Bisoprolol Fumarate and Hydrochlorthiazide Tablets USP 2.5mg/6.25mg, 5mg/6.25mg, 10mg/6.25mg, 5mg/12.5mg

1. Name of the medicinal product

Bisoprolol Fumarate and Hydrochlorthiazide Tablets USP 2.5mg/6.25mg Taj Pharma

Bisoprolol Fumarate and Hydrochlorthiazide Tablets USP 5mg/6.25mg Taj Pharma

Bisoprolol Fumarate and Hydrochlorthiazide Tablets USP 10mg/6.25mg Taj Pharma

Bisoprolol Fumarate and Hydrochlorthiazide Tablets USP 5mg/12.5mg Taj Pharma

2. Qualitative and quantitative composition

a) Each film-coated tablet contains:
Bisoprolol fumarate USP 2.5mg
Hydrochlorothiazide USP 6.25mg
Excipients: q.s.
Colours: Yellow Oxide of Iron and Titanium Dioxide

b) Each film-coated tablet contains:
Bisoprolol fumarate USP 5mg
Hydrochlorothiazide USP 6.25mg
Excipients: q.s.
Colours: Yellow Oxide of Iron and Titanium Dioxide

c) Each film-coated tablet contains:
Bisoprolol fumarate USP 10mg
Hydrochlorothiazide USP 6.25mg
Excipients: q.s.
Colours: Yellow Oxide of Iron and Titanium Dioxide

d) Each film-coated tablet contains:
Bisoprolol fumarate USP 5mg
Hydrochlorothiazide USP 12.5mg
Excipients: q.s.
Colours: Yellow Oxide of Iron and Titanium Dioxide

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

4. Clinical particulars

Therapeutic indications

Treatment of essential hypertension.

The fixed dose combinations are indicated in patients whose blood pressure is not adequately controlled on bisoprololfumarate or hydrochlorothiazide alone.

4.2 Posology and method of administration

The fixed dose combination (bisoprololfumarate 5 mg/hydrochlorothiazide 12.5 mg) may be administered in patients whose blood pressure is not adequately controlled by bisoprololfumarate5 mgor hydrochlorothiazide 12.5 mg. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Posology

The usual starting dose is 5 mg bisoprolol/12.5 mg hydrochlorothiazide per day.

Individual dose titration with the components is recommended.

The dose may be increased to 5 mgbisoprolol/ 12.5 mghydrochlorothiazide per day, if necessary.

Elderly

No dosage adjustment is normally required. It is recommended to start with the lowest possible dose.

Renal or hepatic insufficiency

In patients with mild to moderate renal insufficiency (creatinine clearance > 30 ml/min) or mild to moderate hepatic insufficiency preference may have to be given to the lower dosage

form (5 mg bisoprolol/12.5 mg hydrochlorothiazide). However, in patients with mild to moderate impairment of the liver function monitoring is recommended (see section 4.4).

In co-existing impairment of kidney and liver function the elimination of the hydrochlorothiazide component of the bisoprololfumarate/hydrochlorothiazide is reduced, so that preference may have to be given to the lower dose (see section 4.4).

Paediatric population

There is no paediatric experience with bisoprololfumarate/hydrochlorothiazide, therefore its use cannot be recommended for children.

Method of administration

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

4.3 Contraindications

- Hypersensitivity to the active substances, other thiazides, sulphonamides or to any of the excipients listed in section 6.1.
- Acute heart failure or during episodes of heart failure decompensation requiring IV inotropic therapy.
- Cardiogenic shock.
- AV block of the 2nd or 3rd degree.
- Sick sinus syndrome.
- Sinoatrial block.
- Bradycardia with less than 60 beats/min prior to the treatment.
- Late stages of peripheral arterial occlusive disease and Raynaud's syndrome.
- Severe bronchial asthma or severe chronic obstructive pulmonary disease.
- Metabolic acidosis.
- Refractory hypokalaemia.
- Severe hyponatraemia.
- Hypercalcaemia.
- Severe renal insufficiency with oliguria or anuria (creatinine clearance < 30 ml/min and/or serum creatinine > 1.8 mg/100 ml).
- Acute glomerulonephritis.
- Severe hepatic insufficiency including hepatic precoma and coma.
- Untreated phaeochromocytoma (see section 4.4).
- Lactation (see section 4.6)
- Concomitant administration of floctafenine and sultopride (see section 4.5).
- Gout.

4.4 Special warnings and precautions for use

The cessation of therapy with β-blockers (e.g. bisoprolol) should not be done abruptly unless clearly indicated. After long-term therapy - particularly in the presence of ischaemic heart disease - bisoprololfumarate/hydrochlorothiazide should be discontinued gradually (dividing in half the dose over 7-10 days), since an abrupt withdrawal may lead to an acute deterioration of the patient's condition.

Patients with any of the following should be monitored closely:

- Heart failure (in patients with concomitant stable chronic heart failure the treatment has to be initiated with the monopreparation of bisoprololfumarate using a special titration phase).

- Diabetes mellitus showing large fluctuations in blood glucose values; symptoms of glycaemia can be masked.
- Strict fasting.
- AV block of 1st degree.

- Prinzmetal's angina.
- Peripheral arterial occlusive disease (intensification of the complaints might happen especially during start of therapy).
- Hypovolaemia.
- Reduced liver function.

As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. This also applies to desensitisation therapy. Adrenaline treatment may not always give the expected therapeutic effect.

Patients with psoriasis or with a history of psoriasis should only be given β-blockers (e.g.

bisoprolol) after carefully balancing the benefits against the risks.

Under treatment with β-blockers (e.g. bisoprolol) the symptoms of a thyrotoxicosis may be masked.

In patients with phaeochromocytoma β-blockers (e.g. bisoprolol) must not be administered until after alpha-receptor blockade.

In patients undergoing general anaesthesia: The anaesthetist must be aware of beta-blockade. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia. Patients undergoing concomitant treatment with inhalation anaesthetics should be monitored closely.

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 β2-stimulants may have to be increased. Patients with bronchospasms (bronchial asthma, obstructive airway diseases) should be monitored closely.

If photosensitivity reactions occur, it is recommended to protect exposed areas to the sun or to artificial UVA light. In severe cases it may be necessary to stop the treatment.

Due to the hydrochlorothiazide component the long-term, continuous administration of bisoprololfumarate/hydrochlorothiazide may lead to disturbance of the fluid and electrolyte balance, especially to hypokalaemia and hyponatraemia, further to hypomagnesaemia and hypochloraemia, as well as hypercalcaemia.

Hypokalaemia facilitates the development of severe arrhythmias, particularly torsades de points, which may be fatal.

During long term-therapy with bisoprololfumarate/hydrochlorothiazide, the serum electrolytes (especially potassium, sodium, and calcium), creatinine and urea, the serum lipids (cholesterol and triglycerides), uric acid as well as blood glucose should be monitored regularly.

During treatment with bisoprololfumarate/ hydrochlorothiazide patients should ensure an adequate supply of fluid and food rich in potassium (e.g. bananas, vegetables, nuts) to compensate for the increased loss of potassium. The potassium losses may be reduced or prevented by concomitant therapy with potassium-sparing diuretics.

In patients with hyperuricaemia the risk for attacks of gout may be increased.

Metabolic alkalosis may worsen due to disturbance of fluid and electrolyte haemostasis.

In patients with cholelithiasis acute cholecystitis has been reported.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitising actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

General information

It should be considered that due to serum potassium disturbances certain medicinal products may be affected.

Contraindicated combinations

Floctafenine: Bisoprolol may inhibit compensatory cardiovascular reactions to floctafenine-induced hypotonia or shock.

Sultopride: concomitant administration with bisoprolol may lead to an increased risk for ventricular arrhythmia.

Combinations not recommended

Lithium:
Bisoprololfumarate/hydrochlorothiazide may intensify the cardiotoxic and neurotoxic effect of lithium through a reduction of lithium excretion.

Calcium antagonists such as the verapamil type and 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.

Centrally-acting antihypertensive agents (e.g. reserpine, alpha-methyldopa, guanfacine, clonidine): Concomitant use of centrally-acting antihypertensive agents may lead to a further reduction in heart rate and cardiac output and to vasodilatation. Abrupt withdrawal may increase the risk of 'rebound hypertension'. These must not be discontinued unless the use of bisoprololfumarate/ hydrochlorothiazide was stopped some days before. This may be then followed by the step-wise withdrawal of the centrally-acting antihypertensive agent.

Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of β-blockers but also risk of hypertensive crisis.

Non-antiarrhythmic medicinal products that may induce torsades de pointes: astemizole, IV erythromycin, halofantrine, pentamidine, sparfloxacin, terfenadine, vincamine. Hypokalaemia may facilitate the occurrence of torsades de pointes. In case of hypokalaemia use medicinal products that do not produce torsades de pointes.

Combinations to be used with caution

Calcium antagonists such as dihydropyridine derivatives (e.g. nifedipine): 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.

Concomitant use with other antihypertensive agents or with other medicinal products with blood pressure lowering potential may increase the risk of hypotension.

ACE inhibitors (e.g. enalapril, captopril), Angiotensin II antagonists (e.g. losartan): Risk of significant fall in blood pressure and/or acute renal failure during initiation of ACE inhibitor therapy in patients with pre-existing sodium depletion (particularly in patients with renal artery stenosis).

If prior diuretic therapy has produced sodium depletion, either stop the diuretic 3 days before starting ACE inhibitor therapy, or initiate ACE inhibitor therapy at a low dose.

Class-I antiarrhythmic agents (e.g. disopyramide, quinidine): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

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

Antiarrhythmic medicinal products that may produce torsades de pointes: Class IA medicinal products (quinidine, disopyramide), amiodarone, sotalol. Prevent and, if necessary, correct hypokalaemia. Monitor QT interval. In case of torsades de pointes do not administer antiarrhythmics (electrical pacing).

Parasympathomimetic medicinal products (including tacrine): Atrio-ventricular conduction time and the risk of bradycardia may be increased.

Topical β-blockers, including eye drops, may add to the systemic effects of bisoprolol.

Insulin and oral antidiabetic agents: Intensification of blood sugar lowering effect. Blockade of β-adrenoceptors may mask symptoms of hypoglycaemia.

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension. Continuation of β-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving a β-blocker (e.g. bisoprolol) (see section 4.4).

Digitalis glycosides: Prolongation of atrio-ventricular conduction time, reduction in heart rate. In hypokalaemia and/or hypomagnesaemia developing during treatment with bisoprololfumarate/ hydrochlorothiazide the myocardium may show increased sensitivity to cardiac glycosides, thus leading to a potentiation of their effects and adverse effects of the glycosides.

Prostaglandin synthetase inhibiting medicinal products: Decreased hypotensive effects. In high-dose salicylate administration the toxic effect of salicylates on the central nervous system may be potentiated.

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

In patients developing hypovolaemia the concomitant administration of non-steroidal anti-inflammatory medicinal products (NSAIDs) can trigger acute renal failure.

Beta-sympathomimetics: Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetic medicinal products: Combination with bisoprolol may reduce the effect of both medicinal products. Higher doses of epinephrine may be necessary for treatment of allergic reactions.

Sympathomimetics that activate both beta- and alpha-adrenoceptors: Combination with bisoprolol may lead to blood pressure increase. Such interactions are considered to be more likely with nonselective beta-blockers.

The concurrent use of bisoprololfumarate/hydrochlorothiazide and potassium-wasting agents (e.g.

glucocorticoids, ACTH, carbenoxolone, amphotericin B, furosemide or laxatives) may result in increased potassium losses.

Methyldopa: haemolysis due to the formation of antibodies to hydrochlorothiazide has been described in isolated cases.

The effect of uric-acid-lowering medicinal products may be attenuated in concomitant administration of bisoprololfumarate/hydrochlorothiazide.

Cholestyramine, colestipol: reduces the absorption of the hydrochlorothiazide component of bisoprololfumarate/hydrochlorothiazide.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

Tricyclic antidepressants, barbiturates, phenothiazines: Increased blood pressure lowering effect.

Rifampicin: Slight reduction of the half -life of bisoprolol possible due to the induction of hepatic medicinal product-metabolising enzymes. Normally a dosage adjustment is not necessary.

The effect of curare-type muscle relaxants may be potentiated or prolonged by bisoprololfumarate/hydrochlorothiazide.

Cytostatics (e.g. cyclophosphamide, fluorouracil, methotrexate): increased bone marrow toxicity is to be expected.

Other concomitant treatment that should be used with caution: oral anticoagulants (the antithrombotic effect can be reduced by the use of thiazides) and probenecid (diminished diuretic action).

Combinations to be considered

Mefloquine: increased risk of bradycardia.

Corticosteroids: Reduced antihypertensive effect.

4.6 Fertility, pregnancy and lactation

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 shouldbe 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.

4.7 Effects on ability to drive and use machines

Bisoprololfumarate/hydrochlorothiazide has no or negligible influence on the ability to drive and use machines.

However, due to individual variations in reactions to the medicinal product, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of therapy and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

The reported undesirable effects of this medicinal product are generally attributable to its pharmacological effects.

These symptoms specially occur at the beginning of the therapy. They are generally mild and often disappear within 1-2 weeks.

Description of selected adverse reactions

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Special notes

Clinical signs of hypokalaemia: tiredness, fatigue, muscular weakness, paraesthesia, paresis, apathy, adynamia of smooth muscles with constipation, meteorism or cardiac arrhythmia, paralytic ileus, disturbances of consciousness, coma and ECG alterations.

The therapy should be discontinued in:

- Refractory disturbances of the electrolyte balance.

- Orthostatic regulatory disturbances.
- Hypersensitivity reactions.
- Pronounced gastrointestinal complaints.
- Central nervous disorder.
- Pancreatitis.
- Changes in blood count (anaemia, leukopenia, thrombocytopenia).
- Acute cholecystitis.
- Occurrence of vasculitis.
- Deterioration of existing myopia.
- Serum creatinine concentrations more than 1.8 mg/100 ml or creatinine clearance ≤ 30 ml/min.

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.

4.9 Overdose

Symptoms

The most common symptoms expected with overdose of a beta-blocker include bradycardia, hypotension, bronchospasm, acute cardiac insufficiency, hypoglycaemia and conduction disorders on ECG. 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.

The clinical picture in acute or chronic overdose of hydrochlorothiazide is characterised by the extent of fluid and electrolyte loss. Most common signs are dizziness, nausea, somnolence, hypovolaemia, hypotension, hypokalaemia.

Management

In general, if overdose occurs, discontinuation of bisoprololfumarate/hydrochlorothiazide and supportive and symptomatic treatment is recommended.

Bradycardia arising from an overdose is treated with atropine (1 mg to 2 mg intravenous), isoprenaline or temporarily with a pacemaker. The decrease of blood pressure is treated with intravenous liquids and, if necessary, vasopressors such as catecholamines.

Bronchospasms can be treated with theophylline, theophylline derivatives or □-mimetic medicinal products.

If a short time (0-2h) has passed from the overdose, active charcoal is given to the patient and gastric lavage may be considered. Heart rate, blood pressure, electrolyte- and glucose balance has to be monitored. Haemodialysis does not significantly increase the elimination of bisoprolol. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective and thiazides

Bisoprolol

Bisoprolol is a beta-blocker which occupies an intermediate position with regard to

lipophilia/ hydrophilia. Bisoprolol is highly β_1-selective ("cardioselective") without any intrinsic sympathomimetic activity (ISA) and without any clinically relevant membrane-stabilising effect. Through blockade of cardiac β-receptors bisoprolol depresses the response to sympathoadrenergic activity. This causes a decrease in heart rate and in contractility and thus a reduction of myocardial oxygen consumption.

Hydrochlorothiazide

Hydrochlorothiazide is a benzothiadiazine derivative which primarily increases electrolyte excretion and secondarily enhances urinary flow by osmotically bound water.

The sodium transport from the renal tubule to the blood is inhibited. This hinders sodium reabsorption. The natriuretic effect is accompanied by an increased potassium and magnesium excretion.

Hydrochlorothiazide inhibits predominantly sodium absorption in the distal tubule, so that maximally about 15 % of the sodium undergoing glomerular filtration can be excreted. The extent of chloride excretion roughly corresponds to that of sodium excretion.

Hydrochlorothiazide also causes an increase in potassium excretion which is essentially determined by the potassium secretion in the distal tubule and in the collecting tube (increased exchange between sodium and potassium ions). The saluretic or diuretic effect of hydrochlorothiazide is not influenced to any appreciable extent by acidosis or alkalosis.

The glomerular filtration rate is initially diminished to a slight extent. During long-term therapy with hydrochlorothiazide, the calcium excretion via the kidneys is reduced so that hypercalcaemia may result.

Hydrochlorothiazide reduces the peripheral resistance by relaxing smooth muscles of the blood vessels.

In patients with chronic renal insufficiency (creatinine clearance less than 30 ml/min and/or serum creatinine above 1.8 mg/100 ml) hydrochlorothiazide is practically ineffective. In patients with renal and ADH-sensitive diabetes insipidus, hydrochlorothiazide has an antidiuretic effect.

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥ 50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95 % CI: 1.23-1.35) for BCC and 3.98 (95 % CI: 3.68- 4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk -set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95 % CI: 1.7-2.6)

increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Bisoprolol

The bioavailability of bisoprolol from the film coated tablets is about 90 %. Bisoprolol is absorbed almost completely (> 90 %) from the gastrointestinal tract. Together with the very small first pass effect in the liver (< 10 %) this results in an absolute bioavailability of 88 %. Bisoprolol can be taken on an empty stomach or with breakfast, without any change in the absorption or bioavailability. The plasma protein binding of bisoprolol is about 30 %. Pathophysiological changes in plasma proteins like a1 glycoproteins, do not have an effect on the pharmacokinetics of bisoprolol. Peak plasma concentrations are usually measured after 1-3 hours after administration. Bisoprolol is only moderately lipophilic, and therefore it binds only weakly to plasma proteins, its distribution volume being 226 ± 11 l (x ± SEM).

Bisoprolol is removed from the organism via two equally effective clearance routes: half of it is transformed into inactive metabolites in the liver with excretion of the metabolites via the

kidneys, and half are excreted as unchanged substance via the kidneys. The plasma elimination half-life is 10-12 hours. The C_{max} and AUC-values of bisoprolol in the steady state are bioequivalent in the fixed combination with hydrochlorothiazide and in the monodrug preparation.

Hydrochlorothiazide

After oral administration about 80 % of hydrochlorothiazide is absorbed from the gastrointestinal tract. The systemic availability is 71 ± 15 %.

The plasma protein binding of hydrochlorothiazide is 64 %; the relative volume of distribution is 0.5-1.1 l/kg.

In healthy humans more than 95 % of hydrochlorothiazide is excreted via the kidneys as unchanged substance.

With normal kidney function the elimination half-life is 9-13 hours. Peak plasma concentrations are usually measured after 2-5 hours. This period increases in the presence of impaired kidney function and is about 20 hours in patients with terminal renal insufficiency.

The diuretic effect sets in within 1-2 hours and lasts for 10-12 hours depending on the dose; the antihypertensive effect lasts for up to 24 hours.

5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose, calcium hydrogen phosphate, pregelatinised maize starch, colloidal anhydrous silica, magnesium stearate

Tablet coating

Hypromellose, dimeticone ,macrogol, titanium dioxide, iron oxide red.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package

Do not store above 30 °C

6.5 Special precautions for disposal and other handling

No special requirements.

7. Manufactured in India by:
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