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

# CORBIS T/ TELSAR BISO

## 1. Generic Name

Bisoprolol Fumarate & Telmisartan Tablets (2.5+40mg, 5+40mg)

## 2. Qualitative and quantitative composition

**CORBIS T/ TELSAR BISO 2.5+40mg**

Each film coated tablet contains:

Bisoprolol Fumarate I.P…… 2.5 mg

Telmisartan I.P…….. 40 mg

Excipients……. q.s.

Colours: Ferric Oxide Red USP-NF & Titanium dioxide I.P.

The excipients used are Microcrystalline Cellulose, Glyceryl Behenate, Croscarmellose Sodium, Colloidal Silicon Dioxide, PVPK 30, Sodium Hydroxide Pellets, Meglumine, Isopropyl Alcohol, Methylene Chloride, Carbomer, Pearlitol, Sodium Stearyl Fumarate & Crosspovidone XL 10.

**CORBIS T/ TELSAR BISO 5+40mg**

Each film coated tablet contains:

Bisoprolol Fumarate I.P…… 5 mg

Telmisartan I.P……. 40 mg

Excipients……. q.s.

Colours: Ferric Oxide Yellow USP-NF & Titanium dioxide I.P

The excipients used are Microcrystalline Cellulose, Glyceryl Behenate, Croscarmellose Sodium, Colloidal Silicon Dioxide, PVPK 30, Sodium Hydroxide Pellets, Meglumine, Isopropyl Alcohol, Methylene Chloride, Carbomer, Pearlitol, Sodium Stearyl Fumarate & Crosspovidone XL 10.

## 3. Dosage form and strength

**Dosage form:** Film coated Tablet

**Strength:** Bisoprolol Fumarate & Telmisartan Tablets (2.5+40mg, 5+40mg)

## 4. Clinical particulars

### 4.1 Therapeutic Indication

It is indicated for the treatment of mild to moderate hypertension

### 4.2 Posology and Method of Administration

**Posology**

***Treatment of essential hypertension***

The usually effective dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, the dose of telmisartan can be increased to a maximum of 80 mg once daily. Alternatively, telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide, which has been shown to have an additive blood pressure lowering effect with telmisartan. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment.

***Cardiovascular prevention***

The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of telmisartan are effective in reducing cardiovascular morbidity.

When initiating telmisartan therapy for the reduction of cardiovascular morbidity, close monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

***Renal impairment***

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

***Hepatic impairment***

CORBIS T/ TELSAR BISO is contraindicated in patients with severe hepatic impairment.

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

***Elderly***

No dose adjustment is necessary for elderly patients.

*Paediatric population*

The safety and efficacy of CORBIS T/ TELSAR BISO in children and adolescents aged below 18 years have not been established.

**Method of administration**

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

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

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

## 4.3 Contraindications

**Telmisartan:**

- 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 < 60 ml/min/1.73 $m^2$).

**Bisoprolol:**

Bisoprolol is contraindicated in chronic heart failure patients with:

- Acute heart failure or during episodes of heart failure decompensation requiring i.v. Inotropic therapy.
- Cardiogenic shock
- Second or third degree AV block
- Sick sinus syndrome
- Sinoatrial block
- Symptomatic bradycardia
- Symptomatic hypotension
- Severe bronchial asthma
- Severe forms of peripheral arterial occlusive disease or severe forms of raynaud's syndrome.
- Untreated phaeochromocytoma
- Metabolic acidosis
- Hypersensitivity to bisoprolol or to any of the excipients.

## 4.4 Special Warnings and Precautions for Use

**Telmisartan:**

**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.

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

CORBIS T/ TELSAR BISO 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. CORBIS T/ TELSAR BISO 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 CORBIS T/ TELSAR BISO 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 CORBIS T/ TELSAR BISO in patients with recent kidney transplantation.

Intravascular hypovolaemia

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

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, hyper azotaemia, 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, immunosuppressive (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.

**Bisoprolol:**

There is no therapeutic experience of bisoprolol treatment of heart failure in patients with the following diseases and conditions:

- Insulin dependent diabetes mellitus (type I)
- Severely impaired renal function
- Severely impaired hepatic function
- Restrictive cardiomyopathy
- Congenital heart disease
- Haemodynamically significant organic valvular disease

- Myocardial infarction within 3 months
- Bisoprolol must be used with caution in:
- Bronchospasm (bronchial asthma, obstructive airways diseases)
- Diabetes mellitus with large fluctuations in blood glucose values; Symptoms of hypoglycaemia can be masked
- Strict fasting
- Ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment does not always yield the expected therapeutic effect.
- First degree AV block
- Prinzmetal's angina: Cases of coronary vasospasm have been observed. Despite its high beta1-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina.
- Peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.
- General anaesthesia

## 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, immunosuppressive (cyclosporin or tacrolimus), and trimethoprim).

The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.

Concomitant use not recommended.

Potassium sparing diuretics or potassium supplements

Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. 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 non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the $AUC_{0-24}$ and $C_{max}$ of ramipril and Ramiprilat. The clinical relevance of this observation is not known.

Diuretics (thiazide or loop diuretics)

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

To be taken into account with concomitant use. Other antihypertensive agents

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

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or

aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensive including telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route) Reduction of the antihypertensive effect.

**Bisoprolol:**

Combinations not recommended

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.

Class I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution

Calcium antagonists of the dihydropyridine type such as felodipine and amlodipine: Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.

Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.

Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Insulin and oral antidiabetic drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension.

Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.

β-Sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both β- and α-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the α-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective β-blockers.

Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered

Mefloquine: increased risk of bradycardia

Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the

beta-blockers but also risk for hypertensive crisis.

**4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)**

**Telmisartan:**

Pregnancy

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|---|
| -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. |
| Warning: Fetal Toxicity<br><br>When pregnancy is detected, discontinue the product as soon as possible.<br><br>Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. |

There are no adequate data from the use of CORBIS T/ TELSAR BISO in pregnant women. Studies in animals have shown reproductive toxicity.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of drugs. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, and hyperkalaemia).Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

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

Breast-feeding

Because no information is available regarding the use of CORBIS T/ TELSAR BISO during breast-feeding, CORBIS T/ TELSAR BISO is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

In preclinical studies, no effects of CORBIS T/ TELSAR BISO on male and female fertility were observed.

**Bisoprolol:**

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the fetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, beta1-selective adrenoceptor blockers are preferable.

Bisoprolol should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breast-feeding

It is not known whether this drug is excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol.

## 4.7 Effects on Ability to Drive and Use Machines

**Telmisartan:**

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 CORBIS T/ TELSAR BISO.

**Bisoprolol:**

In a reported clinical study, with coronary heart disease patients bisoprolol did not impair driving performance. However, due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol.

## 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 trials in patients treated for hypertension. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients. The safety profile of telmisartan in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

The adverse reactions listed below have been accumulated from controlled clinical trials in patients treated for hypertension and from post-marketing reports. The listing also takes into account serious adverse reactions and adverse reactions leading to discontinuation reported in three clinical long-term studies including 21,642 patients treated with telmisartan for the

reduction of cardiovascular morbidity for up to six years.

Tabulated list of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

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

| | |
|---|---|
| **Infections and infestations** | |
| Uncommon: | Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis |
| Rare: | Sepsis including fatal outcome[1] |

| | |
|---|---|
| **Blood and the lymphatic system disorders** | |
| Uncommon: | Anaemia |
| Rare: | Eosinophilia, thrombocytopenia |
| **Immune system disorders** | |
| Rare: | Anaphylactic reaction, hypersensitivity |
| **Metabolism and nutrition disorders** | |
| Uncommon: | Hyperkalaemia |
| Rare: | Hypoglycaemia (in diabetic patients) |
| **Psychiatric disorders** | |
| Uncommon: | Insomnia, depression |
| Rare: | Anxiety |
| **Nervous system disorders** | |
| Uncommon: | Syncope |
| Rare: | Somnolence |
| **Eye disorders** | |

| | |
|---|---|
| Rare: | Visual disturbance |
| **Ear and labyrinth disorders** | |
| Uncommon: | Vertigo |
| **Cardiac disorders** | |
| Uncommon: | Bradycardia |
| Rare: | Tachycardia |
| **Vascular disorders** | |
| Uncommon: | Hypotension[2], orthostatic hypotension |
| **Respiratory, thoracic and mediastinal disorders** | |
| Uncommon: | Dyspnoea, cough |
| Very rare: | Interstitial lung disease[4] |
| **Gastrointestinal disorders** | |
| Uncommon: Rare: | Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting<br>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 PRoFESS trial, an increased incidence of sepsis was observed with telmisartan compared with placebo. The event may be a chance finding or related to a mechanism currently not known.

*Hypotension*

This adverse reaction was reported as common in patients with controlled blood pressure who were treated with telmisartan for the reduction of cardiovascular morbidity on top of standard care.

*Hepatic function abnormal / liver disorder*

Most cases of hepatic function abnormal / liver disorder from post-marketing experience occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

*Interstitial lung disease*

Cases of interstitial lung disease have been reported from post-marketing experience in temporal association with the intake of telmisartan. However, a causal relationship has not been established.

**Bisoprolol:**

The following definitions apply to the frequency terminology used hereafter:

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

| **System organ class** | **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)** |
|---|---|---|---|---|
| Psychiatric Disorders | | | Sleep disorders (including vivid dreams), depression | Nightmares, hallucinations, anxiety, psychosis, confusion |
| Nervous system disorders | | Dizziness*, Headache* | | Syncope |
| Eye disorders | | | | dry eyes, impaired vision |
| Ear and labyrinth disorders | | | | Hearing disorders |
| Cardiac disorders | | | AV-conduction disturbances, worsening of pre-existing heart failure, bradycardia (decrease in pulse rate) | |
| Vascular disorders | | Feeling of coldness or numbness in the extremities, hypotension | Orthostatic hypotension | Cyanosis of extremities, paraesthesia<br>If you already have Raynaud's disease or intermittent claudication (pain in the legs while walking) Bisoprolol may make these worse. |

| | | | | |
|---|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease | Allergic rhinitis |
| Gastro- intestinal disorders | | | Gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation | |
| Hepatobilary disorders | | | | increased liver enzymes (ALAT, ASAT), Hepatitis |
| Reproductive system and breast disorders | | | | potency disorders |
| Skin and subcutaneous tissue disorders | | | | Hypersensitivity reactions (itching, flush, rash) |
| Musculoskeletal and Connective tissue disorders | | | Muscular weakness and cramps | muscle and joint ache |
| General disorders and administration site conditions | | lassitude fatigue* | asthenia | Perspiration, Oedema |
| **Metabolism and nutrition disorders** | | | | Increased triglycerides.<br>Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia. |

*These symptoms especially occur at the beginning of the therapy.

They are generally mild and often disappear within 1-2 weeks.

**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.

By reporting side effects, you can help provide more information on the safety of this medicine.

**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.

**Bisoproolol:**

Symptoms

With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000 mg) with bisoprolol have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension; all patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

Management

If overdose occurs, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is hardly dialysable. Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted.

Bradycardia: Administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

Hypotension: Intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

## 5. Pharmacological Properties

### 5.1 Mechanism of Action

**Telmisartan:**

Telmisartan is an orally active and specific angiotensin II receptor (type $AT_1$) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the $AT_1$ receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the $AT_1$ receptor. Telmisartan selectively binds the $AT_1$ receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including $AT_2$ and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore, it is not expected to potentiate bradykinin-mediated adverse effects.

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

**Bisoprolol:**

Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

### 5.2 Pharmacodynamic Properties

**Telmisartan:**

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC Code: C09CA07. Clinical efficacy and safety

***Treatment of essential hypertension***

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

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

diastolic blood pressure (DBP) are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The contribution of the medicinal product's diuretic and natriuretic effect to its hypotensive activity has still to be defined. The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes of antihypertensive medicinal products (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril).

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

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

***Cardiovascular prevention***

**ONTARGET** (**ON**going **T**elmisartan **A**lone and in Combination with **R**amipril **G**lobal **E**ndpoint **T**rial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, TIA, peripheral arterial disease, or type 2 diabetes 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.

In reported study Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years.

Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7 %) and ramipril (16.5 %) groups. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13). The all-cause mortality rate was 11.6 % and 11.8 % among telmisartan and ramipril treated patients, respectively.

Telmisartan was found to be similarly effective to ramipril in the pre-specified secondary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.99 (97.5 % CI 0.90 - 1.08), p (non-inferiority) = 0.0004], the primary endpoint in the reference study HOPE (The **H**eart **O**utcomes **P**revention **E**valuation Study), which had investigated the effect of ramipril vs. placebo.

TRANSCEND randomized ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to telmisartan 80 mg (n=2954) or placebo (n=2972), both given on top of standard care. The mean duration of follow up was 4 years and 8 months. No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found [15.7 % in the telmisartan and 17.0 % in the placebo groups with a hazard ratio of

0.92 (95 % CI 0.81 - 1.05, p = 0.22)]. There was evidence for a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95 % CI 0.76 - 1.00, p = 0.048)]. There was

no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95 % CI 0.85 - 1.24).

Cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. CV mortality and all-cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore, the use of a combination of telmisartan and ramipril is not recommended in this population.

In the "Prevention Regimen for Effectively avoiding Second Strokes" (PRoFESS) trial in patients 50 years and older, who recently experienced stroke, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70 % vs. 0.49 % [RR 1.43 (95 % confidence interval 1.00 - 2.06)]; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33 %) vs. patients taking placebo (0.16 %) [RR 2.07 (95 % confidence interval

1.14 - 3.76)]. The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known.

The reported two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. For more detailed information, see above under the heading “Cardiovascular prevention”. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy. These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers. ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of

an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric population

The safety and efficacy of CORBIS T/ TELSAR BISO in children and adolescents aged below 18 years have not been established.

The blood pressure lowering effects of two doses of telmisartan were assessed in 76 hypertensive, largely overweight patients aged 6 to < 18 years (body weight ≥ 20 kg and ≤ 120

kg, mean 74.6 kg), after taking telmisartan 1 mg/kg (n = 29 treated) or 2 mg/kg (n = 31 treated) over a four-week treatment period. By inclusion the presence of secondary hypertension was not investigated. In some of the investigated patients the doses used were higher than those recommended in the treatment of hypertension in the adult population, reaching a daily dose comparable to 160 mg, which was tested in adults. After adjustment for age group effects mean SBP changes from baseline (primary objective) were -14.5 (1.7) mm Hg in the telmisartan 2 mg/kg group, -9.7 (1.7) mm Hg in the telmisartan 1 mg/kg group, and -6.0 (2.4) in the placebo group. The adjusted DBP changes from baseline were -8.4 (1.5) mm Hg, -4.5 (1.6) mm Hg and

-3.5 (2.1) mm Hg respectively. The change was dose dependent. The safety data from this study in patients aged 6 to < 18 years appeared generally similar to that observed in adults. The safety of long term treatment of telmisartan in children and adolescents was not evaluated.

An increase in eosinophils reported in this patient population has not been recorded in adults. Its clinical significance and relevance is unknown.

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

**Bisoprolol:**

Pharmacotherapeutic group: Beta blocking agents, selective

ATC code: C07A B07

In total 2647 patients were included in the reported CIBIS II trial. 83% (n = 2202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction <35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1010 patients aged ≥65 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction ≤35%, who had not been treated previously with ACE inhibitors, beta-blockers, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either bisoprolol or enalapril.

There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months treatment. Non-inferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at study end (32.4% in the bisoprolol-first group vs. 33.1 % in the enalapril-first group, per-protocol population). The study shows that bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate disease.

Bisoprolol is also used for the treatment of hypertension and angina.

In acute administration in patients with coronary heart disease without chronic heart failure

bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

## 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 ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Linearity/non-linearity

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

istribution

Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution ($V_{dss}$) 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 ($C_{max}$) 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 ($Cl_{tot}$) 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 $C_{max}$.

Gender

Differences in plasma concentrations were observed, with $C_{max}$ 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.

**Bisoprolol:**

Absorption

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration.

Distribution

The distribution volume is 3.5 l/kg. The plasma protein binding of bisoprolol is about 30%.

Biotransformation and Elimination

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

Linearity

The kinetics of bisoprolol are linear and independent of age.

Special population

Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency. The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied. In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64+21 ng/ml at a daily dose of 10 mg and the half-life is 17+5 hours

## 6. Nonclinical Properties

### 6.1 Animal Toxicology or Pharmacology

**Telisartan:**

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 haemodynamic (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 offspring's 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.

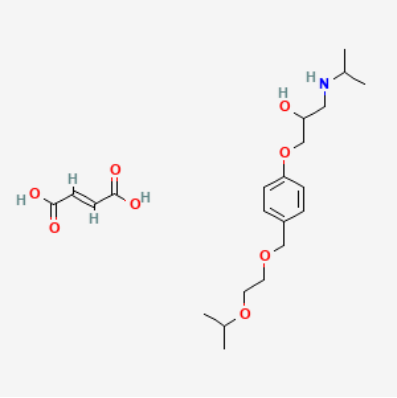
**Bisoprolol:**

Reported preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity. Like other beta-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

## 7. Description

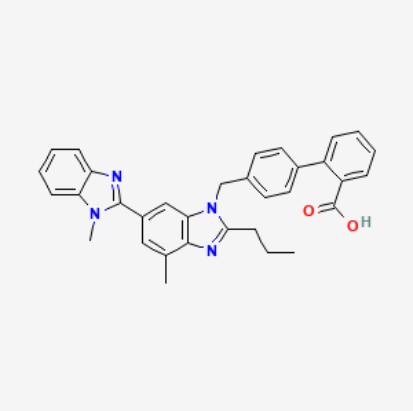
**Bisoprolol Fumarate:**

Bisoprolol Fumarate is (E)-but-2-enedioic acid;1-(propan-2-ylamino)-3-[4-(2-propan-2-yloxyethoxymethyl)phenoxy]propan-2-ol. The empirical formula is $C_{22}H_{35}NO_8$ and its molecular weight is 441.5g/mol. The chemical structure of Bisoprolol Fumarate is



**Telmisartan**

Telmisartan is 2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl]methyl]phenyl]benzoic acid. The empirical formula is $C_{33}H_{30}N_4O_2$ and molecular weight is 514.6g/mol. The chemical structure is:



**CORBIS T/ TELSAR BISO 2.5+40mg**

Bisoprolol Fumarate and Telmisartan Tablets are peach colored, round shaped, biconvex film coated tablet having both sides plain.

The excipients used are Microcrystalline Cellulose, Glyceryl Behenate, Croscarmellose Sodium, Colloidal Silicon Dioxide, PVPK 30, Sodium Hydroxide Pellets, Meglumine, Isopropyl Alcohol, Methylene Chloride, Carbomer, Pearlitol, Sodium Stearyl Fumarate & Crosspovidone XL 10.

**CORBIS T/ TELSAR BISO 5+40mg**

Bisoprolol Fumarate and Telmisartan Tablets are light yellow colored, round shape, biconvex film coated tablet, plain on both sides.

The excipients used are Microcrystalline Cellulose, Glyceryl Behenate, Croscarmellose Sodium, Colloidal Silicon Dioxide, PVPK 30, Sodium Hydroxide Pellets, Meglumine, Isopropyl Alcohol, Methylene Chloride, Carbomer, Pearlitol, Sodium Stearyl Fumarate & Crosspovidone XL 10.

## 8. PHARMACEUTICAL PARTICULARS

### 8.1 Incompatibilities

Not applicable.

### 8.2 Shelf-life

Do not use later than date of expiry.

### 8.3 Packaging information

**CORBIS T/ TELSAR BISO** is available in blister pack of 10 tablets

### 8.4 Storage and Handing Instructions

Store in a dry & dark place at a temperature not exceeding 30°C.

Keep out of reach of children.

## 9. Patient Counselling Information

**Package leaflet:**

**Information for the user CORBIS T/ TELSAR BISO 20, 40 and 80 mg tablets**

Telmisartan

**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 further questions, 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 CORBIS T/ TELSAR BISO is and what it is used for

CORBIS T/TELSAR BISO contain Bisoprolol Fumarate & Telmisartan Tablets (2.5+40mg, 5+40mg)

**CORBIS T/ TELSAR BISO is used for**

It is indicated for the treatment of mild to moderate hypertension.

## 9.2 What you need to know before you take CORBIS T/ TELSAR BISO Do not take CORBIS T/ TELSAR BISO

**Do not take CORBIS T/ TELSAR BISO if:**

- If you are allergic to CORBIS T/TELSAR BISO or any other ingredients of this medicine.
- If you are more than 3 months pregnant. (It is also better to avoid CORBIS T/ TELSAR BISO in early pregnancy)
- 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.

- Allergy (hypersensitivity) to CORBIS T/TELSAR BISO or to any of the other ingredients
- Severe asthma
- Severe blood circulation problems in your limbs (such as Raynaud's syndrome), which may cause your fingers and toes to tingle or turn pale or blue
- Untreated phaeochromocytoma, which is a rare tumour of the adrenal gland
- Metabolic acidosis, which is a condition when there is too much acid in the blood.

Do not take CORBIS T/TELSAR BISO if you have one of the following heart problems:

- Acute heart failure
- Worsening heart failure requiring injection of medicines into a vein, that increase the force of contraction of the heart
- Slow heart rate
- Low blood pressure
- Certain heart conditions causing a very slow heart rate or irregular heartbeat
- Cardiogenic shock, which is an acute serious heart condition causing low blood pressure and circulatory failure

If any of the above applies to you, tell your doctor or pharmacist before taking CORBIS T/ TELSAR BISO.

**Warnings and precautions**

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

**Telmisartan:**

- Kidney disease or kidney transplant.
- Renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- Liver disease.
- 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.

Talk to your doctor before taking CORBIS T/ TELSAR BISO:

- 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 CORBIS T/ TELSAR BISO".

**Bisoprolol:**

Talk to your doctor before taking CORBIS T/ TELSAR BISO if you are suffering or have ever suffered from any of the following conditions or illnesses

- Diabetes
- Strict fasting
- Certain heart diseases such as disturbances in heart rhythm, or severe chest pain at rest(prinzmetal's angina)
- Kidney or liver problems
- Less severe blood circulation problems in your limbs
- Chronic lung disease or less severe asthma
- History of a scaly skin rash (psoriasis)
- Tumour of the adrenal gland (phaeochromocytoma)
- Thyroid disorder

**In addition, tell your doctor if you are going to have:**

- Desensitization therapy (for example for the prevention of hay fever), because CORBIS T/ TELSAR BISOmay make it more likely that you experience an allergic reaction, or such reaction may be more severe.
- Anaesthesia (for example for surgery), because CORBIS T/ TELSAR BISO may influence how your body reacts to this situation.

If you have chronic lung disease or less severe asthma please inform your doctor immediately if you start to experience new difficulties in breathing, cough, wheezing after exercise, etc. when using CORBIS T/ TELSAR BISO.

**Children and adolescents**

The use of CORBIS T/ TELSAR BISO in children and adolescents up to the age of 18 years is not recommended.

**Other medicines and CORBIS T/ TELSAR BISO**

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 CORBIS T/ TELSAR BISO:

**Telmisartan:**

- 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, immunosuppressive (e.g. cyclosporin or tacrolimus), and the antibiotic trimethoprim.

- Diuretics ('water tablets'), especially if taken in high doses together with CORBIS T/ TELSAR BISO, 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 CORBIS T/ TELSAR BISO” and “Warnings and precautions”).

- Digoxin.

**Bisoprolol:**

- certain medicines used to treat high blood pressure or angina pectoris (dihydropyridine-type calcium antagonists such as felodipine and amlodipine)

- certain medicines used to treat irregular or abnormal heartbeat (Class III antiarrhythmic medicines such as amiodarone).

- beta-blockers applied locally (such as timolol eye drops for glaucoma treatment).

- certain medicines used to treat for example Alzheimer’s disease or glaucoma (parasympathomimetics such as tacrine or carbachol) or medicines that are used to treat acute heart problems (sympathomimetics such as isoprenaline and dobutamine).

- antidiabetic medicines including insulin anaesthetic agents (for example during surgery).

- digitalis, used to treat heart failure.

- non-steroidal anti-inflammatory medicines (NSAIDs) used to treat arthritis, pain or inflammation (for example ibuprofen or diclofenac).

- any medicine, which can lower blood pressure as a desired or undesired effect such as antihypertensives, certain medicines for depression (tricyclic antidepressants such as imipramine or amitriptyline), certain medicines used to treat epilepsy or during anaesthesia (barbiturates such as phenobarbital), or certain medicines to treat mental illness characterized by a loss of contact with reality (phenothiazines such as levomepromazine).

- mefloquine, used for prevention or treatment of malaria.

- depression treatment medicines called monoamine oxidase inhibitors (except MAO-B inhibitors) such as moclobemide.

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

CORBIS T/ TELSAR BISO 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 CORBIS T/ TELSAR BISO.

**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 CORBIS T/ TELSAR BISO before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of CORBIS T/ TELSAR BISO. CORBIS T/ TELSAR BISO 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. CORBIS T/ TELSAR BISO 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**

Your ability to drive or use machinery may be affected depending on how well you tolerate the medicine. Please be especially cautious at the start of treatment, when the dose is increased or the medication is changed, as well as in combination with alcohol.

## 9.3 How to take CORBIS T/ TELSAR BISO

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

The recommended dose is one tablet a day. Try to take the tablet at the same time each day.

You can take CORBIS T/ TELSAR BISO with or without food. The tablets should be swallowed with some water or other non-alcoholic drink. It is important that you take CORBIS T/ TELSAR BISO every day until your doctor tells you otherwise. If you have the impression that the effect of CORBIS T/ TELSAR BISO is too strong or too weak, talk to your doctor or pharmacist.

**If you take more CORBIS T/ TELSAR BISO 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 CORBIS T/ TELSAR BISO**

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.

## 9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Telmisartan:**

**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.

**Possible side effects of CORBIS T/ TELSAR BISO**

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

Low blood pressure (hypotension) in users treated for reduction of cardiovascular events.

**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, and 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.

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

Progressive scarring of lung tissue (interstitial lung disease) **.

* The event may have happened by chance or could be related to a mechanism currently not known.

** Cases of progressive scarring of lung tissue have been reported during intake of telmisartan.

However, it is not known whether telmisartan was the cause.

**Bisoprolol:**

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

- Tiredness, dizziness, headache
- Feeling of coldness or numbness in hands or feet
- Low blood pressure
- Stomach or intestine problems such as nausea, vomiting, diarrhoea, or constipation.

**Uncommon (affects less than 1 in 100 people)**

- Sleep disturbances (including vivid dreams)
- Interference with normal heart rate, slow pulse.
- Worsening heart failure
- Feeling weak , muscle weakness, muscle cramps
- Depression
- Dizziness when standing up
- Breathing problems in patients with asthma or chronic lung disease

**Rare (affects less than 1 in 1000 people)**

- Hearing problems
- Allergic runny nose, sneezing and itching
- Reduced tear flow (dry eyes), impaired vision
- Inflammation of the liver which can cause yellowing of the skin or whites of the eyes
- Certain blood test results for liver function or fat levels differing from normal
- Allergy-like reactions such as itching, flush, rash
- Impaired erection
- Nightmares, hallucinations, anxiety, psychosis, confusion
- Fainting
- Muscle and joint ache
- Blue fingers and toes
- Sweating
- Pins and needles, Oedema (swelling)

**Very Rare (affects less than 1 in 10,000 people)**

- Irritation and redness of the eye (conjunctivitis)
- Hair loss
- Appearance or worsening of scaly skin rash (psoriasis); psoriasis-like rash

**Not known**: angioedema

**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.

By reporting side effects, you can help provide more information on the safety of this medicine.

## 9.5 How to store CORBIS T/ TELSAR BISO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.

Store in a dry & dark place at a temperature not exceeding 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help protect the environment.

## 9.6 Contents of the pack and other information

### What CORBIS T/ TELSAR BISO contains

The active substances are Bisoprolol Fumarate and Telmisartan.

CORBIS T/ TELSAR BISO 2.5+40mg

The excipients used are Microcrystalline Cellulose, Glyceryl Behenate, Croscarmellose Sodium, Colloidal Silicon Dioxide, PVPK 30, Sodium Hydroxide Pellets, Meglumine, Isopropyl Alcohol, Methylene Chloride, Carbomer, Pearlitol, Sodium Stearyl Fumarate & Crosspovidone XL 10

CORBIS T/ TELSAR BISO 5+40mg

The excipients used are Microcrystalline Cellulose, Glyceryl Behenate, Croscarmellose Sodium, Colloidal Silicon Dioxide, PVPK 30, Sodium Hydroxide Pellets, Meglumine, Isopropyl Alcohol, Methylene Chloride, Carbomer, Pearlitol, Sodium Stearyl Fumarate & Crosspovidone XL 10.

### What CORBIS T/ TELSAR BISO looks like and contents of the pack

CORBIS T/ TELSAR BISO 2.5+40mg

Bisoprolol Fumarate and Telmisartan Tablets are peach colored, round shaped, biconvex film coated tablet having both sides plain.

CORBIS T/ TELSAR BISO 5+40mg

Bisoprolol Fumarate and Telmisartan Tablets are light yellow colored, round shape, biconvex film coated tablet, plain on both sides.

**CORBIS T/ TELSAR BISO** is available in blister pack of 10 tablets

## 10. Details of manufacturer

M/s. Ravenbhel Healthcare Pvt. Ltd.

At : EPIP, SIDCO, Kartholi,

Bari Brahmana, Jammu - 181133

**11. Details of Permission or Licence Number with Date**

Lic.No. JK/01/17-18/LL/251 Issued on 10.12.2022

**12. Date of revision**

NA

**MARKETED BY**

TORRENT PHARMACEUTICALS LTD.

**IN/CORBIS T/ TELSAR BISO 2.5+40mg, 5+40mg/Dec-22/01/PI**