Telarb®
(Telmisartan)

1. NAME OF THE PRODUCT
Telarb® (Telmisartan) 20mg Tablet
Telarb® (Telmisartan) 40mg Tablet
Telarb® (Telmisartan) 80mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Telarb® 20mg Tablet
Each film coated tablet contains:
Telmisartan USP.....20mg

Telarb® 40mg Tablet
Each film coated tablet contains:
Telmisartan USP.....40mg

Telarb® 80mg Tablet
Each film coated tablet contains:
Telmisartan USP.....….80mg

3. PHARMACEUTICAL FORM
Film coated tablet

Appearance:
Telarb® 20mg Tablet: Pink colored, oval shaped film coated tablet, plain on one side and break line on other side.
Telarb® 40mg Tablet: Light brown colored, oblong shaped film coated tablet, plain from both sides.
Telarb® 80mg Tablet: Purple colored, oval shaped film coated tablet, plain from both sides.

4. CLINICAL PARTICULARS
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 40mg once daily. Some patients may already benefit at a daily dose of 20mg. In cases where the target blood pressure is not achieved, the dose of **Telarb®** can be increased to a maximum of 80mg once daily. Alternatively, **Telarb®** 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 **Telarb®**. 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 80mg once daily. It is not known whether doses lower than 80mg of telmisartan are effective in reducing cardiovascular morbidity. When initiating **Telarb®** therapy for the reduction of cardiovascular morbidity, close monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Special populations:

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

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

Elderly patients: No dose adjustment is necessary for elderly patients.

Paediatric population: The safety and efficacy of **Telarb®** in children and adolescents aged below 18 have not been established.

Method of administration:

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

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.

The concomitant use of Telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73m^2).

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 reninangiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect

this system such as telmisartan has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

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 dehydration, 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 ischaemia, rhabdomyolysis, extend trauma).

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

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

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

Intestinal angioedema: Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists. These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, Telmisartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:

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 (ciclosporin 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. spironolactone, 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 nonselective 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.

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.

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

4.6. FERTILITY, PREGNANCY AND LACTATION:

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

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.

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.

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:

Adverse reactions have been ranked under headings of frequency using the following convention: Very common (≥1/10), common (≥1/100 to <1/10),

uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), 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.
Blood and lymphatic system disorders:
Uncommon: Anaemia.
Rare: Eosinophilia, thrombocytopenia.
Immune system disorders
Rare: Anaphylactic reaction, hypersensitivity.
Metabolism and nutrition disorders:
Uncommon: Hyperkalemia.
Rare: Hypoglycaemia (in diabetic patients).
Psychiatric disorders:
Uncommon: Insomnia, depression.
Rare: Anxiety.
Nervous system disorders:
Uncommon: Syncope.
Rare: Somnolence.
Eye disorders:
Rare: Vision disturbance.
Eye and labyrinth disorders:
Uncommon: Vertigo.
Cardiac disorders:
Uncommon: Bradycardia.
Rare: Tachycardia.
Vascular disorders:
Uncommon: Hypotension, orthostatic hypotension.
Respiratory, thoracic and mediastinal disorders:
Uncommon: Dyspnoea.
Very rare: Interstitial lung disease.
Gastrointestinal disorders:
Uncommon: Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting.
Rare: Dry mouth, stomach discomfort, dysgeusia.
Hepato-biliary disorders:
Rare: Hepatic function abnormal/liver disorder.
Skin and subcutaneous tissue disorders:
Uncommon: Pruritus, hyperhidrosis, rash.
Rare: Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption.

Musculoskeletal and connective tissue disorders:
Uncommon: Back pain (e.g. sciatica), muscle spasms, myalgia.
Rare: Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms).
Renal and urinary disorders:
Uncommon: Renal impairment including acute renal failure.
General disorders and administration site conditions:
Uncommon: Chest pain, asthenia (weakness).
Rare: Influenza-like illness.
Investigations:
Uncommon: Blood creatinine increased.
Rare: Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased.

4.9. OVERDOSE:

There is limited information available with regard to overdose in humans.
Symptoms: The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia dizziness, increase in serum creatinine, and acute renal failure have also been reported.
Treatment: Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdosage. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacement given quickly.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Angiotensin II Antagonists, 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 characterized 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 80mg 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.

5.2. PHARMACOKINETICS 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% (40mg dose) to approximately 19% (160mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

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

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

Elimination: Telmisartan is characterized by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy. After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1% of dose. Total plasma clearance (C_{ltot}) is high (approximately 1,000ml/min) compared with hepatic blood flow (about 1,500ml/min).

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 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:

Telarb® 20mg Tablet:

- Microcrystalline cellulose
- Meglumine
- Crosscarmellose sodium
- Crospovidone
- Sodium starch glycolate
- Sodium hydroxide pellets
- Magnesium stearate
- Isopropyl alcohol
- Purified water
- Hydroxypropyl methyl cellulose
- Polyethylene glycol
- Polyvinyl pyrrolidone
- Titanium dioxide
- Talcum powder
- Erythrosine lake color

Telarb® 40mg Tablet:

- Microcrystalline cellulose
- Meglumine
- Crosscarmellose sodium
- Crospovidone
- Sodium starch glycolate
- Sodium hydroxide pellets
- Magnesium stearate
- Isopropyl alcohol
- Purified water
- Hydroxypropyl methyl cellulose
- Polyethylene glycol
- Polyvinyl pyrrolidone

- Titanium dioxide
- Talcum powder
- Brown HT lake color

Telarb® 80mg Tablet:

- Microcrystalline cellulose
- Meglumine
- Crosscarmellose sodium
- Crospovidone
- Sodium starch glycolate
- Sodium hydroxide pellets
- Magnesium stearate
- Isopropyl alcohol
- Purified water
- Hydroxypropyl methyl cellulose
- Polyethylene glycol
- Polyvinyl pyrrolidone
- Titanium dioxide
- Talcum powder
- Amaranth lake color

6.2. INCOMPATIBILITIES:

Not applicable.

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Telarb® 20mg Tablet: Alu/Alu blister, pack size is 14's.
Telarb® 40mg Tablet: Alu/Alu blister, pack size is 14's.
Telarb® 80mg Tablet: Alu/Alu blister, pack size is 14's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Any unused product should be disposed of in accordance to local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

Telarb® 20mg Tablet: USP Specs.

Telarb® 40mg Tablet: USP Specs.
Telarb® 80mg Tablet: USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

Telarb® 20mg Tablet: 083158
Telarb® 40mg Tablet: 083157
Telarb® 80mg Tablet: 083159

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Telarb® 20mg Tablet: 15th March, 2017
Telarb® 40mg Tablet: 15th March, 2017
Telarb® 80mg Tablet: 15th March, 2017

10. DATE OF REVISION OF THE TEXT

ٹیل آرب® ٹیبلٹ

(ٹیلمیسارٹن)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری

سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔