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

CORBIS-H 5

1. Generic Name

Bisoprolol Fumarate and Hydrochlorothiazide Tablets I.P.

2. Qualitative and quantitative composition

Each film coated tablet contains:

Bisoprolol Fumarate I.P. …….5 mg

Hydrochlorothiazide I.P. …….6.25 mg

Excipients……. q. s

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

The excipients used are Dibasic Calcium Phosphate, Microcrystalline Cellulose, Starch, Povidone, Isopropyl Alcohol, Magnesium Stearate, Ferric Oxide Yellow, Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Methylene Chloride and Methanol.

3. Dosage form and strength Dosage

form: Film coated tablet

Strength: Bisoprolol Fumarate 5 mg and Hydrochlorothiazide 6.25 mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Posology

The fixed dose combination (bisoprolol hemifumarate 5 mg / hydrochlorothiazide 6.25 mg) may be used in patients whose blood pressure is inadequately controlled by the monosubstances, bisoprolol hemifumarate 5 mg or hydrochlorothiazide 6.25 mg. An individual dose adjustment with the individual substances is recommended. If clinically appropriate, a direct switchover from monotherapy to fixed combination may be considered.

The usual dose is 5 mg bisoprolol and 6.25 mg hydrochlorothiazide once daily (equivalent to 1 filmt coated tablet Bisoprolol Fumarate 5 mg and Hydrochlorothiazide 6.25 mg).

If the blood pressure is inadequately lowered, the dose may be increased up to 10 mg once daily Bisoprolol and Hydrochlorothiazide 12.5 mg (corresponding to 2 film-coated tablets of bisoprolol hemifumarate 5 mg or hydrochlorothiazide 6.25 mg).

Older patients:

Dose adjustment is usually not required. The baseline therapy should be with the lowest possible dosage.

Renal or hepatic impairment:

In patients with mild to moderate renal impairment (creatinine clearance > 30 ml / min) and mild to moderate hepatic impairment, dose adjustment is not required. However, in patients with mild to moderate hepatic impairment, monitoring is recommended.

With simultaneous reduced renal and hepatic function, the elimination of the hydrochlorothiazide portion of bisoprolol hemifumarate / hydrochlorothiazide is reduced so the least dose formulation is recommended.

Paediatric population:

As there is no experience on the use of bisoprolol fumarate / hydrochlorothiazide in children, it is not recommended for paediatric population.

Method of administration:

The film-coated tablets are to be swallowed whole with some liquid at breakfast.

4.3 Contraindications

- Hypersensitivity to hydrochlorothiazide and other thiazides, Sulphonamides, bisoprolol or any of the other ingredients
- Acute cardiac failure or during decompensation cardiac failure, where i. v.- inotropic therapy is warranted
- Cardiogenic shock
- AV block Grade II Or III (without pacemaker)
- Sick sinus syndrome
- SA block
- Bradycardia less than 60 beats / minute before the start of treatment
- Late stages of peripheral arterial disease and Raynaud's syndrome
- Severe bronchial asthma or severe chronic obstructive pulmonary disease
- Metabolic acidosis
- Therapy resistant hypokalemia
- Severe hyponatremia
- Hypercalcemia
- Severe renal impairment with oliguria or anuria (creatinine clearance < 30 ml / min and / or serum creatinine > 1.8 mg / 100 ml)
- Acute glomerulonephritis
- Severe hepatic impairment including hepatic precoma and coma
- Untreated pheochromocytoma;
- Pregnancy
- lactation
- concomitant use of floctafenine and sultopride

4.4 Special warnings and precautions for use

Careful monitoring is required in case of

- Cardiac failure (in patients with concomitant stable chronic heart failure, monotherapy with bisoprolol hemifumarate must be started with a special titration phase)
- Bronchospasm (bronchial asthma, obstructive airway disease)
- Simultaneous treatment with inhalation anesthetics
- Diabetes mellitus with strongly fluctuating blood sugar levels (Hypoglycemic symptoms may be obscured)
- Strict fasting
- Simultaneous desensitization therapy
- AV block I degree
- Prinzmetal's angina
- Peripheral arterial occlusive disease (aggravation of discomfort especially possible at the beginning of treatment)
- Hypovolemia
- Impaired hepatic function
- Patients with hyperuricemia; here the risk of a gout attack is increased
- General anesthesia

  In patients receiving general anesthesia, beta blockers reduce the occurrence of arrhythmias and myocardial ischemia during the anesthetic induction, intubation and postoperatively. It is currently recommended that an existing beta-blocker therapy should not be stopped during surgery. The anesthesiologist must be intimated regarding beta-blocker therapy, as it may result in potential interactions with other drugs, bradyarrhythmias, attenuation of reflex tachycardia, and compensation for blood loss through decreased reflex responses. If discontinuation of betablocker therapy is required prior to surgery, it should be done gradually and concluded until about 48 hours before the anesthesia;.

  Photosensitivity reactions associated with thiazide diuretics may occur. If photosensitivity reactions occur, it is recommended to protect exposed areas of the body from sun or UVA rays. In severe cases, treatment with CORBIS-H 5 must be discontinued.

  Non-melanocytic skin cancer

  In two reported epidemiological studies based on the Danish National Cancer Registry, an increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] was observed with increasing cumulative dose of hydrochlorothiazide (HCTZ).

  Photosensitizing effects of HCTZ could contribute to the development of NMSC.

  Patients taking HCTZ should be advised of the NMSC risk and advised to regularly check their skin for new lesions and to report any suspicious lesions immediately.

  Patients should be advised of possible preventive measures to minimize the risk of skin cancer; for example- Limitation of exposure to sunlight and UV radiation or, in case of exposure, use of adequate sunscreen. Suspicious lesions should be promptly evaluated, including histological

examination of biopsies, if applicable. In patients who have already had NMSC, the use of HCTZ should be reviewed.

Concomitant bronchodilator therapy is warranted in bronchial asthma or other chronic obstructive pulmonary disease, which can lead to symptoms. Occasionally, asthma patients may experience an increase in airway resistance, therefore, the dose of beta-2sympathomimetics may need to be increased.

Due to the hydrochlorothiazide component of bisoprolol hemifumarate / hydrochlorothiazide, longterm therapy with may, lead to disturbances of the fluid and electrolyte balance, in particular lead to hypokalemia and hyponatremia, as well as to hypomagnesemia, hypochloremia and hypercalcemia.

Hypokalemia can favor the development of serious cardiac arrhythmias, in particular development of the potentially fatal Torsade de Pointes.

A metabolic alkalosis may be worsened due to the disturbed fluid and electrolyte balance.

Like other beta-blockers, bisoprolol can augment the sensitivity to allergens as well as the severity of anaphylactic reactions.

Adrenaline administration does not always show the expected therapeutic effect.

In patients with psoriasis or a history of psoriasis, beta-blockers (eg bisoprolol) should only be used after careful consideration of the risks and benefits.

In patients with pheochromocytoma, beta blockers (eg bisoprolol) may only be used after alphareceptor blockade.

During treatment with beta-blockers (eg bisoprolol), the symptoms of hyperthyroidism may be obscured.

Therapy with beta-blockers (eg bisoprolol) should not be stopped abruptly without compulsory indication.

Acute cholecystitis has been reported in patients with cholelithiasis.

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Pregnancy

In case of patients who desire to get pregnant, a switch to an alternative antihypertensive treatment with a suitable safety profile for pregnant women should be made. If pregnancy is detected, the treatment with HCTZ is to be immediately ceased and, if necessary, an alternative therapy initiated.

Note:

During long-term therapy with bisoprolol hemifumarate / hydrochlorothiazide, serum electrolytes (especially potassium, sodium, calcium), creatinine and urea, serum lipids (cholesterol and triglycerides), uric acid and blood sugar should be monitored regularly. During treatment with bisoprolol fumarate / hydrochlorothiazide, adequate hydration and a highpotassium diet (eg bananas, vegetables, nuts) should be ensured to compensate for the

increased potassium loss. Potassium losses can be reduced or avoided by concomitant therapy with potassium sparing diuretics.

4.5 Drugs interactions

Bisoprolol Fumarate

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.

Para sympathomimetic 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 betaadrenoreceptors 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.

Sympathomimetic 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**.**

Hydrochlorthiazide

Drug Interactions: When given concurrently the following drugs may interact with thiazide diuretics. Alcohol, Barbiturates or Narcotics: Potentiation of orthostatic hypotension may occur. Antidiabetic Drugs (Oral Agents and Insulin): Dosage adjustment of the antidiabetic drug may be required. Other Antihypertensive Drugs:

Additive effect or potentiation. Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia. Pressor Amines (e.g., Norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use. Skeletal Muscle Relaxants, Nondepolarizing (e.g., Tubocurarine): Possible increased responsiveness to the muscle relaxant. Lithium: Generally, should not be given with diuretics.

Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with hydrochlorothiazide. Non-Steroidal Anti-Inflammatory Drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

Therefore, Reference ID: 3001472 when hydrochlorothiazide and non-steroidal antiinflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. Drug/Laboratory Test Interactions: Thiazides should be discontinued before carrying out tests for parathyroid function. Carcinogenesis, Mutagenesis, Impairment of Fertility: Two year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice. Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration. Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

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

Pregnancy

There is limited experience with hydrochlorothiazide or bisoprolol during pregnancy, especially during the first trimester. Animal studies are insufficient for hydrochlorothiazide and do not indicate any teratogenic effect with bisoprolol. Bisoprolol, β-adrenoceptor blocking agents reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse reactions (e.g. hypoglycaemia, bradycardia) may occur in the foetus and newborn infant. If treatment with β-adrenoceptor blocking agents is necessary, those with better established safety profile should be considered. The uteroplacental blood flow and foetal growth should be monitored. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 5 days. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto- placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding

Hydrochlorothiazide is excreted in human milk. So far it is not known whether bisoprolol is excreted in human milk. Therefore this medicine must not be used during breast-feeding. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant. Hydrochlorothiazide can inhibit the milk production.

Fertility

There are no nonclinical data with hydrochlorothiazide and bisoprolol. As with some other drugs used in the treatment of hypertension, clinical reports have suggested that hydrochlorothiazide and bisoprolol may occasionally induce impotence in males.

Pediatric Use: There are no well controlled clinical trials in pediatric patients. Information on dosing in this age group is supported by evidence from empiric use in pediatric patients and published literature regarding the treatment of hypertension in such patients.

4.7 Effects on ability to drive and use machines

Bisoprolol hemifumarate / hydrochlorothiazide has little or negligible influence on the ability to drive and use machines. In a reported study of patients with coronary heart disease, bisoprolol did not limit their ability to drive. However, due to the differing individual reactions to the drug, the ability to drive or the ability to operate machinery may be impaired. This may be seen especially at the beginning of treatment, and changes in the medication and concomitant use of alcohol should be considered.

4.8 Undesirable effects

Bisoprolol Fumarate

The following definitions apply to the frequency terminology used here

after: 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)

Frequency not known (cannot be estimated from available data)

Cardiac disorders	
Very common:	Bradycardia in patients with chronic heart failure
common:	Worsening of pre-existing heart failure in patients with chronic heart failure
Uncommon:	AV-conduction disturbances. Worsening of pre-existing heart failure (in patients with hypertension or angina pectoris); bradycardia (in patients with hypertension or angina pectoris)
Disorders of the blood and of the lymphatic system	
Rare:	Leukocytopenia, thrombocytopenia
Very rare:	Agranulocytosis
Benign, malignant and nonspecific neoplasms (including cysts and polyps)	
Unknown:	Non-melanocytic skin cancer (basal cell carcinoma and squamous cell carcinoma)
Metabolic and nutrition disorders	
Common:	Increased triglyceride and cholesterol, hyperglycemia and glucosuria, hyperuricemia, Disorders of fluid and electrolyte imbalance (especially hypokalemia and hyponatremia, and additionally hypomagnesemia and hypochloremia as well hypercalcemia), metabolic alkalosis
Investigations	
Rare:	increased triglycerides, increased liver enzymes (ALAT, ASAT).
Nervous system disorders	
Common:	dizziness, headache
Rare:	Syncope

Eye disorders	
Rare:	reduced tear flow (to be considered if the patient uses lenses)
Very rare:	conjunctivitis.
Ear and labyrinth disorders	
Rare:	hearing disorders.
Respiratory, thoracic and mediastinal disorders	
Uncommon:	bronchospasm in patients with bronchial asthma or a history of obstructive airways disease.
Rare:	allergic rhinitis, Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders	
Common:	gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation.
Uncommon:	Loss of appetite, Stomach ache, increase in the amylase, pancreatitis
Skin and subcutaneous tissue disorders	
Rare:	hypersensitivity reactions (itching, flush, rash).
Very rare:	Alopecia, Beta-blockers may provoke or worsen psoriasis or induce psoriasislike rash; Cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	
Uncommon:	muscular weakness and cramps.
Vascular disorders	
Common:	feeling of coldness or numbness in the extremities, hypotension(especially in patients with heart failure)
Uncommon:	orthostatic hypotension.
General disorders	
Common:	asthenia(patients with chronic heart failure), fatigue.

Hepatobiliary disorders	
Rare:	hepatitis.
Reproductive system and breast disorders	
Rare:	erectile disorders.
Psychiatric disorders	
Uncommon:	sleep disorders, depression.
Rare:	nightmares, hallucinations.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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 of overdose include bradycardia, hypotension, bronchospasm, acute cardiac failure and conduction disturbances on the ECG. Bradycardia due to overdose is treated with atropine (1 - 2 mg intravenously), isoprenaline or temporarily with a pacemaker. Hypotension is treated by intravenous fluid administration and, if necessary, by vasopressors such as catecholamines. The treatment of bronchospasm can be done with theophylline, theophylline derivatives or betamimetics. If the overdose is only a short time (0 - 2 hours), the patient is given activated charcoal and gastric lavage may be considered. Heart rate, blood pressure, electrolyte and glucose balance should be monitored. The elimination of bisoprolol cannot be appreciably increased by hemodialysis.

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.

Hydrochlorthiazide

Hydrochlorothiazide blocks the reabsorption of sodium and chloride ions, and it thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen ions. With continued use of hydrochlorothiazide and depletion of

sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen and chloride ions. Hydrochlorothiazide also decreases the excretion of calcium and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate. Metabolic toxicities associated with excessive electrolyte changes caused by hydrochlorothiazide have been shown to be dose-related.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta-blockers and thiazides.

ATC Code: C07BB07

Bisoprolol Fumarate

Bisoprolol is a beta-blocker that has an intermediate lipophilic / hydrophilic character. Bisoprolol is highly beta-1-selective ("cardioselective") without an intrinsic sympathomimetic effect (ISA), and without a clinically relevant membrane stabilizing effect. By blocking cardiac beta-receptors, bisoprolol reduces the response to sympatho-adrenergic activity. Heart rate and contractility are lowered, thus reducing the oxygen consumption of the heart.

Hydrochlorthiazide

Hydrochlorothiazide is a benzothiadiazine derivative which primarily increases the electrolyte excretion and secondarily increases the urine flow by osmotically bound water. The sodium transport from the renal tubule into the blood is inhibited, thus preventing sodium reabsorption. This natriuretic effect is accompanied with an increased potassium and magnesium excretion. Hydrochlorothiazide mainly inhibits sodium absorption in the distal tubule, so that a maximum of about 15% of the glomerular filtered sodium can be excreted. The extent of chloride excretion is approximately equal to sodium excretion. Hydrochlorothiazide also causes an increase in potassium excretion, which is determined by the potassium secretion into the distal tubule and the collecting tubule (increased exchange between potassium and sodium ions). The saluretic or diuretic effect of hydrochlorothiazide is not significantly affected by acidosis or alkalosis. The glomerular filtration rate is initially slightly reduced. During prolonged therapy with hydrochlorothiazide, calcium excretion via the kidneys is reduced, which can lead to hypercalcemia. Hydrochlorothiazide reduces peripheral resistance through its relaxing effect on the smooth muscle of the blood vessels. In patients with chronic renal impairment (creatinine clearance < 30 ml / min and / or serum creatinine > 1.8 mg / 100 ml), hydrochlorothiazide is virtually ineffective. In patients with renal and ADH sensitive diabetes insipidus, hydrochlorothiazide has an antidiuretic effect.

Non-melanocytic skin cancer

Based on available data from epidemiological studies, a cumulative dose-related association between HCTZ and NMSC was observed. One reported study included a population of 71,533 cases of BCC and 8,629 cases of SCC with control groups of 1,430,833 and 172,462 individuals, respectively. A high dose of HCTZ (≥ 50,000 mg cumulative) was associated with an adjusted odds ratio of 1.29 (95% confidence interval: 1.23 - 1.35) for BCC and 3.98 (95% confidence interval: 3.68 - 4.31) for SCC. For both BCC and SCC, a clear cumulative dose-response relationship was established. Another reported study revealed a possible association

between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip cancer were compared to a control group of 63,067 people using a risk based sampling procedure. A cumulative dose-response relationship was found with an adjusted odds ratio of 2.1 (95% confidence interval: 1.7 - 2.6), which at high exposure (~ 25,000 mg) was at an odds ratio of 3,9 (3.0 - 4.9) and increased to an odds ratio of 7.7 (5.7 - 10.5) at the highest cumulative dose (~ 100,000 mg).

5.3 Pharmacokinetic properties

Bisoprolol Fumarate

The bioavailability of bisoprolol from the film-coated tablets is approximately 90%. Bisoprolol is absorbed almost completely (> 90%) from the GI tract. Combined with a very low first-pass effect in the liver (<10%), it leads to an absolute bioavailability of 88%. Bisoprolol can be taken on an empty stomach or at breakfast with no change in absorption or bioavailability. The plasma protein binding of bisoprolol is about 30%. Pathophysiological changes of the plasma proteins such as alpha-1 glycoproteins have no effect on the pharmacokinetics of Bisoprolol. Maximum plasma levels are usually reached 1 - 3 hours after intake. As a moderately lipophilic substance, bisoprolol has only a low plasma protein binding and a distribution volume of 226 +/- 11 l (x +/-SEM). Bisoprolol is eliminated from the body via two equivalent clearance pathways: half of the bisoprolol dose used is converted in the liver to inactive metabolites that are excreted renally. The other half is excreted as unchanged substance via the renal path. The plasma elimination half-life is 10 to 12 hours. The C-max and AUC values of bisoprolol in the steady state in a fixed combination with hydrochlorothiazide is bioequivalent to the monopreparation.

Hydrochlorthiazide

After oral administration, hydrochlorothiazide is approximately 80% absorbed from the GI tract. The systemic availability is 71 +/-15%. The plasma protein binding of hydrochlorothiazide is 64%. The relative Distribution volume is 0.5 - 1.1 l / kg. In healthy individuals more than 95% of Hydrochlorothiazide is excreted unchanged by the kidneys. In normal renal function, the elimination half-life is 9-13 hours. Maximum plasma levels are usually measured after 2 to 5 hours. This time period increases with impaired renal function and is about 20 hours in patients with terminal renal failure. The diuretic effect starts within 1 to 2 hours and lasts for 10 to 12 hours depending on the dose. The hypotensive effect lasts up to 24 hours.

6. Nonclinical properties

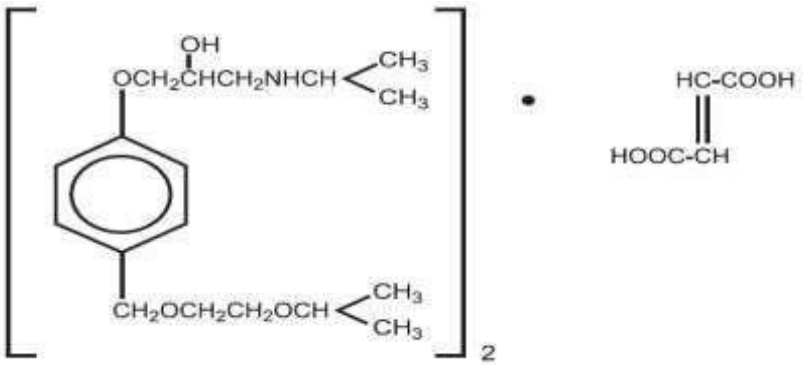
6.1 Animal Toxicology or Pharmacology

Bisoprolol or hydrochlorothiazide has not been found to be hazardous to humans according to the standard preclinical toxicity tests (long term toxicity, mutagenicity, genotoxicity and carcinogenicity tests). Like other beta-blockers, bisoprolol at high doses has been found in animal experiments to cause toxic effects to the mother (decreased food intake and body weight gain) and to the embryo/foetus (increased late resorptions, reduced birth weight of the offspring, retardation of the physical development up to the end of lactation). However, bisoprolol as well as hydrochlorothiazide were not teratogenic. There was no increase in toxicity when both components were given in combination.

7. Description

Bisoprolol fumarate

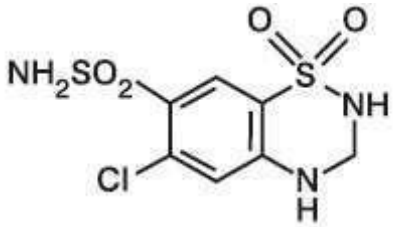
Bisoprolol fumarate is chemically described as 2-propanol,1-[4-[[2-(1-methylethoxy) ethoxy) methyl]phenoxy]-3-[(1-methylethyl)amino]-,(±)-,(E)-2-butenedioate. Its molecular formula is $(C_{18}H_{31}NO_4)_2 \bullet C_4H_4O_4$ and it has a molecular weight of 766.97. Its structural formula is:



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.

Hydrochlorothiazide

Hydrochlorothiazide is a white or almost white, crystalline powder; odourless with a molecular weight of 297.74. It is soluble in acetone; sparingly soluble in ethanol (95%); very slightly soluble in water. It dissolves in dilute solutions of alkali hydroxides. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$, and its structural formula is:



Bisoprolol fumarate and hydrochlorothiazide tablets are ivory coloured film coated round tablets with breakline on one side and plain on other side. The excipients used are Dibasic Calcium Phosphate, Microcrystalline Cellulose, Starch, Povidone, Isopropyl Alcohol, Magnesium Stearate, Ferric Oxide Yellow, Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Methylene Chloride and Methanol.

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-H 5 is available in strip of 10 tablets each.

8.4 Storage and handing instructions

Store in a cool and dry place. Protect from light. Keep all medicines out of reach of children.

9. Patient Counselling Information

CORBIS-H

(Bisoprolol Fumarate and Hydrochlorothiazide Tablets I.P.)

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 your 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-H 5 is and what it is used for

CORBIS-H 5 is combination of the active substance in Bisoprolol fumarate and Hydrochlorothiazide. Bisoprolol fumarate belongs to a group of medicines called betablockers. These medicines work by affecting the body`s response to some nerve impulses, especially in the heart. As a result bisoprolol fumarate 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-H 5 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).

Hydrochlorothiazide belongs to a group of medications known as thiazide diuretics; it is a medication which causes increased volume of urine. It is only available with a doctor's prescription**.**

9.2 What you need to know before you take CORBIS-H 5

Do not take CORBIS-H 5

Do not take CORBIS-H 5 if one of the following conditions applies to you:

- Allergy (hypersensitivity) to CORBIS-H 5 and Hydrochlorothiazide 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-H 5 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.

Warnings and precautions

If you have any of the following conditions tell your doctor before taking CORBIS-H 5 he or she may want to take special care (for example give additional treatment or perform more frequent checks

- Heart failure
- Diabetes
- Bronchospasm
- Simultaneous treatment with inhalation anesthetics
- Strict fasting
- Simultaneous desensitization therapy
- Angina
- blockage or narrowing of an artery in the legs
- decreased volume of circulating blood in the body
- Impaired liver function
- high level of uric acid in the blood
- General anesthesia
- Respiratory distress (including pneumonitis and pulmonary oedema)
- non-melanoma skin cancer
- Children and adolescents
- CORBIS-H 5 is not recommended for use in children or adolescents

Other medicines and CORBIS-H 5

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-H 5 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-H 5 your doctor may need to check your condition more frequently:

- Certain medicines used to treat high blood pressure or angina pectoris (dihydropyridinetype 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 (sympathomimetic 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 antihypertensive, 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

There is a risk that use of CORBIS-H 5 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-H 5 during pregnancy.

Breast-feeding

It is not known whether CORBIS-H 5 passes into human breast milk. Therefore, breastfeeding is not recommended during therapy with CORBIS-H 5.

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-H?

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.

It is important that this medication is taken only as directed and not given to other people. Take this medicine exactly as your doctor ordered.

If you take more CORBIS-H 5 than you should

If you have taken more CORBIS-H 5 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-H

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-H 5 requires regular monitoring by your doctor.

If you stop taking CORBIS-H

Never stop taking CORBIS-H 5 unless on your doctor's advice. Otherwise your condition could become much worse. If you have any further questions on the use of this product, ask your doctor or pharmacist.

USE OF OTHER MEDICINES

Care must be taken when using hydrochlorothiazide containing medicine with some other medications. Check with your doctor or pharmacist before using any other medications including those you buy without a prescription from the pharmacy, supermarket or health food shop.

9.4 Possible side effects

Like all medicines, this medicine 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.

The most serious side effects are related to the heart function:

- slowing of heart rate (may affect more than 1 in 10 people)
- worsening of heart failure (may affect up to 1 in 10 people)
- Slow or irregular heartbeat (may affect up to 1 in 100 people)

If you feel dizzy or weak, or have breathing difficulties please contact your doctor as soon as possible.

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

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

- Increased triglyceride and cholesterol, hyperglycemia and glucosuria, hyperuricemia, Disorders of fluid and electrolyte imbalance (especially hypokalemia and hyponatremia, and additionally hypomagnesemia and hypochloremia as well hypercalcemia), metabolic alkalosis
- Tiredness, feeling weak, 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 (may affect up to 1 in 100 people):

- Slow heart rate
- Worsening of heart failure
- Loss of appetite, Stomach ache, increase in the amylase (enzyme), pancreatitis
- sleep disturbances
- Depression
- breathing problems in patients with asthma or chronic lung disease
- Muscle weakness, muscle cramps.

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

- Leukocytopenia, thrombocytopenia
- Temporary loss of consciousness caused by a fall in blood pressure
- Reduced tear flow (to be considered if the patient uses lenses), blurred vision
- Hearing problems
- Allergic runny nose
- 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, Fainting.
- Respiratory distress (including pneumonitis and pulmonary oedema)

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

- Chest pain
- Agranulocytosis
- Irritation and redness of the eye (conjunctivitis)
- Hair loss
- Appearance or worsening of scaly skin rash (psoriasis); psoriasis-like rash.
- Side effects are uncommon in most patients, and usually depend on the dose needed. They may disappear with time or after the dose has been changed. Others are more serious and require you to check with your doctor.

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-H 5

Store in a cool and dry place. Protect from light. Keep all medicines out of reach of children

9.6. Contents of the pack and other information

CORBIS-H 5 consists of Bisoprolol Fumarate I.P and Hydrochlorothiazide I.P. as active ingredients in strength of 5 mg and 6.25 mg respectively.

The excipients used are Dibasic Calcium Phosphate, Microcrystalline Cellulose, Starch, Povidone, Isopropyl Alcohol, Magnesium Stearate, Ferric Oxide Yellow, Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Methylene Chloride and Methanol.

CORBIS-H 5 is available in strip of 10 tablets each.

10. Details of manufacturer Manufactured by:

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10,

East District, Gangtok. Sikkim-737 135

OR

Uni Medicolabs

21-22, pharmacity, Selaqui, Deharadun, Uttarakhand.

11. Details of permission or licence number with date.

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

OR

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12. Date of revision

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MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/CORBIS-H 5, 6.25 mg/MAY-22/03/PI