepteur AT1 dans de nombreux tissus, comme le muscle lisse vasculaire et les glandes surrénales. Son action est donc indépendante des voies de synthèse de l'angiotensine II. On trouve également un récepteur AT2 dans de nombreux tissus, mais l'AT2 n'est pas associé à l'homéostasie cardiovasculaire. Le telmisartan a une affinité beaucoup plus grande (>3 000 fois) pour le récepteur AT1 que pour le récepteur AT2. Le blocage du système rénine-angiotensine avec les inhibiteurs de l'ECA, qui inhibent la biosynthèse de l'angiotensine II à partir de l'angiotensine I, est largement utilisé dans le traitement de l'hypertension. Les inhibiteurs de l'ECA inhibent également la dégradation de la bradykinine, une réaction également catalysée par l'ECA. Comme le telmisartan n'inhibe pas l'ECA (kininase II), il n'affecte pas la réponse à la bradykinine. On ne sait pas encore si cette différence a une pertinence clinique. Le telmisartan ne se lie pas aux autres récepteurs hormonaux ou canaux ioniques importants pour la régulation cardiovasculaire et ne les bloque pas. Le blocage du récepteur de l'angiotensine II inhibe la rétroaction régulatrice négative de l'angiotensine II sur la sécrétion de rénine, mais l'augmentation de l'activité plasmatique de la rénine et des taux circulant d'angiotensine II qui en résulte ne permet pas de surmonter l'effet du telmisartan sur la pression artérielle

Pharmacocinétique: Après l'administration orale, les concentrations maximales (Cmax) de telmisartan sont atteintes de 0,5 à 1 heure après l'administration. Les aliments réduisent légèrement la biodisponibilité du telmisartan, avec une réduction de l'aire sous la courbe des concentrations plasmatiques en fonction du temps (ASC) d'environ 6 % avec le comprimé de 40 mg et d'environ 20 % après une dose de 160 mg. La biodisponibilité absolue du telmisartan dépend de la dose. Aux doses de 40 et 160 mg, la biodisponibilité était de 42 % et 58 %, respectivement.. La pharmacocinétique du telmisartan administré par voie orale n'est pas linéaire sur la plage posologique de 20 à 160 mg, et les augmentations des concentrations plasmatiques (Cmax et ASC) sont plus importantes que proportionnelles lorsque les doses augmentent. Le telmisartan présente une cinétique de désintégration bi-exponentielle avec une demi-vie d'élimination terminale d'environ 24 heures. Les concentrations plasmatiques minimales de telmisartan administrées une fois par jour représentent environ 10 à 25 % des concentrations plasmatiques maximales. Le telmisartan a un indice d'accumulation dans le plasma de 1,5 à 2 après administration répétée d'une dose quotidienne

Distribution: Letelmisartan se lie fortement aux protéines plasmatiques (>99,5 %), principalement l'albumine et α1 - glycoprotéine acide. La liaison aux protéines plasmatiques est constante sur toute la plage de concentration atteinte avec les doses recommandées. Le volume de distribution du telmisartan est d'environ 500 litres, ce qui indique une liaison tissulaire supplémentaire

Métabolisme et élimination: Après l'administration intraveineuse ou orale de telmisartan marqué au 14C, la plus grande partie de la dose administrée (>97 %) a été éliminée inchangée dans les selles par excrétion biliaire ; on n'a trouvé que des quantités infimes dans l'urine (0,91 % et 0,49 % de la radioactivité totale, respectivement). Le telmisartan est métabolisé par conjugaison pour former un acylglucuronide pharmacologiquement inactif ; le glucuronide du composé parent est le seul métabolite qui a été identifié dans le plasma et l'urine humains

Indications:

Hypertension

Traitement de l'hypertension essentielle chez l'adulte

Prévention cardiovasculaire

Réduction de la morbidité cardiovasculaire chez les adultes atteints de:

Maladie cardiovasculaire athérothrombotique manifeste (antécédents de coronaropathie, d'accident vasculaire cérébral ou de maladie artérielle périphérique) ou

Diabète sucré de type 2 avec dommages documentés aux organes cibles

Posologie et mode d'emploi

Hypertension

La posologie doit être individualisée. La dose initiale habituelle des comprimés de Telmisartan est de 40 mg une fois par jour. La plupart des effets de la tension artérielle sont apparents après 2 semaines et la réduction maximale est généralement atteinte après 4 semaines. Lorsqu'une réduction de la tension artérielle supérieure à celle obtenue avec 80 mg de telmisartan est nécessaire, on peut ajouter un diurétique

Aucun ajustement posologique initial n'est nécessaire chez les patients âgés ou atteints d'insuffisance rénale, y compris ceux qui sont sous hémodialyse. Les patients sous dialyse peuvent développer une hypotension orthostatique ; leur tension artérielle doit être surveillée de près

Le telmisartan en comprimés peut être administré avec d'autres agents antihypertenseurs

Les comprimés de telmisartan peuvent être administrés avec ou sans nourriture

Réduction des risques cardiovasculaires

La dose recommandée des comprimés de Telmisartan est de 80 mg une fois par jour et peut être administrée avec ou sans nourriture. On ignore si des doses inférieures à 80 mg de telmisartan sont efficaces pour réduire le risque de morbidité et de mortalité cardiovasculaires

Lors de l'instauration d'un traitement par Telmisartan pour la réduction du risque cardiovasculaire, il est recommandé de surveiller la tension artérielle et, le cas échéant, d'ajuster les médicaments qui abaissent la tension artérielle au besoin

Contre-indications:

Le telmisartan est contre-indiqué chez les patients présentant une hypersensibilité connue (p. ex. anaphylaxie ou œdème de Quincke) au telmisartan ou à tout autre composant de ce produit

Formes posologiques et concentrations

40 mg, de couleur blanche à blanc cassé, de forme ovale, comprimés biconvexes non enrobés avec ligne de séparation d'un côté et uni de l'autre côté. 80 mg, de couleur blanche à blanc cassé, de forme ovale, comprimés biconvexes non enrobés avec ligne de séparation d'un côté et uni de l'autre côté

AVERTISSEMENT et PRÉCAUTIONS:

Grossesse

Les antagonistes des récepteurs de l'angiotensine II ne doivent pas être amorcés pendant la grossesse. À moins que la poursuite du traitement par antagoniste des récepteurs de l'angiotensine II ne soit jugée essentielle, les patientes qui planifient une grossesse doivent être remplacées par d'autres traitements antihypertenseurs dont le profil d'innocuité est établi pour une utilisation pendant la grossesse. Lorsqu'un diagnostic de grossesse est posé, le traitement avec des antagonistes des récepteurs de l'angiotensine II doit être interrompu immédiatement et, le cas échéant, un autre traitement doit être entrepris

Insuffisance hépatique

Le telmisartan ne doit pas être administré aux patients atteints de cholestase, de troubles biliaires obstructifs ou d'insuffisance hépatique grave, puisque le telmisartan est en grande partie éliminé avec la bile. On peut s'attendre à ce que ces patients présentent une clairance hépatique réduite pour le telmisartan. Le telmisartan ne doit être administré qu'avec prudence chez les patients atteints d'insuffisance hépatique légère à modérée

L'hypertension rénovasculaire

Le risque d'hypotension grave et d'insuffisance rénale est accru lorsque les patients présentant une sténose bilatérale de l'artère rénale ou une sténose de l'artère à un seul rein fonctionnel sont traités avec des médicaments qui agissent sur le système rénine-angiotensine-aldostérone

Insuffisance rénale et transplantation rénale

Lorsque le telmisartan est utilisé chez des patients présentant une insuffisance rénale, il est recommandé de surveiller périodiquement les taux sériques de potassium et de créatinine. Il n'existe aucune expérience concernant l'administration du telmisartan chez les patients ayant récemment subi une transplantation rénale

Hypovolémie intravasculaire

Une hypotension symptomatique, surtout après la première dose de Telmisartan, peut survenir chez les patients dont le volume et/ou le sodium sont diminués par un traitement diurétique vigoureux, une restriction en sel alimentaire, la diarrhée ou des vomissements. De telles conditions doivent être corrigées avant l'administration du Telmisartan. Le volume et/ou la déplétion en sodium doivent être corrigés avant l'administration du Telmisartan

Double blocage du système rénine-angiotensine-aldostérone (RAAS)

Il a été démontré que l'utilisation concomitante d'inhibiteurs de l'ECA, d'antagonistes des récepteurs de l'angiotensine II ou d'aliskirène augmente le risque d'hypotension, d'hyperkaliémie et de diminution de la fonction rénale (incluant l'insuffisance rénale aiguë). Le double blocage du RAAS par l'utilisation combinée d'inhibiteurs de l'ECAA, d'antagonistes des récepteurs de l'angiotensine II ou d'aliskirène n'est donc pas recommandé. Si un traitement à double blocage est jugé absolument nécessaire, il ne doit être administré que sous la supervision d'un spécialiste et sous surveillance étroite et fréquente de la fonction rénale, des électrolytes et de la tension artérielle

Les inhibiteurs de l'ECA et les antagonistes des récepteurs de l'angiotensine II ne doivent pas être utilisés en concomitance chez les patients atteints de néphropathie diabétique

Autres conditions avec stimulation du système rénine-angiotensine-aldostérone

Chez les patients dont le tonus vasculaire et la fonction rénale dépendent principalement de l'activité du système rénine-angiotensine-aldostérone (p. ex. les patients atteints d'insuffisance cardiaque congestive grave ou d'insuffisance rénale sous-jacente, y compris la sténose artérielle rénale), le traitement avec des médicaments qui affectent ce système comme le telmisartan est associé à une hypotension aiguë, une hyperazotamie, une oligurie, voire rarement à un échec rénal aigu

Aldostéronisme primaire

Les patients atteints d'aldostéronisme primaire ne répondent généralement pas aux médicaments antihypertenseurs agissant par inhibition du système rénine-angiotensine. Par conséquent, l'utilisation du telmisartan n'est pas recommandée

Sténose valvulaire aortique et mitrale, cardiomyopathie hypertrophique obstructive

Comme pour les autres vasodilatateurs, une prudence particulière s'impose chez les patients souffrant de sténose aortique ou mitrale ou de cardiomyopathie hypertrophique obstructive

Les patients diabétiques traités avec de l'insuline ou des anti-diabétiques

Chez ces patients, l'hypoglycémie peut survenir sous traitement au telmisartan. Par conséquent, chez ces patients, une surveillance appropriée de la glycémie devrait être envisagée ; un ajustement de la dose d'insuline ou d'antidiabétiques peut être nécessaire, le cas échéant

Hyperkalaémie

L'utilisation de médicaments qui affectent le système rénine-angiotensine-aldostérone peut provoquer une hyperkaliémie

Chez les personnes âgées, les patients souffrant d'insuffisance rénale, les patients diabétiques, les patients traités en concomitance avec d'autres médicaments susceptibles d'augmenter le taux de potassium et/ou les patients présentant des événements intercurrents, l'hyperkaliémie peut être mortelle

Avant d'envisager l'utilisation concomitante de médicaments qui affectent le système rénine-angiotensine-aldostérone, il convient d'évaluer le rapport bénéfice-risque

Les principaux facteurs de risque d'hyperkaliémie à considérer sont les suivants:

- Diabète sucré, insuffisance rénale, âge (>70 ans)

- Combinaison avec un ou plusieurs autres médicaments qui affectent le système rénine-angiotensine-aldostérone et/ou les suppléments de potassium. Les médicaments ou classes thérapeutiques de médicaments qui peuvent provoquer l'hyperkaliémie sont des substituts salins contenant du potassium, des diurétiques d'épargne potassique, des inhibiteurs de l'ECA, des antagonistes des récepteurs de l'angiotensine II, des anti-inflammatoires non stéroïdiens (AINS, dont les inhibiteurs sélectifs de la COX-2), des héparines, des immunosuppresseurs (cyclosporine ou tacrolimus) et du triméthoprime.

- Événements intercurrents, en particulier déshydratation, décompensation cardiaque aiguë, acidose métabolique, aggravation de la fonction rénale, aggravation soudaine de l'affection rénale (par ex. maladies infectieuses), lyse cellulaire (par ex. ischémie aiguë des membres, rhabdomyolyse, traumatisme étendu)

Il est recommandé de surveiller étroitement le taux de potassium sérique chez les patients à risque

Le sorbitol

Ce médicament contient du sorbitol (E420). Les patients présentant de rares problèmes héréditaires d'intolérance au fructose ne devraient pas prendre le telmisartan

Les différences ethniques

Comme on l'a observé pour les inhibiteurs de l'enzyme de conversion de l'angiotensine, le telmisartan et les autres antagonistes des récepteurs de l'angiotensine II sont apparemment moins efficaces pour abaisser la tension artérielle chez les Noirs que chez les non Noirs, peut-être en raison de la prévalence accrue des états hypertendus de faible taux de rénine dans la population noire

Autre

Comme pour tout agent antihypertenseur, une réduction excessive de la tension artérielle chez les patients atteints de cardiopathie ischémique ou de maladie cardiovasculaire ischémique pourrait entraîner un infarctus du myocarde ou un AVC

Interaction avec d'autres médicaments et autres formes d'interaction

La digoxine

Lorsque le telmisartan a été administré en concomitance avec la digoxine, on a observé des augmentations médianes des concentrations plasmatiques maximales (49 %) et minimales (20 %) de la digoxine. Lors de l'instauration, de l'ajustement et de l'arrêt du telmisartan, surveiller les taux de digoxine afin de les maintenir dans la plage thérapeutique

Le lithium

Des augmentations réversibles des concentrations sériques de lithium et de la toxicité ont été signalées pendant l'administration concomitante de lithium et d'antagonistes des récepteurs de l'angiotensine II, dont TELMISARTAN. Par conséquent, surveiller les concentrations sériques de lithium pendant l'utilisation concomitante

Anti-inflammatoires non stéroïdiens, y compris les inhibiteurs sélectifs de la cyclooxygénase-2 (inhibiteurs de la COX-2):

Chez les patients âgés, présentant une hypovolémie (y compris ceux qui suivent un traitement diurétique) ou une insuffisance rénale, l'administration concomitante d'AINS, y compris des inhibiteurs sélectifs de la COX-2, et d'antagonistes des récepteurs de l'angiotensine II, dont le telmisartan, peut entraîner une détérioration de la fonction rénale, voire une insuffisance rénale aiguë. Ces effets sont généralement réversibles. Surveiller périodiquement la fonction rénale chez les patients traités par le telmisartan et les AINS

Ramipril et Ramiprilat : L'administration concomitante de 80 mg de telmisartan une fois par jour et de 10 mg de ramipril une fois par jour à des sujets sains augmente la Cmax et l'ASC du ramipril 2,3 et 2,1 fois, respectivement, et celles du ramiprilat 2,4 et 1,5 fois, respectivement. En revanche, la Cmax et l'ASC du telmisartan diminuent respectivement de 31 % et 16 %. Lorsque le telmisartan et le ramipril sont administrés en concomitance, la réponse peut être plus importante en raison des effets pharmacodynamiques additifs possibles des médicaments combinés et de l'exposition accrue au ramipril et au ramiprilat en présence du telmisartan. L'emploi concomitant du telmisartan et du ramipril n'est pas recommandé. Autres médicaments : L'administration concomitante de telmisartan n'a pas entraîné d'interaction cliniquement significative avec l'acétaminophène, l'amlodipine, le glyburide, la simvastatine, l'hydrochlorothiazide, la warfarine ou l'ibuprofène. Le telmisartan n'est pas métabolisé par le système du cytochrome P450 et n'a eu aucun effet in vitro sur les enzymes du cytochrome P450, sauf une inhibition du CYP2C19. Le telmisartan ne devrait pas interagir avec les médicaments qui inhibent les enzymes du cytochrome P450 ; il ne devrait pas non plus interagir avec les médicaments métabolisés par les enzymes du cytochrome P450, sauf en cas d'inhibition du métabolisme des médicaments métabolisés par le CYP2C19

Utilisation dans une population spécifique

Grossesse Effets tératogènes, catégories de grossesse C (premier trimestre) et D (deuxième et troisième trimestres)

Mères qui allaitent On ne sait pas si le telmisartan est excrété dans le lait humain, mais il a été démontré que le telmisartan est présent dans le lait des rates qui allaitent. En raison de la possibilité d'effets indésirables sur le nourrisson, décider s'il faut cesser l'allaitement ou cesser le médicament, en tenant compte de l'importance du médicament pour la mère

Utilisation pédiatrique L'innocuité et l'efficacité chez les patients pédiatriques n'ont pas été établies

Usage à des fins gériatriques

Sur le nombre total de patients recevant le Telmisartan dans les études cliniques sur l'hypertension, 551 (19 %) étaient âgés de 65 à 74 ans et 130 (4 %) avaient 75 ans ou plus. Aucune différence globale d'efficacité et d'innocuité n'a été observée chez ces patients par rapport aux patients plus jeunes, et d'autres expériences cliniques rapportées n'ont pas identifié de différences dans les réponses entre les patients âgés et les patients plus jeunes, mais une plus grande sensibilité chez certaines personnes âgées ne peut être écartée

Insuffisance hépatique Surveiller attentivement et remonter lentement chez les patients atteints de troubles obstructifs biliaires ou d'insuffisance hépatique

EFFETS INDÉSIRABLES: Résumé du profil d'innocuité : Les réactions indésirables graves aux médicaments comprennent les réactions anaphylactiques et l'œdème de Quincke, qui peuvent survenir rarement (≥ 1/10 000 à <1/1 000), et l'insuffisance rénale aiguë. L'incidence globale des réactions indésirables signalées avec le telmisartan était habituellement comparable au placebo (41,4 % vs 43,9 %) dans les essais contrôlés menés chez des patients traités pour hypertension. L'incidence des effets indésirables n'était pas liée à la dose et ne montrait aucune corrélation avec le sexe, l'âge ou la race des patients. Le profil d'innocuité du telmisartan chez les patients traités pour la réduction de la morbidité cardiovasculaire était conforme à celui obtenu chez les patients hypertendus ; les effets indésirables énumérés ci-dessous ont été cumulés à partir d'essais cliniques contrôlés chez des patients traités pour hypertension et de rapports post-commercialisation. La liste tient également compte des effets indésirables graves et des effets indésirables entraînant l'arrêt du traitement signalés dans trois études cliniques de longue durée, dont 21 642 patients traités par le telmisartan pour réduire la morbidité cardiovasculaire pendant une période maximale de six ans. Liste tabulée des effets indésirables :**Les effets indésirables ont été classés par ordre de fréquence selon la convention suivante : très fréquents (≥1/10) ; fréquents (≥1/100 à <1/10) ; peu fréquents (≥1/1 000 à <1/100) ; rares (≥1/10 000 à <1/1 000) ; rares (≥1/10 000 à <1/1 000) ; très rares (<1/10 000). Dans chaque groupe de fréquence, les effets indésirables sont présentés selon un ordre décroissant de gravité.** Infections et contaminations : **Peu commun : Infection des voies urinaires, y compris cystite, infection des voies respiratoires supérieures, y compris pharyngite et sinusite, Rare : Septicémie, y compris issue fatale**

1)**Le sang et les troubles du système lymphatique** :Peu commun :Anémie,Rare :Éosinophilie, thrombocytopénie,**2)Troubles du système immunitaire :** Rare : Réaction anaphylactique,, hypersensibilité.3)**Troubles du métabolisme et de la nutrition :** Peu commun : Hyperkalaémie, Rare : Hypoglycémie (chez les patients diabétiques).4) **Troubles psychiatriques** : Peu commun : Insomnie, dépression, Rare : Anxiété, 5)**Troubles du système nerveux :** Peu commun : Syncope, Rare : Somnolence,6) **Troubles oculaires :** Rare : Troubles de l'acuité visuelle,7)**Troubles de l'oreille et du labyrinthe :** Peu commun : Vertige,8)**Troubles cardiaques :** Peu commun : Bradycardie, Rare : Tachycardie,9) **Troubles vasculaires :** Peu commun : Hypotension, hypotension orthostatique,10) **Troubles respiratoires, thoraciques et médiastinaux :** Peu commun : Dyspnée, toux, Très rare : Maladie pulmonaire interstitielle,11) **Troubles gastro-intestinaux :** Peu commun : Douleurs abdominales, diarrhée, dyspepsie, flatulence, vomissements, rare : Sécheresse de la bouche, inconfort à l'estomac, dysgueusie,12)**Troubles hépato-biliaires**- Rare : Fonction hépatique anormale/trouble hépatique,13) **Troubles de la peau et des tissus sous-cutanés** : Peu commun : Prurit, hyperhidrose, éruption cutanée, Rare : Œdème de Quincke (également avec issue fatale), eczéma, érythème, urticaire, éruption de médicaments, éruption cutanée toxique,14) **Troubles musculo-squelettiques et du tissu conjonctif**- Peu commun : Douleurs dorsales (p. ex. sciatique), spasmes musculaires, myalgie, myalgie, Rare : Arthralgie, douleur aux extrémités, douleur aux tendons (symptômes semblables à ceux d'une tendinite)15) Troubles rénaux et urinaires - Peu fréquents : Insuffisance rénale, y compris insuffisance rénale aiguë,16) Troubles généraux et affections au point d'administration - Peu fréquents : Douleur thoracique, asthénie (faiblesse), Rare : Maladie de type grippal,17) Enquêtes - Peu fréquent : Augmentation de la créatinine sanguine. Rare : L'hémoglobine a diminué, l'acide urique sanguin a augmenté, l'enzyme hépatique a augmenté, la créatine sanguine phosphokinase a augmenté

Description des effets indésirables sélectionnés:

Septicémie: Dans l'étude PRoFESS, on a observé une incidence accrue de septicémie avec le telmisartan comparativement au placebo. L'événement peut être une découverte fortuite ou être lié à un mécanisme actuellement inconnu

L'hypotension: Cet effet indésirable a été signalé comme étant fréquent chez les patients dont la tension artérielle était contrôlée et qui recevaient du telmisartan pour la réduction de la morbidité cardiovasculaire en plus des soins standard

Fonction hépatique anormale / trouble hépatique: La plupart des cas d'anomalies de la fonction hépatique ou de troubles hépatiques observés après la commercialisation du produit sont survenus chez des patients japonais. Les patients japonais sont plus susceptibles d'éprouver ces effets indésirables

Maladie pulmonaire interstitielle: Des cas de pneumopathie interstitielle ont été signalés après la commercialisation en association temporelle avec la prise de telmisartan. Toutefois, aucun lien de causalité n'a été établi

SURDOSAGE

On dispose de peu de données sur le surdosage chez l'humain. La manifestation la plus probable d'un surdosage avec les comprimés de Telmisartan serait l'hypotension, les étourdissements et la tachycardie ; la bradycardie pourrait se manifester par une stimulation parasympathique (vagale). En cas d'hypotension symptomatique, un traitement de soutien doit être instauré. Le telmisartan n'est pas éliminé par hémodialyse

Précautions particulières de stockage: Conserver dans l'emballage d'origine à une température inférieure à 30°C. Tenir hors de portée des enfants

Présentation: Blister Alu-Alu de 3 x 10 comprimés

Alu/Alu Emballage blister: 3 x 10 Comprimés

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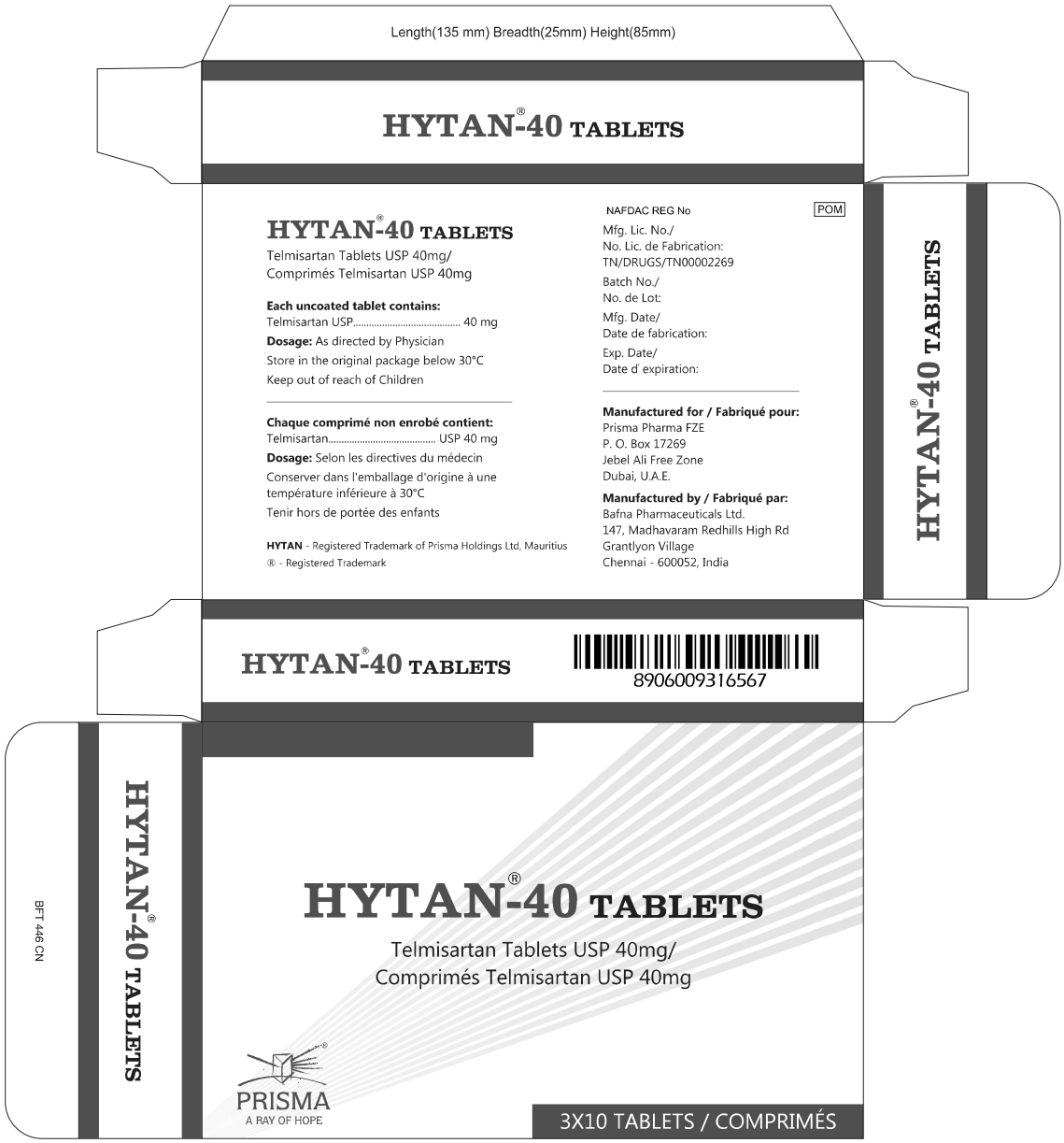
Length (210mm) x Height (297mm)

1.3.2 Labeling (outer & inner labels)

Labeling (outer & inner labels) - Enclosed.



Artworks Check list

Customer Name		**Unvanished Area**	Yes
Manufacturing facility	Grantlyon	**Mfg.Lic.No**	TN/DRUGS/TN00002269
Job Name	Hytan - 40 Tablets	**Batch.No/Exp.Date**	Yes
Country	Kenya	**Storage Condition**	Yes
Language	English		
Dimension	Length(135 mm) Breadth(25mm) Height(85mm)		Orange
Type	Carton		Red
Style	Reverse Tuck in Flap		C(100)xM(100)xY(0)xK(0)
Substrate	320 GSM / Cyber XL		C(100)xM(0)xY(0)xK(0)
Mill	ITC		Black
Varnish / Finish	Aqueous Coating	**Printing**	Front side only
Braille / Embossing			Carton Key line
Barcode	8906009316567	**Manufacturer Logo & Address**	Yes
Registration Code No		**Marketeer Logo & Address**	No
Item Code No	BFT 346 CN	**Bafna Reference file no**	
Special Note		**Software used**	Corel Draw 13

Artist	Regulatory	Manager	QC	QA	
Sign	Sign	Sign	Sign	Sign	

Measurement: (136 mm Aluminium Blister Foil)
Space – 5 mm
Printed Matter Area – 115 mm (with b.no, etc details)
Space – 16 mm
Repeated Printed Matter – 62 mm