117mm

180mm

Tablet

# Bisel

**(Bisoprolol Fumarate)**

بائیسیل ٹیبلیٹ

(بسوپرولول فیوماریٹ)

**COMPOSITION:**

**Bisel Tablet 5mg**

Each film coated tablet contains:

Bisoprolol fumarate .....5mg

**(USP Specifications)**

**Bisel Tablet 10mg**

Each film coated tablet contains:

Bisoprolol fumarate .....10mg

**(USP Specifications)**

## DRUG DESCRIPTION

Bisel (bisoprolol fumarate) is a synthetic, beta1-selective (cardioselective) adrenoceptor blocking agent. It is a white crystalline powder which is approximately equally hydrophilic and lipophilic, and is readily soluble in water, methanol, ethanol, and chloroform.

Bisel (bisoprolol fumarate) is available as 5 and 10 mg tablets for oral administration.

## INDICATIONS

Bisel (bisoprolol fumarate) is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents.

## DOSAGE AND ADMINISTRATION

The dose of Bisel (bisoprolol fumarate) must be individualized to the needs of the patient. The usual starting dose is 5 mg once daily. In some patients, 2.5 mg may be an appropriate starting dose. If the antihypertensive effect of 5 mg is inadequate, the dose may be increased to 10 mg and then, if necessary, to 20 mg once daily.

***Patients with Renal or Hepatic Impairment***

In patients with hepatic impairment (hepatitis or cirrhosis) or renal dysfunction (creatinine clearance less than 40 ml/min), the initial daily dose should be 2.5 mg and caution should be used in dose-titration. Since limited data suggest that bisoprolol fumarate is not dialyzable, drug replacement is not necessary in patients undergoing dialysis.

## CLINICAL PHARMACOLOGY

Bisel (bisoprolol fumarate) is a beta1-selective (cardioselective) adrenoceptor blocking agent without significant membrane stabilizing activity or intrinsic sympathomimetic activity in its therapeutic dosage range. Cardioselectivity is not absolute, however, and at higher doses (≥ 20mg) bisoprolol fumarate also inhibits beta2-adrenoceptors, chiefly located in the bronchial and vascular musculature to retain selectivity it is therefore important to use the lowest effective dose.

***Pharmacokinetics and Metabolism***

The absolute bioavailability after a 10 mg oral dose of bisoprolol fumarate is about 90%. Absorption is not affected by the presence of food. The first pass metabolism of bisoprolol fumarate is about 10%.

Binding to serum proteins is approximately 30%. Peak plasma concentrations occur within 2-4 hours of dosing with 5 to 20 mg, and mean peak values range from 16 ng/ml at 5mg to 70 ng/ml at 20 mg. Once daily dosing with bisoprolol fumarate results in less than twofold intersubject variation in peak plasma levels. The plasma elimination half-life is 9-12 hours and is slightly longer in elderly patients, in part because of decreased renal function in that population. Steady state is attained within 5 days of once daily dosing. In both young and elderly populations, plasma accumulation is low; the accumulation factor ranges from 1.1 to 1.3, and what would be expected from the first order kinetics and once daily dosing. Plasma concentrations are proportional to the administered dose in the range of 5 to 20 mg. Pharmacokinetic characteristics of the two enantiomers are similar.

Bisoprolol fumarate is eliminated equally by renal and non-renal pathways with about 50% of the dose appearing unchanged in the urine and the remainder appearing 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. Bisoprolol fumarate is not metabolized by cytochrome P450 II D6 (debrisoquine 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 cirrhosis of the liver, the elimination of Bisel (bisoprolol fumarate) is more variable in rate and significantly slower than that in healthy subjects, with plasma half-life ranging from 8.3 to 21.7 hours.

***Pharmacodynamics***

The most prominent effect of Bisel (bisoprolol fumarate) is the negative chronotropic effect, resulting in 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. Findings in short-term clinical hemodynamics studies with Biscord (bisoprolol fumarate) are similar to those observed with other beta-blocking agents.

The mechanism of action of its antihypertensive effects has not been completely established. Factors which may be involved include:

1. Decreased cardiac output.
2. Inhibition of renin release by the kidneys.
3. Diminution of tonic sympathetic outflow from the vasomotor centers in the brain.

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

Electrophysiology studies in man have demonstrated that Bisel (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.

$Beta_1$-selectivity of Bisel (bisoprolol fumarate) has been demonstrated in both animal and human studies. No effects at therapeutic doses on beta2-adrenoceptor density have been observed. Pulmonary function studies have been conducted in healthy volunteers, asthmatics, and patients with chronic obstructive pulmonary disease (COPD). Doses of Bisel (bisoprolol fumarate) ranged from 5 to 60mg, atenolol from 50 to 200 mg, metoprolol from 100 to 200 mg, and propranolol from 40 to 80mg. In some studies, slight, asymptomatic increases in airways resistance (AWR) and decreases in forced expiratory volume (FEV1) were observed with doses of bisoprolol fumarate 20mg and higher, similar to the small increases in AWR also noted with the other cardioselective beta-blockers. The changes induced by beta-blockade with all agents were reversed by bronchodilator therapy.

117mm

## SIDE EFFECTS

Safety data are available in more than 30,000 patients or volunteers. Frequency estimates and rates of withdrawl of therapy for adverse events were derived from two U.S. placebo-controlled studies.

***Central Nervous System :*** anxiety/restlessness, decreased concentration/memory.

***Autonomic Nervous System :*** Dry mouth.

***Cardiovascular :*** Bradycardia, palpitations and other rhythm disturbances, cold extremities, claudication, hypotension, orthostatic hypotension, chest pain, congestive heart failure, dyspnea on exertion.

***Psychiatric :*** Vivid dreams, insomnia, depression.

***Gastrointestinal :*** Gastric/epigastric/abdominal pain, gastritis, dyspepsia, nausea, vomiting, diarrhea, constipation, peptic ulcer.

***Musculoskeletal :*** Muscle/joint pain, *arthralgia*, back/neck pain, muscle cramps, twitching/tremor.

***Skin :*** Rash, acne, eczema, psoriasis, skin irritation, pruritus, flushing, sweating, alopecia, *dermatitis, angioedema, exfoliative dermatitis*, cutaneous vasculitis.

***Special Senses :*** Visual disturbances, ocular pain/pressure, abnormal lacrimation, tinnitus, *decreased hearing*, earache, taste abnormalities.

***Metabolic :*** Gout.

***Respiratory :*** Asthma/bronchospasm, bronchitis, coughing, dyspnea, pharyngitis, rhinitis, sinusitis, URI.

***General :*** Fatigue, asthenia, chest pain, malaise, edema, weight gain, angioedema.

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Bisel (bisoprolol fumarate) :

## DRUG INTERACTIONS

Bisel (bisoprolol fumarate) 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 Bisel (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 Bisel (bisoprolol fumarate) be discontinued for several days before the withdrawal of clonidine.

Bisel (bisoprolol fumarate) should be used with care 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.

Concurrent use of rifampin increases the metabolic clearance of Bisel (bisoprolol fumarate) , resulting in a shortened elimination half-life of Bisel (bisoprolol fumarate) . 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 Bisel (bisoprolol fumarate) on prothrombin time in patients on stable doses of warfarin.

## PRECAUTIONS

***Impaired Renal or Hepatic Function***

Use caution in adjusting the dose of Bisel (bisoprolol fumarate) in patients with renal or hepatic impairment

***Pregnancy Category C***

In rats, bisoprolol fumarate was not teratogenic at doses up to 150 mg/kg/day which is 375 and 77 times the MRHD on the basis of body weight and body surface area, respectively. Bisoprolol fumarate was fetotoxic (increased late resorptions) at 50 mg/kg/day and maternotoxic (decreased food intake and body weight gain) at 150 mg/kg/day. The fetotoxicity in rats occurred at 125 times the MRHD on a body weight basis and 26 times the MRHD on the basis of body surface area. The maternotoxicity occurred at 375 times the MRHD on a body weight basis and 77 times the MRHD on the basis of body surface area. In rabbits, bisoprolol fumarate was not teratogenic at doses up to 12.5 mg/kg/day, which is 31 and 12 times the MRHD based on body weight and body surface area respectively but was embryolethal (increased early resorptions) at 12.5 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Bisel (bisoprolol fumarate) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

## STORAGE & INSTRUCTIONS

Store between 15-25°C.

Protect from heat, sunlight and moisture.

Keep away from the reach of children.

**To be sold on prescription of registered medical practitioner only.**

## HOW SUPPLIED

**Bisel Tablet 5mg**

20's Tablets.

**Bisel Tablet 10mg**

20's Tablets.

## خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

## ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Manufactured by:

**PHARMASOL**

PRIVATE LIMITED

Plot # 549, Sundar Industrial Estate,

Lahore, Pakistan.