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

TELSAR BETA

1. **Generic Name**

   Telmisartan and Metoprolol (ER) Tablets

2. **Qualitative and quantitative composition**

   TELSAR BETA 25

   Each film coated bilayered tablet contains:

   Telmisartan I.P. …….40 mg

   Metoprolol Succinate I.P. 23.75 mg

   equivalent to Metoprolol Tartrate …….25 mg

   (As Extended Release Form)

   Excipients……q.s.

   Colours: Tartrazine, Red Oxide of Iron & Titanium Dioxide I.P.

   The excipients used are Di Basic Calcium Phosphate, Acrypol, Methocel K 100 M, Titanium Dioxide, Talc Powder, Magnesium Stearate, Acrypol / Carbopol 71 G, Microcrystalline Cellulose, Lactose, Crospovidone XL – 10, Croscarmellose Sodium, Tartrazine Lake Colour, PVPK – 30, Talc Powder, Colloidal Silicon Dioxide, Meddi Coatt UNI – (WT 335), Red Oxide Of Iron Lake Colour, Isopropyl Alcohol and Methylene Chloride.

   TELSAR BETA 50

   Each film coated bilayered tablet contains:

   Telmisartan I.P. …….40 mg

   Metoprolol Succinate I.P. 47.50 mg

   equivalent to Metoprolol Tartrate ……..50 mg

   (As Extended Release Form)

   Excipients……q.s.

   Colours: Tartrazine, Red Oxide of Iron & Titanium Dioxide I.P.

   The excipients used are Di Basic Calcium Phosphate, Acrypol, Methocel K 100 M, Titanium Dioxide, Talc Powder, Magnesium Stearate, Acrypol / Carbopol 71 G, Microcrystalline Cellulose, Lactose, Crospovidone XL – 10, Croscarmellose Sodium, Tartrazine Lake Colour, PVPK – 30, Talc Powder, Colloidal Silicon Dioxide, Meddi Coatt UNI – (WT 335), Red Oxide Of Iron Lake Colour, Isopropyl Alcohol and Methylene Chloride.

3. **Dosage form and strength**

   TELSAR BETA 25

Dosage form: Film coated bilayered tablet

Strength: Telmisartan I.P 40 mg and Metoprolol Tartrate 25 mg

TELSAR BETA 50

Dosage form: Film coated bilayered tablet

Strength: Telmisartan I.P 40 mg and Metoprolol Tartrate 50 mg

4. Clinical particulars

4.1 Therapeutic indication

TELSAR BETA is indicated for the treatment of essential hypertension.

4.2 Posology and method of administration

Posology

Dose: As directed by the Physician.

Method of administration

TELSAR BETA Film coated bilayered tablets should be administered orally.

4.3 Contraindications

- Hypersensitivity to telmisartan or metoprolol or related derivatives or any other β-blockers 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 < 60 ml/min/1.73 m2)
- Second-or third-degree atrioventricular block
- Uncontrolled heart failure
- Clinically relevant sinus bradycardia (< 45-50 bpm)
- Sick sinus syndrome (unless a pacemaker is in situ).
- Prinzmetal's angina
- Myocardial infarction complicated by significant bradycardia, first degree heart block, systolic hypotension (less than 100mmHg) and/or severe heart failure and cardiogenic shock
- Severe peripheral arterial disease
- Asthma and history of bronchospasm
- Untreated pheochromocytoma
- Metabolic acidosis

- Concomitant intravenous administration of calcium blockers of the type verapamil or diltiazem or other antiarrhythmics (such as disopyramide) is contraindicated (exception: intensive care unit).
- Hypotension
- Diabetes if associated with frequent episodes of hypoglycaemia
- Chronic obstructive pulmonary disease

4.4 Special warnings and precautions for use

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue the product as soon as possible.

Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Telmisartan

Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hepatic impairment

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

Intravascular hypovolaemia

Symptomatic hypotension, especially after the first dose of TELSAR BETA, 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 TELSAR BETA. Volume and/or sodium depletion should be corrected prior to administration of TELSAR BETA.

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 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 ischemia, rhabdomyolysis, extend trauma).

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

Ethnic differences

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

Other

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

Metoprolol

Abrupt cessation of therapy with a beta-blocker should be avoided especially in patients with ischaemic heart disease. When possible, metoprolol should be withdrawn gradually over a period of 10 days, the doses diminishing to 25mg for the last 6 days. If necessary, at the same time, initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop. When it has been decided to interrupt a beta-blockade in preparation for surgery, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypertension may be increased as well. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. The patient may be protected against vagal reactions by intravenous administration of atropine. During its withdrawal the patient should be kept under close surveillance.

Although cardioselective beta blockers may have less effect on lung function than non-selective beta blockers these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use. Although metoprolol has proved safe in a large number of asthmatic patients, it is advisable to exercise care in the treatment of patients with chronic obstructive pulmonary disease. Therapy with a beta2-stimulant may become necessary or current therapy require adjustment. Therefore, non selective beta blockers should not be used for these patients, and beta1-selective blockers only with the utmost care.

Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta blocker should be gradual.

Metoprolol Tartrate tablets may not be administered to patients with untreated congestive heart failure. The congestive heart failure needs to be brought under control first of all. If concomitant digoxin treatment is taking place, it must be borne in mind that both medicinal products slow AV conduction and that there is therefore a risk of AV dissociation. In addition, mild cardiovascular complications may occur, manifesting as dizziness, bradycardia, and a tendency to collapse.

When a beta blocker is being taken, a serious, sometimes even life-threatening deterioration in cardiac function can occur, in particular in patients in whom the action of the heart is dependent on the presence of sympathetic system support. This is due less to an excessive beta-blocking effect and more to the fact that patients with marginal heart function tolerate poorly a reduction in sympathetic nervous system activity, even where this reduction is slight. This causes contractility to become weaker and the heart rate to reduce and slows down AV conduction. The consequence of this can be pulmonary oedema, AV block, and shock. Occasionally, an existing AV conduction disturbance can deteriorate, which can lead to AV block. In patients with a pheochromocytoma, an alpha blocker should be given concomitantly.

Before a patient undergoes an operation, the anaesthetist must be informed that metoprolol is being taken. Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.

Beta-blockers mask some of the clinical signs of thyrotoxicosis. Therefore, Metoprolol should be administered with caution to patients having, or suspected of developing, thyrotoxicosis, and both thyroid and cardiac function should be monitored closely.

Simultaneous administration of adrenaline (epinephrine), noradrenaline (norepinephrine) and β blockers may lead to increase in blood pressure and bradycardia.

Metoprolol may induce or aggravate bradycardia, symptoms of peripheral arterial circulatory disorders and anaphylactic shock. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dosage should be reduced.

Metoprolol may be administered when heart failure has been controlled. Digitalisation and/or diuretic therapy should also be considered for patients with a history of heart failure or patients known to have a poor cardiac reserve.

Metoprolol may reduce the effect of diabetes treatment and mask the symptoms of hypoglycaemia. The risk of a carbohydrate metabolism disorder or masking of the symptoms of hypoglycaemia is lower when using metoprolol prolonged release tablets than when using regular tablet forms for beta1 selective beta blockers and significantly lower than when using nonselective beta blockers. In labile and insulin-dependent diabetes, it may be necessary to adjust the hypoglycaemic therapy.

In case of unstable or insulin-dependent diabetes mellitus, it may be necessary to adjust the hypoglycaemic treatment (because of the likelihood of severe hypoglycaemic conditions).

In patients with significant hepatic dysfunction it may be necessary to adjust the dosage because metoprolol undergoes biotransformation in the liver. Patients with hepatic or renal insufficiency may need a lower dosage, and metoprolol is contraindicated in patients with hepatic or renal disease/failure. The elderly should be treated with caution, starting with a lower

dosage but tolerance is usually good in the elderly. It may be necessary to use a lower strength formulation in elderly patients and patients with hepatic or renal impairment and an alternative product should be prescribed.

Patients with anamnestically known psoriasis should take beta-blockers only after careful consideration as the medicine may cause aggravation of psoriasis.

Beta blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Adrenaline (epinephrine) treatment does not always give the desired therapeutic effect in individuals receiving beta blockers.

Beta blockers may unmask myasthenia gravis.

In the presence of liver cirrhosis, the bioavailability of metoprolol may be increased, and dosage should be adjusted accordingly.

Dry eyes either alone or, occasionally, with skin rashes has occurred. In most cases the symptoms cleared when metoprolol treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such effects occur, discontinuation of metoprolol should be considered.

4.5 Drugs interactions

Telmisartan

Digoxin

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

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia. The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporine 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 reported study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC_{0-24} and Cmax of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Diuretics (thiazide or loop diuretics)

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

To be taken into account with concomitant use.

Other antihypertensive agents

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

Clinical trial data reported 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.

Metoprolol

Anaesthetic drugs may attenuate reflex tachycardia and increase the risk of hypotension. Metoprolol therapy should be reported to the anaesthetist before the administration of a general anaesthetic. If possible, withdrawal of metoprolol should be completed at least 48 hours before anaesthesia. However, for some patients undergoing elective surgery, it may be desirable to employ a beta-blocker as premedication. By shielding the heart against the effect of stress, metoprolol may prevent excessive sympathetic stimulation which is liable to provoke such cardiac disturbance as arrhythmias or acute coronary insufficiency during induction and intubation. Anaesthetic agents causing myocardial depression, such as cyclopropane and trichlorethylene, are best avoided. In a patient under beta-blockade an anaesthetic with as little negative inotropic activity as possible (halothane/nitrous oxide) should be selected.

It may be necessary to adjust the dose of the hypoglycaemic agent in labile or insulin-dependent diabetes. Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).

Like all beta-blockers, metoprolol should not be given in combination with calcium channel blockers i.e. verapamil and to a lesser extent diltiazem since this may cause bradycardia, hypotension, heart failure and asystole and may increase auriculoventricular conduction time. However, combinations of antihypertensive drugs may often be used with benefit to improve control of hypertension. Calcium blockers of the verapamil type should not be administered intravenously to patients receiving beta blockers.

Care should also be taken when beta-blockers are given in combination with sympathetic ganglion blocking agents, other beta blockers or MAO inhibitors. Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents may increase the blood pressure lowering effect.

Calcium channel blockers (such as dihydropyridine derivatives e.g. nifedipine) should not be given in combination with metoprolol because of the increased risk of hypotension and heart failure. In patients with latent cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure. Beta-blockers used in conjunction with clonidine increase the risk of “rebound hypertension”. If combination treatment with clonidine is to be discontinued, metoprolol should be withdrawn several days before clonidine.

The effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive, and care should be taken to avoid hypotension.

NSAIDs (especially indometacin) may reduce the antihypertensive effects of beta-blockers possibly by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention.

Digitalis Glycosides and/or diuretics should be considered for patients with a previous history of heart failure or in patients known to have a poor cardiac reserve. Digitalis glycosides in association with beta-blockers may increase in auriculo-ventricular conduction time.

The administration of adrenaline (epinephrine) or noradrenaline (norepinephrine) to patients undergoing beta-blockade can result in an increase in blood pressure and bradycardia, although this is less likely to occur with beta1-selective drugs. As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity e.g.

ergotamine are given concurrently. Concurrent use of moxisylyte may result in possible severe postural hypotension.

The effect of adrenaline (epinephrine) in the treatment of anaphylactic reactions may be weakened in patients receiving beta blockers.

Metoprolol will antagonise the beta1-effects of sympathomimetic agents but should have little influence on the bronchodilator effects of beta2-agonists at normal therapeutic doses.

Enzyme inducing agents (e.g. rifampicin) may reduce plasma concentrations of metoprolol, whereas enzyme inhibitors (e.g. cimetidine, hydralazine and alcohol), selective serotonin reuptake inhibitors (SSRIs) as paroxetine, fluoxetine and sertraline, diphenhydramine, hydroxychloroquine, celecoxib, terbinafine may increase plasma concentrations of hepatically metabolized beta blockers.

As with all beta-blockers particular caution is called for when metoprolol is administered together with prazosin for the first time as the co-administration of metoprolol and prazosin may produce a first dose hypotensive effect.

Class 1 antiarrhythmic drugs, e.g. disopyramide, quinidine and amiodarone may have potentiating effects on atrial conduction time and induce negative inotropic effect. Concurrent use of propafenone may result in significant increases in plasma concentrations and half-life of metoprolol. Plasma propafenone concentrations are unaffected. Dosage reduction of metoprolol may be necessary.

During concomitant ingestion of alcohol and metoprolol the concentration of blood alcohol may reach higher levels and may decrease more slowly. The concomitant ingestion of alcohol may enhance hypotensive effects.

Metoprolol may impair the elimination of lidocaine.

Prostaglandin synthetase inhibiting drugs may decrease the hypotensive effects of beta-blockers.

Concurrent use of oestrogens may decrease the antihypertensive effect of beta-blockers because oestrogen induced fluid retention may lead to increased blood pressure.

Concurrent use of xanthines, especially aminophylline or theophylline, may result in mutual inhibition of therapeutic effects.

Xanthine clearance may also be decreased especially in patients with increased theophylline clearance induced by smoking.

Concurrent use requires careful monitoring.

Concurrent use of aldesleukin may result in an enhanced hypotensive effect.

Concurrent use of alprostadil may result in an enhanced hypotensive effect.

There is an increased risk of bradycardia following concomitant use of mefloquine with metoprolol.

Concomitant use with anxiolytics and hypnotics may result in an enhanced hypotensive effect.

Concomitant use with corticosteroids may result in antagonism of the hypotensive effect.

The manufacturer of tropisetron advises caution in concomitant administration due to the risk of ventricular arrhythmias.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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 TELSAR BETA in pregnant women. Reported 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

The concentration of metoprolol in breast milk is approximately three times higher than the one in the mother's plasma. The risk of adverse effects in the breastfeeding baby would appear to be low after administration of therapeutic doses of the medicinal product (except in individuals with poor metabolic capacity). Cases of neonatal hypoglycaemia and bradycardia have been described with beta-blockers with low plasma protein binding. Metoprolol is excreted in human milk. Even though the metoprolol concentration in milk is very low, breast-feeding should be discontinued during treatment with metoprolol. In case of treatment during breast feeding, infants should be monitored carefully for symptoms of beta blockade.

Fertility

In reported preclinical studies, no effects of TELSAR BETA 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 and fatigue may occasionally occur when taking antihypertensive therapy such as TELSAR BETA. Patient should be warned accordingly. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Telmisartan

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 reported 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 reported 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: Rare:	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting Dry mouth, stomach discomfort, dysgeusia
Hepato-biliary disorders	
Rare:	Hepatic function abnormal/liver disorder[3]
Skin and subcutaneous tissue disorders	
Uncommon:	Pruritus, hyperhidrosis, rash
Rare:	Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
Musculoskeletal and connective tissue disorders	
Uncommon:	Back pain (e.g. sciatica), muscle spasms, myalgia
Rare:	Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms)
Renal and urinary disorders	
Uncommon:	Renal impairment including acute renal failure
General disorders and administration site conditions	
Uncommon:	Chest pain, asthenia (weakness)
Rare:	Influenza-like illness
Investigations	
Uncommon:	Blood creatinine increased

Rare:	Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

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

Description of selected adverse reactions

Sepsis

In the reported 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 reported 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

Reported 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.

Metoprolol

Frequency estimates: 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); not known (cannot be estimated from the available data)

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, agranulocytosis
Psychiatric disorders	
Rare	Depression, nightmares, Nervousness, anxiety, impotence
Very rare	Hallucinations, personality disorder, Amnesia / memory impairment
Nervous system disorders	
Common	Dizziness, headache
Rare	Alertness decreased, somnolence or insomnia, paraesthesia
Eye disorders	
Very rare	Visual disturbance (e.g. blurred vision, dry eyes and/or eye irritation
Ear and labyrinth disorders	
Very rare	Tinnitus, and, in doses exceeding those recommended, "hearing disorders (eg. hypoacusis or deafness)

Cardiac disorders	
Common	Bradycardia
Rare	Heart failure, cardiac arrhythmias, palpitation
Very rare	Cardiac conduction disorders, precordial pain
Not Known	Increase in existing intermittent claudication
Vascular disorders	
Common	Orthostatic hypotension (occasionally with syncope)
Rare	Oedema, Raynaud's phenomenon
Very rare	Gangrene in patients with pre existing severe peripheral circulatory disorders
Respiratory, thoracic and mediastinal disorders	
Common	Exertional dyspnoea
Rare	Bronchospasm(which may occur in patients without a history of obstructive lung disease)
Very rare	Rhinitis
Gastrointestinal disorders	
Common	Nausea and vomiting, abdominal pain
Rare	Diarrhoea or constipation
Very rare	Dry mouth
Not Known	Retroperitoneal fibrosis *
Hepatobiliary disorders	
Not Known	Hepatitis
Skin and subcutaneous tissue disorders	
Rare	Skin rash (in the form of urticaria, psoriasiform and dystrophic skin lesions)
Very rare	Photosensitivity, hyperhidrosis, alopecia, worsening of psoriasis
Not Known	Occurrence of antinuclear antibodies (not associated with SLE)
Musculoskeletal and connective tissue disorders	
Rare	Muscle cramps
Very rare	Arthritis
Reproductive system and breast disorders	
Very rare	Disturbances of Libido and potency
Not Known	Peyronie's disease *
General disorders and administration site conditions	
Common	Fatigue
Very rare	Dysgeusia (Taste disturbances)
Investigations	
Very rare	Weight increase, liver function test abnormal

* (relationship to Metoprolol has not been definitely established).

Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.

Post Marketing Experience

The following adverse reactions have been reported during post-approval use of metoprolol: confusional state, an increase in blood triglycerides and a decrease in high density lipoprotein (HDL). Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

Telmisartan

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

Symptoms

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

Management

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.

Metoprolol

Poisoning due to an overdose of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma, nausea, vomiting, cyanosis, hypoglycaemia and, occasionally, hyperkalaemia. The first manifestations usually appear 20 minutes to two hours after drug ingestion.

After ingestion of an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive- care ward. Absorption of any drug material still present in the gastrointestinal tract can be prevented by induction of vomiting, gastric lavage, administration of activated charcoal and a laxative. Artificial respiration may be required.

Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 micrograms/minute, or dobutamine, starting with a dose of 2.5micrograms/minute, until required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous

administration of 8-10mg glucagon may be considered. If required the injection should be repeated within one hour, to be followed – if required – by an i.v. infusion of glucagon at an administration rate of 1-3mg/hour. Administration of calcium ions, or the use of a cardiac pacemaker may also be considered. In patients intoxicated with hydrophilic beta-blocking agents haemodialysis or haemoperfusion may be considered.

5. Pharmacological properties

5.1 Mechanism of Action

Telmisartan

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.

Metoprolol

Metoprolol tartrate is a cardioselective beta-adrenergic blocking agent. It has a relatively greater blocking effect on beta1-receptors (ie those mediating adrenergic stimulation of heart rate and contractility and release of free fatty acids from fat stores) than on beta2-receptors, which are chiefly involved in broncho and vasodilation.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC Code: C09CA07.

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 reported 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 reported in clinical trials directly comparing the two antihypertensive treatments.

Cardiovascular prevention

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) a reported clinical 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 reported in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo.

TRANSCEND, a reported study 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 reported "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 reported 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 reported 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 reported 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 reported 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.

As per the reported data, 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 reported clinical data do not allow to make conclusions on the efficacy and safety of telmisartan in hypertensive paediatric population.

Metoprolol

Pharmacotherapeutic group: Beta blockers, selective.

ATC code: C 07 AB 02.

5.3 Pharmacokinetic properties

Telmisartan

Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC0-∞) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Linearity/non-linearity

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

Distribution

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

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 do not differ between the elderly and those younger than 65 years.

Renal impairment

In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient patients and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Hepatic impairment

Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100 %. The elimination half-life is not changed in patients with hepatic impairment.

Metoprolol

Absorption

Metoprolol is readily and completely absorbed from the gastrointestinal tract. Metoprolol is absorbed fully after oral administration. Within the therapeutic dosage range, the plasma concentrations increase in a linear manner in relation to dosage. Peak plasma levels are achieved after approx. 1.5–2 hours. Even though the plasma profile displays a broader interindividual variability, this appears to be easily reproducible on an individual basis. Due to the extensive first-pass effect, bioavailability after a single oral dose is approx. 50%. After repeated administration, the systemic availability of the dose increases to approx. 70%. After oral intake with food, the systemic availability of an oral dose increases by [SIC] approx. 30–40%.

Distribution

Peak plasma concentrations occur about 1½ hours after a single oral dose. Peak plasma metoprolol concentrations at steady state with usual doses have been reported as 20-340ng/ ml. Metoprolol is widely distributed, it crosses the bloodbrain barrier, the placenta. It is slightly bound to plasma protein. The medicinal product is approx. 5–10% bound to plasma proteins.

Biotransformation

Metoprolol is metabolised through oxidation in the liver mainly by the CYP2D6 isoenzyme. Even though three main metabolites have been identified, none of them has a clinically significant beta-blocking effect. Generally, 95% of an oral dose is found in the urine. Only 5% of the dose is excreted unmodified via the kidneys; in isolated cases, this figure can reach as high as 30%. The elimination half-life of metoprolol averages 3.5 hours (with extremes of 1 and 9 hours). Total clearance is approx. 1 litre/minute. It is extensively metabolised in the liver; O-dealkylation followed by oxidation and aliphatic hydroxylation. The rate of hydroxylation to alpha-hydroxymetoprolol is reported to be determined by genetic polymorphism; the half-life of metoprolol in fast hydroxylators is stated to be 3-4 hours, whereas in poor hydroxylators it is about 7 hours.

Elimination

The metabolites are excreted in the urine together with only small amounts of unchanged metoprolol. Metoprolol is excreted in breast milk.

Special population

Elderly:

In comparison with administration to younger patients, the pharmacokinetics of metoprolol when administered to older patients shows no significant differences.

Renal impairment:

Renal dysfunction has barely any effect on the bioavailability of metoprolol. However, the excretion of metabolites is reduced. In patients with a glomerular filtration rate of less than 5 ml/minute, a significant accumulation of metabolites has been observed. This accumulation of metabolites, however, produces no increase in the beta blockade.

Hepatic impairment:

The pharmacokinetics of metoprolol are influenced only minimally by reduced hepatic function. However, in patients with serious hepatic cirrhosis and a portacaval shunt, the bioavailability of metoprolol can increase, and the total clearance can be reduced. Patients with

portacaval anastomosis had a total clearance of approx. 0.3 litres/minute and AUC values that were 6 times higher than those found in healthy persons.

Severe angina pectoris

Intrinsic sympathomimetic activity (ISA) may be a disadvantage for the patient with severe angina pectoris. There are however no indications that the efficacy in hypertensives is influenced by this characteristic. In exceptional cases, however, very high dosages can cause the ISA to predominate over the beta-adrenergic blocking capacity so that restriction of the maximum dosage is indicated.

Respiratory impairment

It has not been proven that beta-blockers with ISA give a lower risk for bronchospasm or enhancement of preexisting bronchospastic complaints.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Telmisartan

In reported 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.

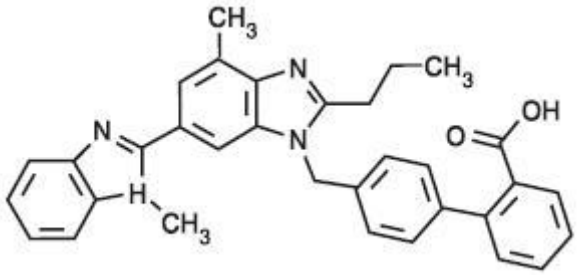
Metoprolol

There are no other relevant preclinical data than those already mentioned in other sections of this summary of product characteristics.

7. Description

Telmisartan

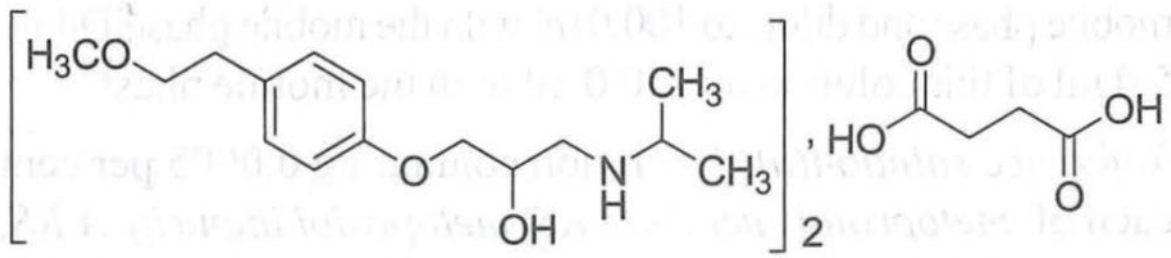
Telmisartan is chemically described as 4'-{[4-methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl}-2-biphenyl-carboxylic acid. Its empirical formula is $C_{33}H_30N_4O_2$, its molecular weight is 514.63, and its structural formula is:



Telmisartan is a white to off-white crystalline powder. It is sparingly soluble in dichloromethane; slightly soluble in methanol; practically insoluble in water.

Metoprolol Succinate

Metoprolol Succinate is (RS)-1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2- ol succinate. Having molecular formula $(C_{15}H_{25}NO_3)_2$, $C_4H_6O_4$ and molecular weight 652.8. The chemical structure is:



TELSAR BETA 25

Telmisartan and Metoprolol ER Tablets are peach colour, circular shaped, biconvex, film coated having both sides plain. The excipients used are Di Basic Calcium Phosphate, Acrypol, Methocel K 100 M, Titanium Dioxide, Talc Powder, Magnesium Stearate, Acrypol / Carbopol 71 G, Microcrystalline Cellulose, Lactose, Crospovidone XL – 10, Croscarmellose Sodium, Tartrazine Lake Colour, PVPK – 30, Talc Powder, Colloidal Silicon Dioxide, Meddi Coatt UNI – (WT 335), Red Oxide Of Iron Lake Colour, Isopropyl Alcohol and Methylene Chloride.

TELSAR BETA 50

Telmisartan and Metoprolol ER Tablets are brick colour, circular shaped, biconvex, film coated having both sides plain. The excipients used are Di Basic Calcium Phosphate, Acrypol, Methocel K 100 M, Titanium Dioxide, Talc Powder, Magnesium Stearate, Acrypol / Carbopol 71 G, Microcrystalline Cellulose, Lactose, Crospovidone XL – 10, Croscarmellose Sodium, Tartrazine Lake Colour, PVPK – 30, Talc Powder, Colloidal Silicon Dioxide, Meddi Coatt UNI – (WT 335), Red Oxide Of Iron Lake Colour, Isopropyl Alcohol and Methylene Chloride.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

TELSAR BETA is available in blister strip of 10 Tablets.

8.4 Storage and handing instructions

Store protected from light and moisture, at a temperature not exceeding 30°C.

Keep all medicines out of reach of children.

9. Patient counselling information

TELSAR BETA

Telmisartan and Metoprolol

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any questions, or if there is anything you do not understand, ask your doctor or pharmacist.
- **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What TELSAR BETA is and what it is used for

TELSAR BETA is combination of Telmisartan and Metoprolol. Telmisartan belongs to a class of medicines known as angiotensin II receptor antagonists. Angiotensin II is a substance produced in your body, which causes your blood vessels to narrow, thus increasing your blood pressure. Telmisartan blocks the effect of angiotensin II so that the blood vessels relax, and your blood pressure is lowered. Metoprolol belongs to a group of medicines called beta blockers.

TELSAR BETA is used to for the treatment of essential hypertension.

9.2 What you need to know before you take TELSAR BETA

Do not take TELSAR BETA Tablets:

- if you are allergic to telmisartan, metoprolol, other beta-blockers or any other ingredients of this medicine
- if you are more than 3 months pregnant. (It is also better to avoid TELSAR BETA in early pregnancy – see pregnancy section.)
- if you have severe liver problems such as cholestasis or biliary obstruction (problems with drainage of the bile from the liver and gall bladder) or any other severe liver disease.
- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.
- suffer with heart conduction or rhythm problems, have severe or uncontrolled heart failure, are in shock caused by heart problems
- suffer with blocked blood vessels, including blood circulation problems (which may cause your fingers and toes to tingle or turn pale or blue)
- have a slow heart rate or have suffered a heart attack which has been complicated by a significantly slow heart rate
- suffer from a tight, painful feeling in the chest in periods of rest (Prinzmetal's angina)
- have or have had breathing difficulties or asthma including COPD (Chronic Obstructive Pulmonary Disease causing cough, wheezing or breathlessness, phlegm or increase in chest infections)
- suffer with untreated pheochromocytoma (high blood pressure due to a tumour near the kidney)
- suffer from increased acidity of the blood (metabolic acidosis)
- have low blood pressure
- suffer with diabetes associated with frequent episodes of low blood sugar (hypoglycaemia)
- have liver or kidney disease or failure
- are given other medicines for blood pressure by injection especially verapamil, diltiazem or disopyramide

If any of the above applies to you, tell your doctor or pharmacist before taking TELSAR BETA.

Warnings and precautions

Talk to your doctor before taking TELSAR BETA if you are suffering or have ever suffered from any of the following conditions or illnesses:

- Kidney disease or kidney transplant
- Renal artery stenosis (narrowing of the blood vessels to one or both kidneys)
- Liver disease
- Heart trouble
- Raised aldosterone levels (water and salt retention in the body along with imbalance of various blood minerals).

- Low blood pressure (hypotension), likely to occur if you are dehydrated (excessive loss of body water) or have salt deficiency due to diuretic therapy ('water tablets'), low-salt diet, diarrhoea, or vomiting.
- Elevated potassium levels in your blood.
- Diabetes
- have a history of allergic reactions, for example to insect stings, foods or other substances,
- have controlled heart failure.
- have a slow heart rate or blood vessel disorder.
- suffer from treated pheochromocytoma(high blood pressure due to tumour near the kidney)
- have or have suffered from psoriasis (severe skin rashes)
- have liver cirrhosis
- are elderly
- have myasthenia gravis.
- If you suffer from dry eyes

Talk to your doctor before taking TELSAR BETA:

If you are taking any of the following medicines used to treat high blood pressure:

- an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have
- diabetes-related kidney problems.
- aliskiren.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals. See also information under the heading “Do not take TELSAR BETA”.

- if you are taking digoxin.

You must tell your doctor if you think you are (or might become) pregnant. TELSAR BETA is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

TELSAR BETA may be less effective in lowering the blood pressure in black patients.

Children and adolescents

The use of TELSAR BETA in children and adolescents up to the age of 18 years is not recommended.

Anaesthetics and surgery

If you are going to have an operation or an anaesthetic, please tell your doctor or dentist that you are taking Metoprolol Tartrate tablets, as your heart beat might slow down too much.

If you are taking other medicines

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may need to change the dose of these other medicines or take other precautions. In some cases you may have to stop taking one of the medicines. This applies especially to the medicines listed below taken at the same time with TELSAR BETA:

- Lithium containing medicines to treat some types of depression.
- Medicines that may increase blood potassium levels such as salt substitutes containing potassium, potassium-sparing diuretics (certain 'water tablets'), ACE inhibitors, angiotensin II receptor antagonists, NSAIDs (non-steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen), heparin, immunosuppressives (e.g. cyclosporin or tacrolimus), and the antibiotic trimethoprim.
- Diuretics ('water tablets'), especially if taken in high doses together with TELSAR BETA, may lead to excessive loss of body water and low blood pressure (hypotension).
- If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not take TELSAR BETA” and “Warnings and precautions”).
- Digoxin

The effect of TELSAR BETA may be reduced when you take NSAIDs (non-steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen) or corticosteroids.

TELSAR BETA may increase the blood pressure lowering effect of other medicines used to treat high blood pressure or of medicines with blood pressure lowering potential (e.g. baclofen, amifostine).

Furthermore, low blood pressure may be aggravated by alcohol, barbiturates, narcotics or antidepressants. You may notice this as dizziness when standing up. You should consult with your doctor if you need to adjust the dose of your other medicine while taking TELSAR BETA.

Do not take TELSAR BETA if you are already taking:

- monoamine oxidase inhibitors (MAOIs) for depression
- other blood pressure lowering medicines such as verapamil, nifedipine and diltiazem
- disopyramide or quinidine (to treat irregular heartbeat (arrhythmia)
- medicines used to treat stomach ulcers such as cimetidine
- medicines used to treat high blood pressure such as hydralazine, clonidine or prazosin
- medicines used to treat irregular heart rhythm such as amiodarone and propafenone
- medicines used to treat depression such as tricyclic or SSRI antidepressants
- medicines used to treat epilepsy such as barbiturates
- medicines used to treat mental illness such as phenothiazines
- anaesthetics such as cyclopropane or trichloroethylene
- medicines used to treat some cancers, particularly cancer of the kidney such as aldesleukin

- medicines used to treat erectile dysfunction such as alprostadil
- anxiolytics or hypnotics (e.g. temazepam, nitrazepam, diazepam)
- indometacin or celecoxib (Non-Steroidal Anti-Inflammatory Drugs (NSAIDs))
- rifampicin (antibiotic) or terbinafine (antifungal)
- oestrogens such as a contraceptive pill or hormone replacement therapy
- corticosteroids (e.g. hydrocortisone, prednisolone)
- other beta-blockers e.g. eye drops.
- adrenaline (epinephrine) or noradrenaline (norepinephrine), used in anaphylactic shock or other sympathomimetics
- medicines used to treat diabetes
- lidocaine (a local anaesthetic)
- moxisylyte (used in Raynaud's syndrome)
- medicines used to treat malaria such as mefloquine
- medicines to prevent nausea and vomiting such as tropisetron
- medicines used to treat asthma such as xanthines such as aminophylline or theophylline
- medicines to treat migraines such as ergotamine
- medicines used to treat heart conditions used
- such as cardiac glycosides e.g. digoxin
- medicines used to treat rheumatoid arthritis such as hydroxychloroquine
- diphenydramine (sedative antihistamine)

You are advised to avoid alcohol whilst taking this medicine. Alcohol may increase the blood pressure lowering effect of TELSAR BETA

Pregnancy and breast feeding

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking TELSAR BETA before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of TELSAR BETA. TELSAR BETA is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. TELSAR BETA is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

TELSAR BETA may make you feel tired and dizzy. If affected, patients should not drive or operate machinery.

9.3 How to take TELSAR BETA

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dose: As directed by Physician

If you take more TELSAR BETA than you should

If you accidentally take too many tablets, contact your doctor, pharmacist, or your nearest hospital emergency department immediately.

If you forget to take TELSAR BETA

If you forget to take a dose, do not worry. Take it as soon as you remember then carry on as before. If you do not take your tablet on one day, take your normal dose on the next day. Do not take a double dose to make up for forgotten individual doses.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you stop taking TELSAR BETA

Do not suddenly stop taking TELSAR BETA as this may cause worsening of heart failure and increase the risk of heart attack. Only change the dose or stop the treatment in consultation with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some side effects can be serious and need immediate medical attention

You should see your doctor immediately if you experience any of the following symptoms:

Sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatory response), rapid swelling of the skin and mucosa (angioedema); these side effects are rare (may affect up to 1 in 1,000 people) but are extremely serious and patients should stop taking the medicine and see their doctor immediately. If these effects are not treated they could be fatal.

Common side effects (may affect up to 1 in 10 people):

- Low blood pressure (hypotension) in users treated for reduction of cardiovascular events.
- tiredness
- dizziness
- headache
- a slow heart rate
- feeling faint on standing due to low blood pressure
- shortness of breath with or without strenuous physical activity

- feeling or being sick
- stomach pain

Uncommon side effects (may affect up to 1 in 100 people):

- Urinary tract infections, upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold)
- deficiency in red blood cells (anaemia)
- high potassium levels
- difficulty falling asleep
- feeling sad (depression)
- fainting (syncope)
- feeling of spinning (vertigo)
- slow heart rate (bradycardia)
- low blood pressure (hypotension) in users treated for high blood pressure
- dizziness on standing up (orthostatic hypotension)
- shortness of breath
- cough
- abdominal pain
- diarrhoea
- discomfort in the abdomen
- bloating, vomiting
- itching
- increased sweating
- drug rash
- back pain, muscle cramps, muscle pain (myalgia)
- kidney impairment including acute kidney failure
- pain in the chest, feeling of weakness
- increased level of creatinine in the blood.

Rare side effects (may affect up to 1 in 1,000 people):

- Sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatory response which can lead to death),
- increase in certain white blood cells (eosinophilia),low platelet count (thrombocytopenia),

- severe allergic reaction (anaphylactic reaction), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure),
- low blood sugar levels (in diabetic patients),
- feeling anxious, somnolence, impaired vision,
- fast heart beat (tachycardia),
- dry mouth, upset stomach, taste disturbance (dysgeusia),
- abnormal liver function (Japanese patients are more likely to experience this side effect),
- rapid swelling of the skin and mucosa which can also lead to death (angioedema also with fatal outcome), eczema (a skin disorder), redness of skin, hives (urticaria), severe drug rash,
- joint pain (arthralgia), pain in extremity, tendon pain,
- flulike-illness, decreased haemoglobin (a blood protein),
- increased levels of uric acid,
- increased hepatic enzymes or creatine phosphokinase in the blood. Changes in the results of blood tests, effects on blood clotting causing easy or unexplained bruising, changes in personality, confusion, hallucinations
- visual disturbances
- dry or irritated eyes
- ringing in the ears
- loss of hearing with high doses
- heart conduction problems
- chest pain
- gangrene in patients with severe poor circulation
- runny nose
- dry mouth
- weight gain sensitivity to light
- increased sweating
- hair loss
- worsening or new psoriasis
- joint inflammation (arthritis)
- disturbances of sexual desire and performance
- changes in liver function tests
- taste disorders

Very rare side effects (may affect up to 1 in 10,000 people):

- Progressive scarring of lung tissue (interstitial lung disease)
- changes in the results of blood tests
- effects on blood clotting causing easy or unexplained bruising
- changes in personality
- confusion
- hallucinations
- visual disturbances
- dry or irritated eyes
- ringing in the ears
- loss of hearing with high doses
- heart conduction problems
- chest pain
- gangrene in patients with severe poor circulation
- runny nose
- dry mouth
- weight gain sensitivity to light
- increased sweating
- hair loss
- worsening or new psoriasis
- joint inflammation (arthritis)
- disturbances of sexual desire and performance
- changes in liver function tests
- taste disorders

Not known (frequency cannot be estimated from the available data):

- worsening or development of limping
- hepatitis (symptoms include fever, sickness and yellowing of the skin or whites of the eyes)
- Peyronie's syndrome (bending of the penis)
- symptoms of high levels of the thyroid hormone or low blood sugar may be hidden
- increase in blood fats or decrease in cholesterol
- retroperitoneal fibrosis (symptoms include lower back pain, high blood pressure)

- occurrence of antinuclear antibodies not associated with systemic lupus erythematosus (SLE).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store TELSAR BETA

Store protected from light and moisture, at a temperature not exceeding 30°C.

9.6 Contents of the pack and other information

What **TELSAR BETA** contains

The active substances **TELSAR BETA** is Telmisartan and Metoprolol Tartrate.

TELSAR BETA 25

Telmisartan I.P 40 mg and Metoprolol Tartrate 25 mg

The excipients used are Di Basic Calcium Phosphate, Acrypol, Methocel K 100 M, Titanium Dioxide, Talc Powder, Magnesium Stearate, Acrypol / Carbopol 71 G, Microcrystalline Cellulose, Lactose, Crospovidone XL – 10, Croscarmellose Sodium, Tartrazine Lake Colour, PVPK – 30, Talc Powder, Colloidal Silicon Dioxide, Meddi Coatt UNI – (WT 335), Red Oxide Of Iron Lake Colour, Isopropyl Alcohol and Methylene Chloride.

TELSAR BETA 50

Telmisartan I.P 40 mg and Metoprolol Tartrate 50 mg

The excipients used are Di Basic Calcium Phosphate, Acrypol, Methocel K 100 M, Titanium Dioxide, Talc Powder, Magnesium Stearate, Acrypol / Carbopol 71 G, Microcrystalline Cellulose, Lactose, Crospovidone XL – 10, Croscarmellose Sodium, Tartrazine Lake Colour, PVPK – 30, Talc Powder, Colloidal Silicon Dioxide, Meddi Coatt UNI – (WT 335), Red Oxide Of Iron Lake Colour, Isopropyl Alcohol and Methylene Chloride.

10. Details of manufacturer

Manufactured in India by:

Ravenbhel Healthcare Pvt. Ltd.

(WHO cGMP Certified Company)

16-17, EPIP, SIDCO, Kartholi, Bari Brahmana, Jammu-181133.

11. Details of permission or licence number with date

Mfg Lic No. JK/01/56 issued on 28.05.2016.

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TELSAR BETA 40,25/50 mg/MAY-20/01/PI