Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Bisocor Plus 2.5/6.25 Tablet
Bisocor Plus 5 / 6.25 Tablet

2. Qualitative and quantitative composition

Bisocor Plus 2.5/6.25 Tablet

Each film coated tablet contains Bisoprolol Fumarate USP 2.5 mg and Hydrochlorothiazide BP 6.25 mg.

For a full list of excipients, see section 6.1

Bisocor Plus 5 / 6.25 Tablet

Each film coated tablet contains Bisoprolol Fumarate USP 5 mg and Hydrochlorothiazide BP 6.25 mg

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Bisocor Plus 2.5/6.25 Tablet

Oral Tablet
A white biconvex, heart shaped, film coated tablets plain on both sides.

Bisocor Plus 5 / 6.25 Tablet.

Oral tablet.
A pink color, heart shaped, film -coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Bisocor Plus 2.5/6.25 Tablet
Indicated in the management of hypertension.

Bisocor Plus 5 / 6.25 Tablet.
Indicated in the management of hypertension.

4.2 Posology and method of administration

management of hypertension

Adults

Bisoprolol is an effective treatment of hypertension in once-daily doses of 2.5 to 40mg, while Hydrochlorothiazide is effective in doses of 12.5 to 50 mg. In clinical trials of Bisoprolol/Hydrochlorothiazide combination therapy using Bisoprolol doses of 2.5 to 20 mg and Hydrochlorothiazide doses of 6.25 to 25 mg, the antihypertensive effects increased with increasing doses of either component.

Initial Therapy

Antihypertensive therapy may be initiated with the lowest dose of Bisocor Plus, one 2.5/6.25 mg tablet once daily. Subsequent titration (14-day intervals) may be carried out with Bisocor Plus Tablets up to the maximum recommended dose 20/12.5 mg once daily, as appropriate.

Replacement Therapy

The combination may be substituted for the titrated individual components.

Therapy Guided by Clinical Effect

A patient whose blood pressure is not adequately controlled with 2.5-20 mg Bisoprolol daily may instead, be given Bisocor Plus. Patients whose blood pressures are adequately controlled with 50 mg of Hydrochlorothiazide daily, but who experience significant potassium loss with this regimen, may achieve similar blood pressure control without electrolyte disturbance if they are switched to Bisocor Plus.

Cessation of Therapy

If withdrawal of Bisocor Plus therapy is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed.see section 4.4

Special populations
Renal or liver impairment

As noted in the WARNINGS section, caution must be used in dosing/titrating patients with hepatic impairment or renal dysfunction. Since there is no indication that hydrochlorothiazide is dialyzable, and limited data suggest that bisoprolol is not dialyzable, drug replacement is not necessary in patients undergoing dialysis.

Geriatric Patients

Dosage adjustment on the basis of age is not usually necessary, unless there is also significant renal or hepatic dysfunction (see section 4.4).

Paediatric Patients

There is no pediatric experience with Bisoprolol Fumarate and Hydrochlorothiazide.

4.3 Contraindications

It is contraindicated in patients in cardiogenic shock, overt cardiac failure (see section 4.4), secondary third-degree AV block, marked sinus bradycardia, anuria and hypersensitivity to either component of this product or to other sulfonamide-derived drugs.

4.4 Special warnings and precautions for use

Warnings

Cardiac Failure

In general, beta-blocking agents should be avoided in patients with overt congestive failure. However, in some patients with compensated cardiac failure, it may be necessary to utilize these agents. In such situations, they must be used cautiously.

Patients Without a History of Cardiac Failure

Continued depression of the myocardium with beta-blockers can, in some patients, precipitate cardiac failure. At the first signs or symptoms of heart failure, discontinuation of Bisocor Plus should be considered. In some cases Bisocor Plus therapy can be continued while heart failure is treated with other drugs.

Abrupt Cessation of Therapy

Exacerbations of angina pectoris and, in some instances, myocardial infarction or ventricular arrhythmia, have been observed in patients with coronary artery disease following abrupt cessation of therapy with beta-blockers. Such patients should, therefore, be cautioned against interruption or discontinuation of therapy without the physician's advice. Even in patients without overt coronary artery disease, it may be advisable to taper therapy with Bisocor Plus (bisoprolol fumarate and hydrochlorothiazide) over approximately 1 week with the patient under careful observation. If withdrawal symptoms occur, beta-blocking agent therapy should be reinstituted, at least temporarily.

Peripheral Vascular Disease

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

Bronchospastic Disease

PATIENTS WITH BRONCHOSPASTIC PULMONARY DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of the relative beta1-selectivity of bisoprolol fumarate, Bisocor Plus may be used with caution in patients with bronchospastic disease who do not respond to, or who cannot tolerate other antihypertensive treatment. Since beta1-selectivity is not absolute, the lowest possible dose of Bisocor Plus should be used. A beta2 agonist (bronchodilator) should be made available.

Major Surgery

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Diabetes and Hyopglycemia

Beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective beta-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Because of its beta1-selectivity, this is less likely with bisoprolol fumarate. However, patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these possibilities. Also, latent diabetes mellitus may become manifest and diabetic patients given thiazides may require adjustment of their insulin dose. Because of the very low dose of HCTZ employed, this may be less likely with Bisocor Plus .

Thyrotoxicosis

Beta-adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

Renal Disease

Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia. In subjects with creatinine clearance less than 40 mL/min, the plasma half-life of bisoprolol fumarate is increased up to threefold, as compared to healthy subjects. If progressive renal impairment becomes apparent, Bisocor Plus should be discontinued (See Pharmacokinetics and Metabolism).

Hepatic Disease

Bisocor Plus should be used with caution in patients with impaired hepatic function or progressive liver disease. Thiazides may alter fluid and electrolyte balance, which may precipitate hepatic coma. Also, elimination of bisoprolol fumarate is significantly slower in patients with cirrhosis than in healthy subjects (See section 5.2).

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

PRECAUTIONS

Hyperuricemia or acute gout may be precipitated in certain patients receiving thiazide diuretics. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop. If withdrawal of this combination therapy is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed.

4.5 Interaction with other medicinal products and other forms of interaction

This combination drug may potentiate the action of other antihypertensive agents used concomitantly. This combination drug should not be combined with other beta blocking agents. Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be closely monitored because the added beta-adrenergic blocking action of Bisoprolol Fumarate may produce excessive reduction of sympathetic activity. In patients receiving concurrent therapy with clonidine, if therapy is to be discontinued, it is suggested that this combination drug be discontinued for several days before the withdrawal of clonidine. This combination drug should be

used with caution when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide, are used concurrently. Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Bisoprolol Fumarate

Concurrent use of rifampin increases the metabolic clearance of bisoprolol fumarate, shortening its elimination half-life. However, initial dose modification is generally not necessary.

Pharmacokinetic studies document no clinically relevant interactions with other agents given concomitantly, including thiazide diuretics and cimetidine. There was no effect of bisoprolol fumarate on prothrombin times in patients on stable doses of warfarin.

Risk of Anaphylactic Reaction
While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

Hydrochlorothiazide

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 cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption in the gastrointestinal tract by up to 85 percent and 43 percent, 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, non-depolarizing (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 Bisocor Plus.

Nonsteroidal anti-inflammatory drugs - In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium sparing, and thiazide diuretics. Therefore, when Bisocor Plus and nonsteroidal antiinflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Photosensitivity reactions and possible exacerbation or activation of systemic lupus erythematosus have been reported in patients receiving thiazides. The antihypertensive effects of thiazides may be enhanced in the post-sympathectomy patient.

4.6 Pregnancy and Lactation

Use in Pregnancy: Pregnancy Category C.

In rats, the bisoprolol fumarate/hydrochlorothiazide (B/H) combination was not teratogenic at doses up to 51.4 mg/kg/day of bisoprolol fumarate in combination with 128.6 mg/kg/day of hydrochlorothiazide. Bisoprolol fumarate and hydrochlorothiazide doses used in the rat study are, as multiples of the MRHD in the combination, 129 and 514 times greater, respectively, on a body weight basis, and 26 and 106 times greater, respectively, on the basis of body surface area. The drug combination was maternotoxic (decreased body weight and food consumption) at B5.7/H14.3 (mg/kg/day) and higher, and fetotoxic (increased late resorptions) at B17.1/H42.9 (mg/kg/day) and higher. Maternotoxicity was present at 14/57 times the MRHD of B/H, respectively, on a body weight basis, and 3/12 times the MRHD of B/H doses, respectively, on the basis of body surface area. Fetotoxicity was present at 43/172 times the MRHD of B/H, respectively, on a body weight basis, and 9/35 times the MRHD of B/H doses, respectively, on the basis of body surface area. In rabbits, the B/H combination was not teratogenic at doses of B10/H25 (mg/kg/day). Bisoprolol fumarate and hydrochlorothiazide used in the rabbit study were not teratogenic at 25/100 times the B/H MRHD, respectively, on a body weight basis, and 10/40 times the B/H MRHD, respectively, on the basis of body surface area. The drug combination was maternotoxic (decreased body weight) at B1/H2.5 (mg/kg/day) and higher, and fetotoxic (increased resorptions) at B10/H25 (mg/kg/day). The multiples of the MRHD for the B/H combination that were maternotoxic are, respectively, 2.5/10 (on the basis of body weight) and 1/4 (on the basis of body surface

area), and for fetotoxicity were, respectively 25/100 (on the basis of body weight) and 10/40 (on the basis of body surface area).

There are no adequate and well-controlled studies in pregnant women. Bisoprolol Fumarate and Hydrochlorothiazide combination should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Use in Nursing Mothers:
Bisoprolol Fumarate alone or in combination with Hydrochlorothiazide has not been studied in nursing mothers. Thiazides are excreted in human breast milk. Small amounts of Bisoprolol Fumarate have been detected in the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

In a 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

General
Generally it is well tolerated. Most side effects have been mild and transient. Sideeffects which may occur: fatigue, dizziness, headache, bradycardia, arrhythmia, peripheral ischemia, chest pain, palpitations, rhythm disturbances, cold extremities, claudication, orthostatic hypotension, diarrhoea, constipation, nausea, dyspepsia, rhinitis, pharyngitis etc**.**

Tabulated list of adverse Drug reactions

In more than 65,000 patients treated worldwide with bisoprolol fumarate, occurrences of bronchospasm have been rare. Discontinuation rates for AEs were similar for bisoprolol fumarate/HCTZ 6.25 mg and placebo-treated patients.

In the United States, 252 patients received bisoprolol fumarate (2.5, 5, 10, or 40 mg)/HCTZ 6.25 mg and 144 patients received placebo in two controlled trials. In Study 1, bisoprolol fumarate 5/HCTZ 6.25 mg was administered for 4 weeks. In Study 2, bisoprolol fumarate 2.5, 10, or 40/HCTZ 6.25 mg was administered for 12 weeks. All adverse experiences, whether drug related or not, and drug related adverse

experiences in patients treated with bisoprolol fumarate 2.510/HCTZ 6.25 mg, reported during comparable, 4 week treatment periods by at least 2% of bisoprolol fumarate/HCTZ 6.25 mg-treated patients (plus additional selected adverse experiences) are presented in the following table:

	% of Patients with Adverse Experiences[a]			
Body System/ Adverse Experience	All Adverse Experiences		Drug Related Adverse Experiences	
	Placebo[b]	B2.5-40/H6.25[b]	Placebo[b]	B2.5-10/H6.25[b]
	(n=144)	(n=252)	(n=144)	(n=221)
	%	%	%	%
Cardiovascular				
bradycardia	0.7	1.1	0.7	0.9
arrhythmia	1.4	0.4	0.0	0.0
peripheral ischemia	0.9	0.7	0.9	0.4
chest pain	0.7	1.8	0.7	0.9
Respiratory				
bronchospasm	0.0	0.0	0.0	0.0
cough	1.0	2.2	0.7	1.5
rhinitis	2.0	0.7	0.7	0.9
URI	2.3	2.1	0.0	0.0
Body as a Whole				
asthenia	0.0	0.0	0.0	0.0
fatigue	2.7	4.6	1.7	3.0
peripheral edema	0.7	1.1	0.7	0.9
Central Nervous System				
dizziness	1.8	5.1	1.8	3.2
headache	4.7	4.5	2.7	0.4
Musculoskeletal				
muscle cramps	0.7	1.2	0.7	1.1
myalgia	1.4	2.4	0.0	0.0
Psychiatric				
insomnia	2.4	1.1	2.0	1.2
somnolence	0.7	1.1	0.7	0.9
loss of libido	1.2	0.4	1.2	0.4
impotence	0.7	1.1	0.7	1.1
Gastrointestinal				
diarrhea	1.4	4.3	1.2	1.1
nausea	0.9	1.1	0.9	0.9
dyspepsia	0.7	1.2	0.7	0.9

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

There are limited data on overdose with this combination product. The most frequently observed signs expected with overdosage of a beta-blocker are bradycardia and hypotension. Lethargy is also common and with severe overdoses, delirium, coma, convulsions and respiratory arrest have been reported to occur. Congestive heart failure, bronchospasm and hypoglycemia may occur. With thiazide diuretics, acute intoxication is rare. The most prominent feature of overdose is acute loss of fluid and electrolytes. Signs and symptoms include cardiovascular (tachycardia, hypotension, shock), neuromuscular (weakness, confusion, dizziness, cramps of the calf muscles, paresthesia, fatigue, impairment of consciousness), gastrointestinal (nausea, vomiting, thirst), renal (polyuria, oliguria or anuria), and laboratory findings (hypokalemia, hyponatremia, hypochloremia, alkalosis, increased BUN [especially in patients with renal insufficiency]).

If over-dosage of bisoprolol fumarate and hydrochlorothiazide is suspected, therapy bisoprolol fumarate and hydrochlorothiazide with should be discontinued and the patient observed closely. Treatment is symptomatic and supportive; there is no specific antidote. Limited data suggest bisoprolol fumarate is not dialyzable; similarly, there is no indication that hydrochlorothiazide is dialyzable. Suggested general measures include induction of emesis and/or gastric lavage, administration of activated charcoal, respiratory support, correction of fluid and electrolyte imbalance, and treatment of convulsions. Based on the expected pharmacologic actions and recommendations for other beta-blockers and hydrochlorothiazide, the following measures should be considered when clinically warranted:

Bradycardia

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

Hypotension, Shock

The patient's legs should be elevated. IV fluids should be administered and lost electrolytes (potassium, sodium) replaced.

Intravenous glucagon may be useful. Vasopressors should be considered.

Heart Block (second or third degree)

Patients should be carefully monitored and treated with isoproterenol infusion or transvenous cardiac pacemaker insertion, as appropriate.

Congestive Heart Failure

Initiate conventional therapy (ie, digitalis, diuretics, vasodilating agents, inotropic agents).

Bronchospasm

Administer a bronchodilator such as isoproterenol and/or aminophylline.

Hypoglycemia

Administer IV glucose.

Surveillance

Fluid and electrolyte balance (especially serum potassium) and renal function should be monitored until normalized.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combined antihypertensive preparations, ATC code: Bisoprolol Fumarate: C07AB07 & Hydrochlorothiazide: C03AA03

Mechanism of action

Bisoprolol Fumarate and Hydrochlorothiazide have been used individually and in combination for the treatment of hypertension. The antihypertensive effects of these agents are additive; Hydrochlorothiazide 6.25 mg significantly increases the antihypertensive effect of Bisoprolol Fumarate. The incidence of hypokalemia with the Bisoprolol Fumarate and Hydrochlorothiazide 6.25 mg combination is significantly lower than with Hydrochlorothiazide 25 mg.

Bisoprolol Fumarate is a β1-selective (cardio selective) adrenoceptor blocking agent without significant membrane stabilizing or intrinsic sympathomimetic activities in its therapeutic dose range. At higher doses (≥ 20 mg) bisoprolol fumarate also inhibits beta2-adrenoreceptors located in bronchial and vascular musculature. To retain relative selectivity, it is important to use the lowest effective dose.

Hydrochlorothiazide is a benzothiadiazide diuretic. Thiazides affect renal tubular mechanisms of electrolyte reabsorption and increase excretion of sodium and chloride in approximately equivalent amounts.

Pharmacodynamics effects

Bisoprolol Fumarate

Findings in clinical hemodynamics studies with bisoprolol fumarate are similar to those observed with other beta-blockers. The most prominent effect is the negative chronotropic effect, giving a reduction in resting and exercise heart rate. There is a fall in resting and exercise cardiac output with little observed change in stroke volume, and only a small increase in right atrial pressure, or pulmonary capillary wedge pressure at rest or during exercise.

In normal volunteers, bisoprolol fumarate therapy resulted in a reduction of exercise- and isoproterenol-induced tachycardia. The maximal effect occurred within 1-4 hours post-dosing. Effects generally persisted for 24 hours at doses of 5 mg or greater.

In controlled clinical trials, bisoprolol fumarate given as a single daily dose has been shown to be an effective antihypertensive agent when used alone or concomitantly with thiazide diuretics (see CLINICAL STUDIES).

The mechanism of bisoprolol fumarate's antihypertensive effect has not been completely established. Factors that may be involved include:

1) Decreased cardiac output,

2) Inhibition of renin release by the kidneys,

3) Diminution of tonic sympathetic outflow from vasomotor centers in the brain.

Beta1-selectivity of bisoprolol fumarate has been demonstrated in both animal and human studies. No effects at therapeutic doses on beta2-adrenoreceptor density have been observed. Pulmonary function studies have been conducted in healthy volunteers, asthmatics, and patients with chronic obstructive pulmonary disease (COPD). Doses of bisoprolol fumarate ranged from 5 to 60 mg, atenolol from 50 to 200 mg, metoprolol from 100 to 200 mg, and propranolol from 40 to 80 mg. In some studies, slight, asymptomatic increases in airway resistance (AWR) and decreases in forced expiratory volume (FEV1) were observed with doses of bisoprolol fumarate 20 mg and higher, similar to the small increases in AWR noted with other cardioselective beta-blocking agents. The changes induced by beta-blockade with all agents were reversed by bronchodilator therapy.

Electrophysiology studies in man have demonstrated that bisoprolol fumarate significantly decreases heart rate, increases sinus node recovery time, prolongs AV node refractory periods, and, with rapid atrial stimulation, prolongs AV nodal conduction.

Hydrochlorothiazide

Acute effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect, although a direct vasodilatory mechanism has also been proposed. With chronic administration, plasma volume returns toward normal, but peripheral vascular resistance is decreased.

Thiazides do not affect normal blood pressure. Onset of action occurs within 2 hours of dosing, peak effect is observed at about 4 hours, and activity persists for up to 24 hours.

CLINICAL STUDIES

In controlled clinical trials, bisoprolol fumarate/hydrochlorothiazide 6.25 mg has been shown to reduce systolic and diastolic blood pressure throughout a 24-hour period when administered once daily. The effects on systolic and diastolic blood pressure reduction of the combination of bisoprolol fumarate and hydrochlorothiazide were additive. Further, treatment effects were consistent across age groups (<60, ≥ 60 years), racial groups (black, nonblack), and gender (male, female).

In two randomized, double-blind, placebo-controlled trials conducted in the U.S., reductions in systolic and diastolic blood pressure and heart rate 24 hours after dosing in patients with mild-tomoderate hypertension are shown below. In both studies mean systolic/diastolic blood pressure and heart rate at baseline were approximately 151/101 mm Hg and 77 bpm

Sitting Systolic/Diastolic Pressure (BP) and Heart Rate (HR)						
	Mean Decrease (Δ) After 3-4 Weeks					
	Study 1		Study 2			
	Placebo	B5/H6.25 mg	Placebo	H6.25 mg	B2.5 / H6.25 mg	B10/ H6.25 mg
n=	75	150	56	23	28	25
Total ΔBP (mm Hg)	-2.9/-3.9	-15.8/-12.6	-3.0/-3.7	-6.6/-5.8	-14.1/-10.5	-15.3/-14.3
Drug Effect[a]	-/-	-12.9/-8.7	-/-	-3.6/-2.1	-11.1/-6.8	-12.3/-10.6
Total ΔHR (bpm)	-0.3	-6.9	-1.6	-0.8	-3.7	-9.8
Drug Effect	-	-6.6	-	+0.8	-2.1	-8.2

a) Observed mean change from baseline minus placebo.

Blood pressure responses were seen within 1 week of treatment but the maximum effect was apparent after 2 to 3 weeks of treatment. Overall, significantly greater blood pressure reductions were observed on bisoprolol fumarate/hydrochlorothiazide than on placebo. Further, blood pressure reductions were significantly greater for each of the bisoprolol fumarate plus hydrochlorothiazide combinations than for either of the components used alone regardless of race, age, or gender. There were no significant differences in response between black and nonblack patients.

5.2 Pharmacokinetic properties

In healthy volunteers, both bisoprolol fumarate and hydrochlorothiazide are well absorbed following oral administration of bisoprolol fumarate and hydrochlorothiazide Tablet. No change is observed in the bioavailability of either agent when given together in a single tablet. Absorption is not affected whether Bisocor plus Tablet is taken with or without food. Mean peak bisoprolol fumarate plasma concentrations of about 9.0 ng/mL, 19 ng/mL and 36 ng/mL occur approximately 3 hours after the administration of the 2.5 mg/6.25 mg, 5 mg/6.25 mg and 10 mg/6.25 mg combination tablets, respectively. Mean peak plasma hydrochlorothiazide concentrations of 30 ng/mL occur approximately 2.5 hours following the administration of the combination. Dose proportional increases in plasma bisoprolol concentrations are observed between the 2.5 and 5, as well as between the 5 and 10 mg doses. The elimination T1/2 of bisoprolol ranges from 7 to 15 hours, and that of hydrochlorothiazide ranges from 4 to 10 hours. The percent of dose excreted unchanged in urine is about 55% for bisoprolol and about 60% for hydrochlorothiazide.

Bisoprolol Fumarate

The absolute bioavailability after a 10 mg oral dose of bisoprolol fumarate is about 80%. The first pass metabolism of bisoprolol fumarate is about 20%.
The pharmacokinetic profile of bisoprolol fumarate has been examined following single doses and at steady state. Binding to serum proteins is approximately 30%. Peak plasma concentrations occur within 2-4 hours of dosing with 2.5 to 20 mg, and mean peak values range from 9.0 ng/mL at 2.5 mg to 70 ng/mL at 20 mg. Once-daily dosing with bisoprolol fumarate results in less than twofold intersubject variation in peak plasma concentrations. Plasma concentrations are proportional to the administered dose in the range of 2.5 to 20 mg. The plasma elimination half-life is 9-12 hours and is slightly longer in elderly patients, in part because of decreased renal function. Steady state is attained within 5 days with once-daily dosing. In both young and elderly populations, plasma accumulation is low; the accumulation factor ranges from 1.1 to 1.3, and is what would be expected from the

half-life and once-daily dosing. Bisoprolol is eliminated equally by renal and nonrenal pathways with about 50% of the dose appearing unchanged in the urine and the remainder in the form of inactive metabolites. In humans, the known metabolites are labile or have no known pharmacologic activity. Less than 2% of the dose is excreted in the feces. The pharmacokinetic characteristics of the two enantiomers are similar. Bisoprolol is not metabolized by cytochrome P450 II D6 (debrisoquin hydroxylase).
In subjects with creatinine clearance less than 40 mL/min, the plasma half-life is increased approximately threefold compared to healthy subjects.
In patients with liver cirrhosis, the rate of elimination of bisoprolol is more variable and significantly slower than that in healthy subjects, with a plasma half-life ranging from 8 to 22 hours.
In elderly subjects, mean plasma concentrations at steady state are increased, in part attributed to lower creatinine clearance. However, no significant differences in the degree of bisoprolol accumulation are found between young and elderly populations.

Hydrochlorothiazide

Hydrochlorothiazide is well absorbed (65%-75%) following oral administration. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure.
Peak plasma concentrations are observed within 1-5 hours of dosing, and range from 70-490 ng/mL following oral doses of 12.5-100 mg. Plasma concentrations are linearly related to the administered dose. Concentrations of hydrochlorothiazide are 1.6-1.8 times higher in whole blood than in plasma. Binding to serum proteins has been reported to be approximately 40% to 68%. The plasma elimination half-life has been reported to be 6-15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways. Following oral doses of 12.5-100 mg, 55%-77% of the administered dose appears in urine and greater than 95% of the absorbed dose is excreted in urine as unchanged drug. Plasma concentrations of hydrochlorothiazide are increased and the elimination half-life is prolonged in patients with renal disease.

5.3 Preclinical safety data

Not available.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose (PH 102)
Pregelatinised starch
Anhydrous Calcium Hydrogen Phosphate
Colloidal Silicon Dioxide (Aerosil 200)
Magnesium Stearate

Opadry II 85G68918 (White)

6.2 Incompatibilities

Not Applicable.

6.3 Shelf-Life

2 Years (24 Months).

6.4 Special Precautions for storage

Store below 30°C. Protect from light and moisture. Keep the Medicine out of reach of children.

6.5 Nature and Content of container

3 × 10'S; 10 Tablets in an Alu - Alu blister pack.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

SQUARE Pharmaceuticals PLC.
Square Road, Salgaria, Pabna 6600
BANGLADESH.
Tel: + 8802588842582—86
Cell: + 88 01777712318

8. Marketing Authorization Number

Bisocor Plus 2.5/6.25 Tablet

CTD10377

Bisocor Plus 5 / 6.25 Tablet

CTD10376

9. Date of first authorization/renewal of the authorization

Bisocor Plus 2.5/6.25 Tablet

23/08/2024

Bisocor Plus 5 / 6.25 Tablet

23/08/2024

10. Date of revision of the text

9/5/2025