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

CORBIS

1. Generic Name

Bisoprolol Fumarate Tablets U.S.P.

2. Qualitative and quantitative composition

CORBIS-1.25

Each film coated tablet contains:

Bisoprolol Fumarate I.P…….1.25 mg

Colours: Titanium Dioxide I.P.

Other inactive ingredients are Calcium Hydrogen phosphate, anhydrous, Butylhydroxyanisole, Microcrystalline Cellulose, Crospovidone, Pregelatinized Starch, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Macrogol 400 and Titanium Dioxide.

CORBIS 2.5

Each film coated tablet contains:

Bisoprolol Fumarate I.P…….2.5 mg

Excipients……q. s

Colours: Brilliant Blue Lake and Titanium Dioxide I.P.

The excipients used are Dibasic Calcium Phosphate, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Pregelatinized Starch, Magnesium Stearate, Lake of Brilliant Blue, Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Methanol and Methylene Chloride.

CORBIS 5

Each film coated tablet contains:

Bisoprolol Fumarate I.P…….5 mg

Excipients……. q. s

Colours: Yellow Oxide of Iron USPNF and Titanium Dioxide I.P.

The excipients used are Dibasic Calcium Phosphate, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Pregelatinized Starch, Magnesium Stearate, Yellow Oxide of Iron, Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Methanol and Methylene Chloride.

CORBIS 10

Each film coated tablet contains:

Bisoprolol Fumarate I.P…….10 mg

Colour: Titanium Dioxide I.P.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Crospovidone, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol, Talc and Titanium Dioxide.

3. Dosage form and strength

Dosage form: Film Coated Tablets

Strength: 1.25 mg, 2.5 mg, 5 mg and 10 mg

4. Clinical particulars

4.1 Therapeutic indication

CORBIS 1.25: For the treatment of Congestive Heart Failure (CHF)

CORBIS 2.5: For the treatment of hypertension, Coronary heart disease (angina pectoris) and congestive heart failure.

CORBIS 5, 10: For the treatment of hypertension, Coronary heart disease (angina pectoris).

4.2 Posology and method of administration

Standard treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocker, diuretics, and when appropriate cardiac glycosides. Patients should be stable (without acute failure) when bisoprolol treatment is initiated.

It is recommended that the treating physician should be experienced in the management of chronic heart failure.

Transient worsening of heart failure, hypotension, or bradycardia may occur during the titration period and thereafter.

Posology

Congestive Heart Failure (CHF)

Titration phase

The treatment of stable chronic heart failure with bisoprolol requires a titration phase.

The treatment with bisoprolol is to be started with a gradual up titration according to the following steps:

- 1.25 mg once daily for 1 week, if well tolerated increase to
- 2.5 mg once daily for a further week, if well tolerated increase to
- 3.75 mg once daily for a further week, if well tolerated increase to
- 5 mg once daily for the 4 following weeks, if well tolerated increase to
- 7.5 mg once daily for the 4 following weeks, if well tolerated increase to
- 10 mg once daily for the maintenance therapy.

The maximum recommended dose is 10 mg once daily.

Close monitoring of vital signs (heart rate, blood pressure) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first day after initiating the therapy.

Treatment modification

If the maximum recommended dose is not well-tolerated, gradual dose reduction may be considered.

In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation.

The reintroduction and/or up titration of bisoprolol should always be considered when the patient becomes stable again.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patient's condition.

Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

Hypertension

The usual adult dose is 10 mg once daily with a maximum recommended dose of 20 mg per day. In some patients, 5 mg per day may be adequate.

Patients with hepatic or renal impairment

There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired hepatic or renal function. Up titration of the dose in these populations should therefore be made with additional caution. In patients with final stage impairment of renal function (creatinine clearance less than 20 ml/min) or in patients with severe hepatic dysfunction, the dosage should not exceed 10 mg bisoprolol once daily. Experience of use of bisoprolol in renal dialysis patients is limited, however. It is thought that bisoprolol fumarate cannot be dialysed.

Older people

No dosage adjustment is required but 5 mg per day may be adequate in some elderly patients; as for other adults, the dosage may have to be reduced in cases of severe renal or hepatic dysfunction.

Paediatric population

There is no paediatric experience with bisoprolol, therefore its use cannot be recommended in paediatric patients.

Method of administration

Bisoprolol tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

4.3 Contraindications

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

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase.

Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition.

The initiation and cessation of treatment with bisoprolol necessitates regular monitoring.

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

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthesist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhytmic drugs and with centrally acting antihypertensive drugs is generally not recommended.

Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, CORBIS may be used with caution. In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of $beta_2$-stimulants may have to be increased.

Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (e.g. bisoprolol) after carefully balancing the benefits against the risks.

In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockade.

Under treatment with bisoprolol the symptoms of a thyreotoxicosis may be masked.

4.5 Drugs interactions

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.)

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, $beta_1$-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

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

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)**	**Very rare (< 1/10,000)**
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	Conjunctivitis

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 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)	Alopecia. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash. Not known: angioedema
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. 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.

4.9 Overdose

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. Therefore, it is mandatory to initiate the treatment of these patients with a gradual up titration according to the scheme given in section 4.2.

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, $beta_2$-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

5. Pharmacological properties

5.1 Mechanism of Action

Bisoprolol is a highly $beta_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the $beta_2$-receptor of the smooth muscles of bronchi and vessels as well as to the $beta_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and $beta_2$-mediated metabolic effects. Its $beta_1$-selectivity extends beyond the therapeutic dose range.

5.2 Pharmacodynamic properties

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

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

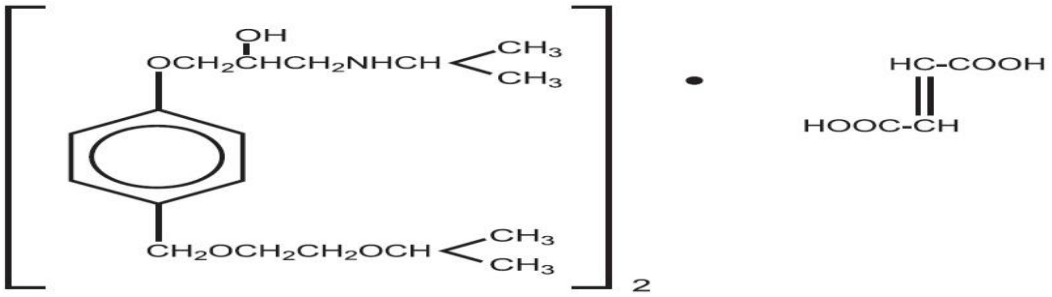
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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 is chemically described as 2-propanol,1-[4-[[2-(1-methylethoxy) ethoxy) methyl]phenoxy]-3-[(1-methylethyl)amino]-,(±)-,(E)-2-butenedioate. Its molecular formula is $(C_{18}H_{31}NO_4)2•C_4H_4O_4$ and it has a molecular weight of 766.97. Its structural formula is:



Bisoprolol fumarate is a white crystalline powder and very soluble in water and in methanol; freely soluble in chloroform, in glacial acetic acid, and in alcohol; slightly soluble in acetone and in ethyl acetate.

CORBIS-1.25

Bisoprolol Fumarate Tablets are white to off white coloured, round, biconvex, film-coated tablets, plain on both sides.

The excipients used are Calcium Hydrogen phosphate, anhydrous, Butylhydroxyanisole, Microcrystalline Cellulose, Crospovidone, Pregelatinized Starch, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Macrogol 400 and Titanium Dioxide

CORBIS 2.5

Bisoprolol Fumarate Tablets are light blue coloured, round, biconvex, film coated tablets with break line on one side and plain on other side.

The excipients used are Dibasic Calcium Phosphate, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Pregelatinized Starch, Magnesium Stearate, Lake of Brilliant Blue, Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Methanol and Methylene Chloride.

CORBIS 5

Bisoprolol Fumarate Tablets are light yellow coloured, round, biconvex, film coated tablets with break line on one side.

The excipients used are Dibasic Calcium Phosphate, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Pregelatinized Starch, Magnesium Stearate, Yellow Oxide of Iron, Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Methanol and Methylene Chloride.

CORBIS 10

Bisoprolol Fumarate Tablets are white coloured, circular shaped, biconvex, film coated tablets with plain on both sides.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Crospovidone, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol, Talc and Titanium Dioxide.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

CORBIS-1.25 is available in blister strip of 15 tablets

CORBIS 2.5 & 5 is available in strip of 15 tablets.

CORBIS 10 is available in blister strip of 10 tablets.

8.4 Storage and handing instructions

CORBIS-1.25

Store below 30°C, protected from light and moisture'.

CORBIS 2.5 & 5

Store in a cool & dry place. Protected from light.

CORBIS 10

Do not store above 30°C. Protect from light.

Keep all medicines out of reach of children.

9. Patient Counselling Information

CORBIS

Bisoprolol Fumarate Tablets U.S.P

Read all of this leaflet carefully before you start using 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. See section 9.4.

What is in this leaflet?

9.1 What CORBIS is and what it is used for

The active substance in CORBIS is bisoprolol Fumarate. Bisoprolol belongs to a group of medicines called beta-blockers. These medicines work by affecting the body`s response to some nerve impulses, especially in the heart. As a result, bisoprolol slows down the heart rate and makes the heart more efficient at pumping blood around the body.

Heart failure occurs when the heart muscle is weak and unable to pump enough blood to supply the body's needs. CORBIS is used to treat stable chronic heart failure.

It is used in combination with other medicines suitable for this condition (such as ACE-inhibitors, diuretics, and heart glycosides).

9.2 What you need to know before you use CORBIS.

Do not take CORBIS if one of the following conditions applies to you:

- Allergy (hypersensitivity) to bisoprolol 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.

<u>Do not take CORBIS if you have one of the following heart problems:</u>

- 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

Warnings and precautions

If you have any of the following conditions tell your doctor before taking CORBIS; he or she may want to take special care (for example give additional treatment or perform more frequent checks):

- 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 may make it more likely that you experience an allergic reaction, or such reaction may be more severe.
- Anaesthesia (for example for surgery), because CORBIS 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.

Children and adolescents

CORBIS is not recommended for use in children or adolescents.

Other medicines and CORBIS

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take the following medicines with CORBIS without special advice from your doctor:

- certain medicines used to treat irregular or abnormal heartbeat (Class I antiarrhythmic medicines such as quinidine, disopyramide, lidocaine, phenytoin; flecainide, propafenone)
- certain medicines used to treat high blood pressure, angina pectoris or irregular heartbeat (calcium antagonists such as verapamil and diltiazem)
- certain medicines used to treat high blood pressure such as clonidine, methyldopa, moxonodine, rilmenidine. However, do not stop taking these medicines without checking with your doctor first.

Check with your doctor before taking the following medicines with CORBIS; your doctor may need to check your condition more frequently:

- 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.

Pregnancy and breast-feeding

Pregnancy

There is a risk that use of CORBIS during pregnancy may harm the baby. If you are pregnant or planning to become pregnant, tell your doctor. He or she will decide whether you can take CORBIS during pregnancy.

Breast-feeding

It is not known whether bisoprolol passes into human breast milk. Therefore, breastfeeding is not recommended during therapy with CORBIS.

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 use CORBIS

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

Treatment with CORBIS requires regular monitoring by your doctor. This is particularly necessary at the start of treatment, during dose increase and when you stop treatment.

Take the tablet with some water in the morning, with or without food. Do not crush or chew the tablet. The scored tablets can be divided into two equal doses.

Treatment with CORBIS is usually long-term

Adults including the elderly:

Treatment with bisoprolol must be started at a low dose and increased gradually.

Your doctor will decide how to increase the dose, and this will normally be done in the following way:
• 1.25 mg bisoprolol once daily for one week
• 2.5 mg bisoprolol once daily for one week
• 3.75 mg bisoprolol once daily for one week
• 5 mg bisoprolol once daily for four weeks
• 7.5 mg bisoprolol once daily for four weeks
• 10 mg bisoprolol once daily for maintenance (on-going) therapy.

The maximum recommended daily dose is 10 mg bisoprolol for CHF.

For Hypertension, the usual adult dose is 10 mg once daily with a maximum recommended dose of 20 mg per day. In some patients, 5 mg per day may be adequate.

Depending on how well you tolerate the medicine, your doctor may also decide to lengthen the time between dose increases. If your condition gets worse or you no longer tolerate the drug, it may be necessary to reduce the dose again or to interrupt treatment. In some patients a maintenance dose lower than 10 mg bisoprolol may be sufficient.

Your doctor will tell you what to do.

If you have to stop treatment entirely, your doctor will usually advise you to reduce the dose gradually; as otherwise, your condition may become worse.

If you take more CORBIS than you should
If you have taken more CORBIS tablets than you should, tell your doctor immediately. Your doctor will decide what measures are necessary.

Symptoms of an overdose may include slowed heart rate, severe difficulty in breathing, feeling dizzy, or trembling (due to decreased blood sugar).

If you forget to take CORBIS
Do not take a double dose to make up for a forgotten dose. Take your usual dose the next morning.

If you stop taking CORBIS
Never stop taking CORBIS unless on your doctor's advice. Otherwise, your condition could become much worse.

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, these tablets can cause side effects, although not everybody gets them.

To prevent serious reactions, speak to a doctor immediately if a side effect is severe, occurred suddenly or gets worse rapidly.

- Allergic reaction such as itching, redness and skin rash. You should see a doctor straight away if you experience more severe allergic reactions, which may involve hands, feet, ankles, face, neck, tongue, mouth or throat swelling, or difficulty breathing.
- Sudden attacks of unconsciousness
- Shortness of breath or wheezing
- Light headedness

- Worsening of heart failure causing increased breathlessness and/or retention of fluid.
- If you already have Raynaud's disease (a condition in which fingers and toes become white, numb and painful in cold weather) or intermittent claudication (pain in the legs while walking. Bisoprolol may make these worse.

Further side effects are listed below according to how frequently they may occur:

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

- 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 blister and the carton after EXP. The expiry date refers to the last date of that month.
- Store in a cool and dry place. Protect from light. Keep all medicines out of reach of children.

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 contains:

CORBIS-1.25

CORBIS 1.25 contains Bisoprolol Fumarate as active ingredients with strength of 1.25 mg. Other inactive ingredients are Calcium Hydrogen phosphate, anhydrous, Butylhydroxyanisole, Microcrystalline Cellulose, Crospovidone, Pregelatinized Starch, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Macrogol 400 and Titanium Dioxide.

CORBIS 2.5

CORBIS 2.5 contains Bisoprolol Fumarate as active ingredients with strength of 2.5 mg. The excipients used are Dibasic Calcium Phosphate, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Pregelatinized Starch, Magnesium Stearate, Lake of Brilliant Blue, Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Methanol and Methylene Chloride.

CORBIS 5

CORBIS 5 contains Bisoprolol Fumarate as active ingredients with strength of 5 mg. The excipients used are Dibasic Calcium Phosphate, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Pregelatinized Starch, Magnesium Stearate, Yellow Oxide of Iron, Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Methanol and Methylene Chloride.

CORBIS 10

CORBIS 10 contains Bisoprolol Fumarate as active ingredients with strength of 10 mg. The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Crospovidone, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol, Talc and Titanium Dioxide.

10. Details of manufacturer

CORBIS-1.25

Manufactured by:

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10, East District, Gangtok. Sikkim-737 135.

CORBIS- 2.5 & 5

Manufactured by:

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10, East District, Gangtok. Sikkim-737 135.

OR

Uni Medico labs

21-22, Pharmacy, Selaqui, Dehradun, Uttarakhand.

CORBIS 10

Ordain Healthcare Global Pvt Ltd.

532, Uthiramerur Road, Karunguzhi Post, Madurantagam Taluk,

Kanchipuram District – 603303, Tamil Nadu, India.

11. Details of permission or licence number with date

CORBIS-1.25

Mfg Licence No.: M/563/2010 issued on 30.08.2019

CORBIS 2.5

Mfg Licence No.: M/563/2010 issued on 24.07.2018

Mfg Licence No.: 65/UA/2015 issued on 28.08.2020

CORBIS 5

Mfg Licence No.: M/563/2010 issued on 24.07.2018

Mfg Licence No.:65/UA/2015 issued on 06.01.2021

CORBIS 10

Mfg Licence No.: TN00003296 issued on 06.02.2018

12. Date of revision

MAR-2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/CORBIS®-1.25, 2.5, 5 and 10 mg/Mar-2021/04/PI