1.3.1 Summary of product characteristics (SmPC)

Summary of products characteristics (SmPC) of Corbis 5 (Bisoprolol Fumarate Tablets USP 5 mg) is enclosed overleaf.

CORBIS 5
(Bisoprolol Fumarate Tablets USP 5 mg)

1. Name of the Medicinal Product

1.1 Product name : CORBIS 5

1.2 Strength : Bisoprolol Fumarate Tablets USP 5 mg

1.3 Pharmaceutical Dosage form : Tablets

2. Qualitative and Quantitative Composition

2.1 Qualitative Declaration : The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.
Refer Standard Batch Formula enclosed overleaf.

2.2 Quantitative Declaration : The quantity of the active substance must be expressed per dosage unit (for metered dose inhalation products, per puff) per unit volume or per unit of weight).
Refer Standard Batch Formula enclosed overleaf.

Sr. No.	Ingredients	Quantity /mg	Function
1	Bisoprolol Fumarate USP	5.000	Active
2	Calcium Hydrogen Phosphate Anhydrous Ph.Eur./BP	40.000	Diluent
3	Microcrystalline Cellulose BP	85.000	Diluent
4	Colloidal Silicone Dioxide BP	0.300	Glidant
5	Pregelatinised Starch BP	19.000	Disintegrate
6	Magnesium Stearate BP	0.700	Lubricant
7	Ferric Oxide Yellow USP/NF***	0.010	Colouring Agent
8	Titanium Dioxide BP***	0.669	Opacifier
9	Triacetin BP***	0.365	Plasticizer
10	Hydroxypropyl Methyl Cellulose BP ***	1.946	Film Former
11	Ethyl Cellulose BP***	0.010	Film Former
12	Methanol BP***	q.s.	Coating solvent
13	Methylene Chloride BP ***	q.s.	Coating solvent

***- Includes 30% process overages to compensate loss during coating.

3. Pharmaceutical Form

Light yellow coloured, round, biconvex film coated tablets with break line on one side.

CORBIS 5
(Bisoprolol Fumarate Tablets USP 5 mg)

4. CLINICAL PARTICULARS

4.1 Therapeutic indication(s)

Bisoprolol fumarate is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents. Bisoprolol fumarate is also indicated in the management of coronary heart disease (Angina pectoris).

4.2 Posology and method of administration

The dose of Bisoprolol should be individualized to the needs of the patient. For the treatment of hypertension or coronary heart disease (Angina pectoris), the usual starting dose is 5 mg once daily. For patients with bronchospastic disease, the starting dose should be 2.5 mg. 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. In patients with hepatic impairment or renal dysfunction, 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.
It is not necessary to adjust the dose in elderly patients, unless there is also significant renal or hepatic dysfunction.
There is no pediatric experience with Bisoprolol.
Method of administration: Via the oral route.

4.3 Contra-indications

Cardiac Failure: Special caution should be exercised when administering Bisoprolol to patients with a history of severe heart failure. Safety and effectiveness of Bisoprolol doses higher than 10 mg per day in patients with heart failure have not been established. In general, β-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 them. In such a situation, they must be used cautiously.
Bisoprolol acts selectively without abolishing the effects of digitalis. However, the positive inotropic effect of digitalis may be reduced by the negative inotropic effect of Bisoprolol when the two drugs are used concomitantly. The effects of β-blockers and digitalis are additive in depressing A-V conduction.
Patients without a History of Cardiac Failure: In patients without a history of cardiac failure, continued depression of the myocardium with β-blockers in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately and the response observed closely. If cardiac failure continues, Bisoprolol therapy should be immediately withdrawn.
Abrupt cessation of therapy with Bisoprolol: Exacerbation 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 β-blockers. 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 Bisoprolol over approximately two weeks and the patient should be carefully observed. The
same frequency of administration should be maintained.

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.
Sinus Bradycardia: Severe sinus bradycardia, resulting from unopposed vagal activity following β-blockade, may occur with the use of Bisoprolol. In such cases, the dosage should be reduced or Bisoprolol discontinued.
Thyrotoxicosis: In patients with thyrotoxicosis, possible deleterious effects from long-term use of Bisoprolol have not been adequately appraised. β-adrenoceptor blockade may mask clinical signs of hyperthyroidism, such as tachycardia or its complications and gives a false impression of improvement. Abrupt withdrawal of β- blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or precipitate thyroid storm. Therefore, in such patients from whom Bisoprolol is to be discontinued, withdrawal should be gradual and the patients monitored closely.

4.4 Special warnings and precautions for use

Bronchospastic Disease: In general, patients with bronchospastic pulmonary disease should not receive β-blockers. However, because Bisoprolol is relatively β1-selective, it may be used cautiously in patients with bronchospastic disease who do not respond to, or who cannot tolerate other antihypertensive treatment.
Since β1-selectivity is not absolute, the lowest possible dose should be employed, a β2-agonist (bronchodilator) should be made available, and the patient should be monitored closely. In patients already on bronchodilator therapy the dose may have to be increased.
Anaesthesia: It is not advisable to withdraw β-adrenoceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using Bisoprolol with anaesthetic agents such as those which may depress the myocardium.
Vagal dominance, if it occurs, may be corrected with atropine (1 to 2 mg i.v.). Some patients receiving β-adrenoceptor blocking agents have been subject to protracted severe hypotension during anaesthesia. In emergency surgery, since Bisoprolol is a competitive antagonist at β-adrenoceptor sites, its effects may be reversed, if required, by sufficient doses of such agonists as isoproterenol or noradrenaline.
Allergic Type Reaction: There may be increased difficulty in treating an allergic type reaction in patients on β-blockers. In these patients, the reaction may be more severe due to pharmacologic effects of the beta-blockers and the problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of β-agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm or norepinephrine to overcome hypotension.
Risk of Anaphylactic Reaction: While taking β-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.
Diabetes Mellitus and Hypoglycemia: β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Therefore, Bisoprolol should be used with caution in

patients subject to spontaneous hypoglycemia, or in diabetic patients (especially those with labile diabetes) receiving insulin or oral hypoglycemic agents.
Impaired Renal or Hepatic Function: Appropriate laboratory tests for monitoring renal, hepatic and hematopoietic function should be performed at regular intervals during long-term treatment with Bisoprolol.
Geriatrics: Bisoprolol has been used in elderly patients with essential hypertension. Although the response rates and mean decreases in diastolic blood pressure were similar to that in younger patients, there was a tendency for older patients to be maintained on higher doses of Bisoprolol. Observed reductions in heart rate were slightly greater in the elderly than in the young and tended to increase with increasing dose.
Pregnancy: Bisoprolol Fumarate was not teratogenic in rabbits at doses up to 12.5 mg/kg/day, which is 31 times the maximum recommended human daily dose, but was embryo lethal (increased early Resorptions) at 12.5 mg/kg/day. There are no studies in pregnant women. Bisoprolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation: Small amounts of Bisoprolol (<2% of the dose) have been detected in the milk of lactating rats. It is not known whether this drug is excreted in human milk. If use of Bisoprolol is considered essential, then mothers should stop nursing.
Children: Safety and effectiveness in children have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Bisoprolol 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 may produce excessive reduction of sympathetic activity. In patients receiving concurrent therapy with clonidine, if therapy is to be discontinued. It is suggested that Bisoprolol should be discontinued for several days before withdrawal of clonidine.
Bisoprolol should be used with caution when myocardial depressants or antiarrhythmic agents are used concurrently. Concurrent use of rifampicin increases the metabolic clearance of Bisoprolol Fumarate, shortening its elimination half-life.
No effect of Bisoprolol Fumarate on prothrombin time in patients on stable doses of warfarin.
While taking beta-blockers, patients with a history of severe anaphylactic reaction may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic and may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

4.6 Fertility, pregnancy and lactation

Pregnancy: Bisoprolol Fumarate was not teratogenic in rabbits at doses up to 12.5 mg/kg/day, which is 31 times the maximum recommended human daily dose, but was embryo lethal (increased early resorptions) at 12.5 mg/kg/day. There are no studies in pregnant women. Bisoprolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation: Small amounts of Bisoprolol (<2% of the dose) have been detected in the milk of lactating rats. It is not known whether this drug is excreted in human milk. If use of Bisoprolol is considered essential, then mothers should stop nursing.

CORBIS 5
(Bisoprolol Fumarate Tablets USP 5 mg)

4.7 Effects on the ability to drive and use machines

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4.8 Undesirable effects

Bisoprolol is generally well tolerated in most patients. Most adverse effects are mild and transient. Headache, dizziness, fatigue may be reported by some patients, especially in early phase of treatment.
They may subside on continued use of the drug.
The other side-effects seen may include bradycardia, bronchospasm, muscle cramps, insomnia, epigastric discomfort and nausea, diarrhoea, dry mouth, skin rashes etc.

4.9 Overdose

Symptoms: The most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, congestive heart failure, bronchospasm, and hypoglycemia.
To date, a few cases of overdose with Bisoprolol have been reported. Bradycardia and/or hypotension were noted.
Treatment: Sympathomimetic agents were given in some cases and all patients recovered. In general, if overdose occurs, therapy with Bisoprolol should be stopped and supportive, symptomatic treatment should be provided. Patients should be monitored closely. Limited data suggest that Bisoprolol is not dialyzable.
Based on the expected pharmacologic actions and recommendations for other betablockers, the Following general measures should be considered when clinically warranted:
Bradycardia: Administer i.v. 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. Intravenous glucagon has been described to be useful.
Hypotension: I.V. fluids and vasopressors such as dopamine or norepinephrine should be administered. Monitor blood pressure continuously. Intravenous glucagon may be useful.
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 (i.e. digitalis, diuretics, inotropic agents, vasodilating agents). Glucagon has been reported to be useful.
Bronchospasm: Administer bronchodilator therapy such as isoproterenol or terbutaline (β2 stimulants) and/or i.v. aminophylline.
Hypoglycemia: Administer i.v. glucose.
Based on the severity of symptoms, management may require intensive support care and facilities for administering cardiac and respiratory support.
It should be remembered that Bisoprolol is a competitive antagonist of isoproterenol and hence large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of Bisoprolol. However, complications of excess isoproterenol should not be overlooked.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Bisoprolol Fumarate is a beta1-selective (cardioselective) adrenoreceptor blocking agent without significant membrane stabilizing or intrinsic sympathomimetic activity in its therapeutic dose range. At higher doses (> 20 mg) Bisoprolol Fumarate also inhibits beta2-

adrenoreceptors located in the bronchial and vascular musculature. To retain relative selectivity, it is important to use the lowest effective dose.

5.2 Pharmacokinetic properties

In healthy volunteers, Bisoprolol Fumarate is well absorbed following oral administration. Absorption is not affected by food. Mean peak Bisoprolol Fumarate plasma concentrations are achieved within 2-4 hours of dosing with 5-20 mg. Plasma concentrations are proportional to the administered dose in the range of 5-20 mg. The elimination half-life of Bisoprolol ranges from 9 to 12 hours. The first pass metabolism of Bisoprolol is about 20%. Binding to serum proteins is approximately 30%. Bisoprolol is eliminated equally by renal and nonrenal route with about 50% of
the dose appearing unchanged in urine.
In subjects with creatinine clearance less than 40mL/min, the plasma half-life is increased Approximately three-fold compared to healthy subjects. Bisoprolol is not
metabolized by cytochrome P450.
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Hydrogen Phosphate Anhydrous BP
Microcrystalline Cellulose (Avicel PH 112) BP
Colloidal Silicon Dioxide (Aerosil 200) BP
Pregelatinised Starch (Starch 1500) BP
Magnesium Stearate BP
Ferric Oxide Yellow USP/NF
Titanium Dioxide BP
Triacetin BP
Hydroxypropyl Methyl Cellulose 5 cps BP
Ethyl Cellulose BP
Methanol BP
Methylene Chloride BP

6.2 Incompatibilities

None known

6.3 Shelf-life

36 months

CORBIS 5
(Bisoprolol Fumarate Tablets USP 5 mg)

6.4 Special precautions for storage

Store below 30º C

6.5 Nature and contents of container
Carton containing 3 aluminium strips of 10 tablets along with pack insert.

6.6 Special precautions for disposal < and other handling >

No special requirements.

7. Marketing authorization holder and manufacturing site addresses

Corporate Office:
Unichem Laboratories Limited,
Unichem Bhavan, Prabhat Estate,
S. V. Road, Jogeshwari (West),
Mumbai – 400 102 , INDIA
Phone: 91-22-66888333
Fax: 91-22-26785198/4391

Manufacturing Site:
Unichem Laboratories Limited,
Unit-II, Village Bhatauli Kalan,
Baddi, Dist. Solan (H.P) – 173 205
Himachal Pradesh - 173205
INDIA
Phone: 00-91-1795-245322/244507
Fax: 00-91-1795-244508

8. Marketing Authorization Number : A4-4670

9. Date of first authorization/renewal of the authorization : 3rd December 2015

10. Date of revision of the text: June 2020

1.3.2 Labelling (primary and secondary packaging)

Enclosed overleaf Printed label and Carton for Corbis 5 (Bisoprolol Fumarate Tablets USP 5 mg)

5 mm | 40 mm | 5 mm | 5 mm | 40 mm | 5 mm | 5 mm | 40 mm | 5 mm

Corbis 5

Bisoprolol Fumarate Tablets USP 5 mg

Store below 30°C.

Zambia Lic . No.: 268/022 POM 12004338

M. L. No. MNB/04/91

Manufactured in India by :

UNICHEM LABORATORIES LTD.

Unit-II, Village Bhatauli Kalan, Baddi,
Dist. Solan (H.P.) - 173 205.

Corbis 5

Bisoprolol Fumarate Tablets USP 5 mg

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Zambia Lic . No.: 268/022 POM 12004338

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Manufactured in India by :

UNICHEM LABORATORIES LTD.

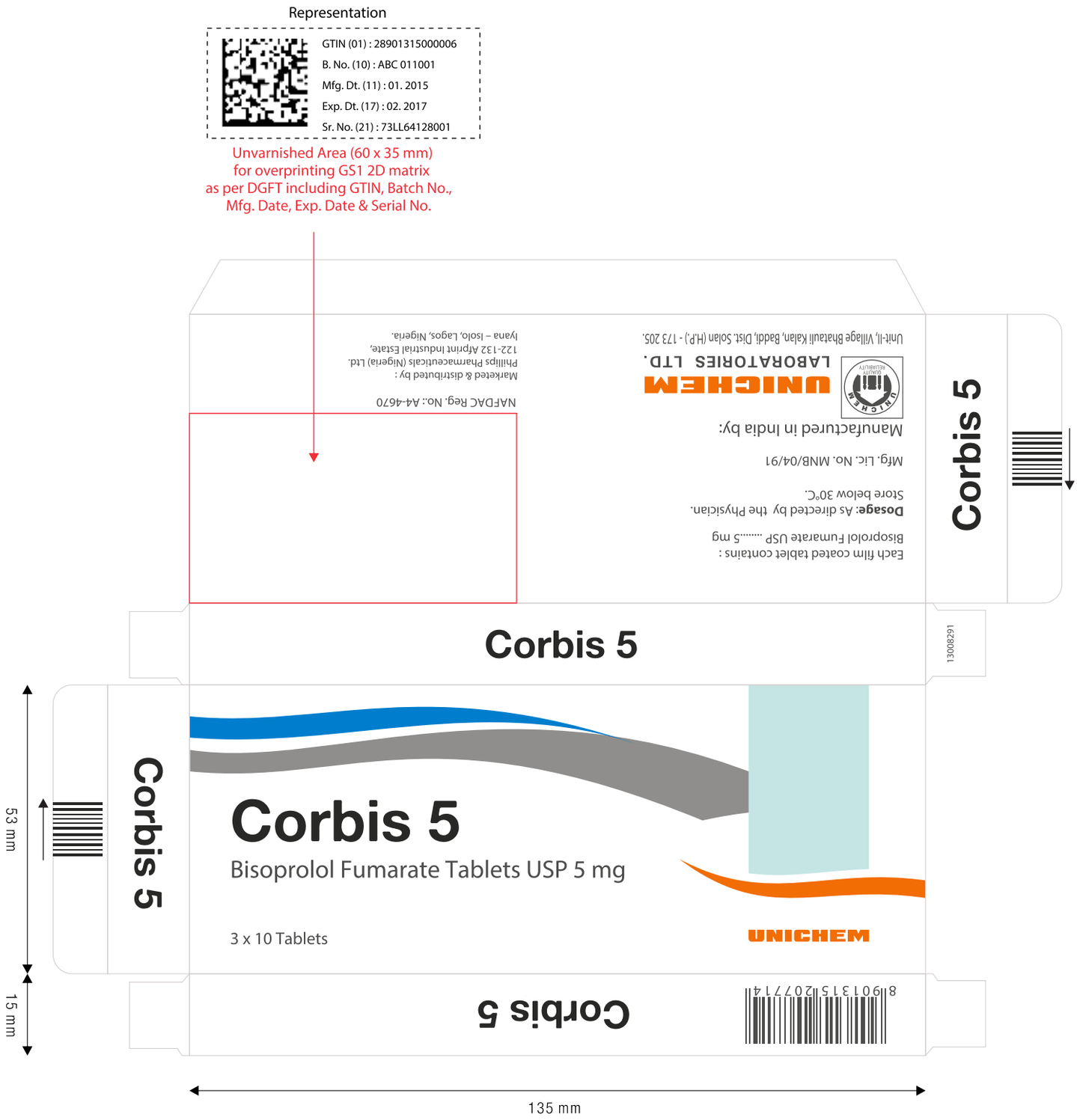
Unit-II, Village Bhatauli Kalan, Baddi,
Dist. Solan (H.P.) - 173 205.

44 mm

150 mm

Company Name : UNICHEM LABORATORIES LTD.		**Date:** 23-10-2015
Agency Name: UNICHEM ARTLAB		**Foil Width:** 150 mm (Repeat Length: 44 mm)
Product: Corbis 5 Foil	**Packing:** 10 Tablets	**Strip Size:** 50 x 130 mm
Item Code: 12004338	**Location:** Baddi Unit II	**Layout No.:**
Specification: 0.03 mm Aluminium thickness foil with LDPE lamination		**Text :** Common export text with 30 degrees.
Colour Scheme: Single colour Black (K 100)		
Reason: The brand name font & the rest text font has been synchronized with the approved fonts on cartons. The text of the artwork has been streamlined with the concurrence of IBD & RA.		

IMPORTANT NOTE : THE PRINTER CAN ASK FOR PRINTED SAMPLE AS COLOUR REFERENCE FOR BETTER REPRODUCTION OF COLOUR SCHEME. DOUBTS REGARDING FONTS/DESIGN/COLOUR SCHEME OR ANY OTHER DISCREPANCY REGARDING THE ARTWORK FILE, DO CONTACT THE PACKAGING DEVELOPMENT DEPARTMENT.



Company Name : UNICHEM LABORATORIES LTD.		**Date:** 16-6-2016, 2-8-17
Agency Name: UNICHEM ARTLAB		**Size:** 53 x 15 x 135 mm
Product: Corbis 5 Carton	**Packing:** 3 x 10 Tablets	**Barcode:** 8901315207714
Item Code: 13008291	**Location:** Baddi II	**Pharmacode:** 3636
Specification: 300 gsm Folding Box Board (CFB)-ITC Cyber XL, with aqua varnish.		**Country :** Nigeria
Reason: Artwork developed with IBD approved – silver wave concept, element & colour scheme. Removed "Heart" from design element to comply with NAFDAC requirements mail dated 24 may 2016. 2-8-17: correct Pharmacode inserted & direction shown.		

Guidelines to printer for processing & printing :

1. 5 colour printing job with PANTONE scheme.
2. 5 PANTONE colours : Pantone 3005 C ■ Pantone 317 C ■ Pantone Orange 021 C ■ Pantone Process Black C ■ Pantone 877 C SILVER ■
3. Shade that need to appear from the 5 colours to be used for printing : 80% Process Black C
4. The printer can ask for printed sample as a colour reference for better reproduction of colour scheme. For doubts, regarding fonts/design/colour scheme or any other discrepancy observed regarding the artwork file, do contact Packaging Development Department.
5. Pantone Orange 021 C should appear as it is on the shade card with varnish. i.e. the light, standard and dark shades of orange should be perceptible as Pantone Orange 021 C to human eye

1.3.3 Package insert and patient information leaflet

Enclosed overleaf Package Insert for Corbis 5 (Bisoprolol Fumarate Tablets USP 5 mg)

165 mm

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

Corbis

Bisoprolol Fumarate Tablets USP

COMPOSITION:

Corbis 2.5

Each film coated tablet contains: Bisoprolol Fumarate USP ..... 2. 5 mg

Excipients: Calcium Hydrogen Phosphate Anhydrous, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Pregelatinised Starch, Magnesium Stearate, Brilliant Blue Lake, Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose 5 cps, Ethyl Cellulose, Methyl Alcohol, Dichloromethane.

Corbis 5

Each film coated tablet contains: Bisoprolol Fumarate USP ..... 5 mg

Excipients: Calcium Hydrogen Phosphate Anhydrous, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Pregelatinised Starch, Magnesium Stearate, Yellow oxide of Iron, Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose 5 cps, Ethyl Cellulose, Methyl Alcohol, Dichloromethane.

Corbis 10

Each film coated tablet contains: Bisoprolol Fumarate USP ..... 10 mg

Excipients: Calcium Hydrogen Phosphate Anhydrous, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Pregelatinised Starch, Magnesium Stearate, Red oxide of Iron , Titanium Dioxide, Triacetin, Hydroxy Propyl Methyl Cellulose 5 cps, Ethyl Cellulose, Methyl Alcohol, Dichloromethane.

DOSAGE FORM : Tablets

CATEGORY OF DISTRIBUTION: Prescription Preparation.

THERAPEUTIC CLASS: Antihypertensive.

DESCRIPTION OF PRODUCT : Corbis 2.5: Light blue coloured, circular, biconvex film coated tablets with breakline on one side and plain on other side.

Corbis 5: Light yellow coloured, round, biconvex film coated tablets with break line on one side.

Corbis 10: Light pink, round, biconvex film coated tablets plain on both the sides.

PHARMACODYNAMICS:

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

Bisoprolol fumarate is indicated for the treatment of hypertension and coronary heart disease (Angina pectoris).

PHARMACOKINETICS:

In healthy volunteers, bisoprolol fumarate is well absorbed following oral administration. Absorption is not affected by food. Mean peak bisoprolol fumarate plasma concentrations are achieved within 2-4 hours of dosing with 5-20 mg. Plasma concentrations are proportional to the administered dose in the range of 5-20 mg. The elimination half-life of bisoprolol ranges from 9 to 12 hours. The first pass metabolism of bisoprolol is about 20 %. Binding to serum proteins is approximately 30 %. Bisoprolol is eliminated equally by renal and nonrenal route with about 50% of the dose appearing unchanged in urine.

In subjects with creatinine clearance less than 40 mL/min, the plasma half-life is increased approximately three-fold compared to healthy subjects. Bisoprolol is not metabolized by cytochrome P450.

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.

INDICATIONS:

Bisoprolol fumarate is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents. Bisoprolol fumarate is also indicated in the management of coronary heart disease (Angina pectoris).

CONTRAINDICATIONS:

In patients with cardiogenic shock, overt heart failure, second or third degree A-V block, right ventricular failure secondary to pulmonary hypertension, and sinus bradycardia.

WARNINGS:

Cardiac Failure: Special caution should be exercised when administering bisoprolol to patients with a history of severe heart failure. Safety and effectiveness of bisoprolol doses higher than 10 mg per day in patients with heart failure have not been established. In general, ß-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 them. In such a situation, they must be used cautiously. Bisoprolol acts selectively without abolishing the effects of digitalis. However, the positive inotropic effect of digitalis may be reduced by the negative inotropic effect of bisoprolol when the two drugs are used concomitantly. The effects of ß-blockers and digitalis are additive in depressing A-V conduction.

Patients Without a History of Cardiac Failure: In patients without a history of cardiac failure continued depression of the myocardium with ß-blockers in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately and the response observed closely. If cardiac failure continues, bisoprolol therapy should be immediately withdrawn.

Abrupt Cessation of Therapy with Bisoprolol: Exacerbation 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 ß-blockers. 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 bisoprolol over approximately two weeks and the patient should be carefully observed. The same frequency of administration should be maintained.

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.

Sinus Bradycardia: Severe sinus bradycardia, resulting from unopposed vagal activity following b-blockade, may occur with the use of bisoprolol. In such cases, the dosage should be reduced or bisoprolol discontinued.

Thyrotoxicosis: In patients with thyrotoxicosis, possible deleterious effects from long-term use of bisoprolol have not been adequately appraised. ß-adrenoceptor blockade may mask clinical signs of hyperthyroidism, such as tachycardia or its complications and gives a false impression of improvement. Abrupt withdrawal of b-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or precipitate thyroid storm. Therefore, in such patients from whom bisoprolol is to be discontinued, withdrawal should be gradual and the patients monitored closely.

PRECAUTIONS:

Appropriate laboratory tests for monitoring renal, hepatic, and hematopoietic function should be performed at regular intervals during long-term treatment with bisoprolol.

Bronchospastic Disease: In general, patients with bronchospastic pulmonary disease should not receive b-blockers. However, because bisoprolol is relatively ß, -selective, it may be used cautiously in patients with bronchospastic disease who do not respond to, or who cannot tolerate other antihypertensive treatment. Since ß, -selectivity is not absolute, the lowest possible dose should be employed, a ß,-agonist (bronchodilator) should be made available, and the patient should be monitored closely. In patients already on bronchodilator therapy the dose may have to be increased.

Anaesthesia: It is not advisable to withdraw ß-adrenoceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using bisoprolol with anaesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1 to 2 mg i.v.). Some patients receiving ß-adrenoceptor blocking agents have been subject to protracted severe hypotension during anaesthesia. In emergency surgery, since bisoprolol is a competitive antagonist at ß-adrenoceptor sites, its effects may be reversed, if required, by sufficient doses of such agonists as isoproterenol or noradrenaline.

Allergic Type Reaction: There may be increased difficulty in treating an allergic type reaction in patients on ß-blockers. In these patients, the reaction may be more severe due to pharmacologic effects of the beta-blockers and the problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine

include vigorous supportive care such as fluids and the use of ß-agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm or norepinephrine to overcome hypotension.

Risk of Anaphylactic Reaction: While taking ß-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.

Diabetes Mellitus and Hypoglycemia: ß-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Therefore, bisoprolol should be used with caution in patients subject to spontaneous hypoglycemia, or in diabetic patients (especially those with labile diabetes) receiving insulin or oral hypoglycemic agents. Impaired Renal or Hepatic Function: Appropriate laboratory tests for monitoring renal, hepatic and hematopoietic function should be performed at regular intervals during long-term treatment.

Geriatrics: Bisoprolol has been used in elderly patients with essential hypertension. Although the response rates and mean decreases in diastolic blood pressure were similar to that in younger patients, there was a tendency for older patients to be maintained on higher doses of bisoprolol. Observed reductions in heart rate were slightly greater in the elderly than in the young and tended to increase with increasing dose.

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Lactation: Small amounts of bisoprolol (<2% of the dose) have been detected in the milk of lactating rats. It is not known whether this drug is excreted in human milk. If use of bisoprolol is considered essential, then mothers should stop nursing.

Children: Safety and effectiveness in children have not been established.

DRUG INTERACTIONS:

Bisoprolol 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 may produce excessive reduction of sympathetic activity. In patients receiving concurrent therapy with clonidine, if therapy is to be discontinued. It is suggested that bisoprolol should be discontinued for several days before withdrawal of clonidine. Bisoprolol should be used with caution when myocardial depressants or antiarrhythmic agents are used concurrently. Concurrent use of rifampicin increases the metabolic clearance of bisoprolol fumarate, shortening its elimination half-life. No effect of bisprolol fumarate on prothrombin time in patients on stable doses of warfarin.

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

ADVERSE EFFECTS:

Bisoprolol is generally well tolerated in most patients. Most adverse effects are mild and transient. Headache, dizziness, fatigue may be reported by some patients, especially in early phase of treatment.

They may subside on continued use of the drug.

The other side-effects seen may include bradycardia, bronchospasm, muscle cramps, insomnia, epigastric discomfort and nausea, diarrhoea, dry mouth, skin rashes etc.

Overdose: Symptoms: The most common signs expected with overdosage of a b-blocker are bradycardia, hypotension, congestive heart failure, bronchospasm, and hypoglycemia. To date, a few cases of overdose with bisoprolol have been reported. Bradycardia and/or hypotension were noted.

Treatment: Sympathomimetic agents were given in some cases, and all patients recovered. In general, if overdose occurs, therapy with bisoprolol should be stopped and supportive, symptomatic treatment should be provided. Patients should be monitored closely. Limited data suggest that bisoprolol is not dialysable. Based on the expected pharmacologic actions and recommendations for other ß- blockers, the following general measures should be considered when clinically warranted:

Bradycardia: Administer i.v. 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. Intravenous glucagon has been described to be useful.

Hypotension: I.V. fluids and vasopressors such as dopamine or norepinephrine should be administered. Monitor blood pressure continuously. Intravenous glucagon may be useful.

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 (i.e., digitalis, diuretics, inotropic agents, vasodilating agents). Glucagon has been reported to be useful.

Bronchospasm: Administer bronchodilator therapy such as isoproterenol or terbutaline (ß, stimulants) and/or i.v. aminophylline.

Hypoglycemia: Administer i.v. glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for administering cardiac and respiratory support.

It should be remembered that bisoprolol is a competitive antagonist of isoproterenol and hence large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of bisoprolol. However, complications of excess isoproterenol should not be overlooked.

DOSAGE AND ADMINISTRATION:

The dose of bisoprolol should be individualized to the needs of the patient. For the treatment of hypertension or coronary heart disease (Angina pectoris), the usual starting dose is 5 mg once daily. For patients with bronchospastic disease, the starting dose should be 2.5 mg. 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.

In patients with hepatic impairment or renal dysfunction, 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.

It is not necessary to adjust the dose in elderly patients, unless there is also significant renal or hepatic dysfunction.

There is no pediatric experience with bisoprolol.

STORAGE:

Store below 30°C.

Protect from light & moisture.

Keep all medicines out of reach of children.

NATURE & CONTENT OF CONTAINER (PRESENTATION) : An Aluminium strip is the container. 10 tablets are packed in this strip. Strip/s & a leaflet in turn are packed in carton/s.

Shelf Life : 24/36 Months (Please refer on the pack).

Product	Zambia Lic. No. POM	Tanzania Registration No. :
Corbis 2.5	—	—
Corbis 5	268/022	TAN 10, 072 C06A UNI
Corbis 10	268/021	TAN 10, 073 C06A UNI

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Company Name : UNICHEM LABORATORIES LTD.		**Date:** 26-10-2015
Agency Name: Unichem Art Lab		**Open Size:** 90 x 165 mm
Product: Corbis Leaflet	**Packing:** NA	**Folded Size:** 45 x 165 mm
Item Code: 13008211	**Location:** Baddi Unit II	**No. of folds:** 1 vertical
Specification: 54 gsm Maplitho Paper	**Text :** Common Export text with 30°C.	
Colour Code: Text in black		
Reason: The brand name font & the rest text font has been synchronized with the approved fonts on cartons. The text of the artwork has been streamlined with the concurrence of IBD & RA.		