PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

BISOPROLOL CO UNICORN 5/6,25 TABLETS

BISOPROLOL CO UNICORN 10/6,25 TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BISOPROLOL CO UNICORN 5/6,25: Each film-coated tablet contains 5 mg bisoprolol fumarate and 6,25 mg hydrochlorothiazide.

BISOPROLOL CO UNICORN 10/6,25: Each film-coated tablet contains 10 mg bisoprolol fumarate and 6,25 mg hydrochlorothiazide.

BISOPROLOL CO UNICORN film-coated tablets are sugar free.

3. PHARMACEUTICAL FORM

BISOPROLOL CO UNICORN 5/6,25: Pink-coloured, film-coated, round tablets debossed with “5” on one side and plain on the other side.

BISOPROLOL CO UNICORN 10/6,25: White to off-white-coloured, film-coated, round tablets debossed with “10” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BISOPROLOL CO UNICORN is indicated for the treatment of hypertension in patients who have been stabilised on the individual components given in the same proportions.

4.2 Posology and method of administration

Adults*:* Antihypertensive therapy may be initiated with the lowest dose of bisoprolol/hydrochlorothiazide 2,5/6,25 mg, taking one tablet once daily. Another formulation should be used. Subsequent dose adjustment may be carried out with **BISOPROLOL CO UNICORN** tablets up to the maximum recommended dose of one 10/6,25 mg tablet once daily as appropriate.

Withdrawal of **BISOPROLOL CO UNICORN** therapy should be achieved gradually over a period of about two weeks. Patients should be carefully monitored.

A daily dose of 10 mg bisoprolol should not be exceeded in patients with mild to moderate renal or hepatic impairment.

Special populations

Elderly:

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

Children:

Efficacy and safety in children less than 12 years have not been established (see section 4.5).

4.3 Contraindications

- Hypersensitivity to bisoprolol or to any of the ingredients of **BISOPROLOL CO UNICORN.**
- Hypersensitivity to hydrochlorothiazide or other sulphonamide derived medicines.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.
- Second and third-degree heart block and bradycardia (less than 50 beats per minute).
- Pregnancy and lactation (see section 4.6).
- Uncontrolled cardiac failure.
- Cardiogenic shock.
- Severe hypotension (systolic blood pressure of less than 100 mmHg).
- Metabolic acidosis.
- Sinus bradycardia (less than 50 beats per minute).
- Phaeochromocytoma.
- Hyperthyroidism, as clinical manifestations may be masked.
- Bronchospasm or asthma, or patients with a history of bronchitis or chronic respiratory diseases.
- Late stage peripheral vascular diseases and Raynaud's phenomenon.
- Addison’s disease.
- Severe renal impairment (creatinine clearance < 30 ml/minute).
- Severe hepatic impairment, in which encephalopathy may be precipitated (see section 4.5).
- Porphyria.

4.4 Special warnings and precautions for use

- Safety and efficacy in children have not been established.
- If the decision is made to withdraw **BISOPROLOL CO UNICORN** before anaesthesia, at least 48 hours should be allowed to elapse between the last dose and surgery. If **BISOPROLOL CO UNICORN** is to be continued, care should be taken when using anaesthetics such as ether, cyclopropane and trichloroethylene. Atropine (1 – 2 mg I.V.) may be used to correct vagal dominance. The patient must be maintained on the usual dosage perioperatively to avoid aggravation of angina pectoris or hypertension.
- Particular caution should be taken in diabetes mellitus, as symptoms and signs of hypoglycaemia, such as tachycardia, may be masked by **BISOPROLOL CO UNICORN**, and response to hypoglycaemia is diminished. **BISOPROLOL CO UNICORN** may also delay recovery of insulin-induced hypoglycaemia.
- A potentially life-threatening reaction may occur between **BISOPROLOL CO UNICORN** and quinidine. The thiazide induced K^+ depletion worsens the quinidine-induced torsades des pointes and the bisoprolol aggravates these effects further.
- Tachycardic responses, due to hypovolaemia or blood loss, may be obscured during or after surgery. Particular caution should be taken in this regard.
- The dosage of **BISOPROLOL CO UNICORN** should be adjusted in patients with renal impairment (see section 4.2).
- Care should be taken in prescribing **BISOPROLOL CO UNICORN** together with Class 1 antidysrhythmic agents such as disopyramide, myocardial depressants, and inhibitors of AV conduction, such as calcium antagonists.

BISOPROLOL CO UNICORN should be used with caution in combination with verapamil in patients with impaired ventricular function. This combination should not be given to patients with conduction abnormalities. Neither medicine should be administered within 48 hours of discontinuing the other.

The intravenous administration of calcium antagonists and antidysrhythmic agents should be avoided during therapy with **BISOPROLOL CO UNICORN.**

- Patients with phaeochromocytoma who are receiving **BISOPROLOL CO UNICORN** require pre-treatment with an alpha-adrenergic blocker (see section 4.3).
- **BISOPROLOL CO UNICORN** may increase sensitivity towards allergens and the incidence of anaphylactic reactions. Treatment of anaphylaxis with epinephrine (adrenaline) does not always have the expected effect.
- Exacerbation of peripheral vascular disease or the development of Raynaud's phenomenon may occur with the use of **BISOPROLOL CO UNICORN** due to unopposed arteriolar alpha-sympathomimetic activation. Peripheral gangrene may be precipitated (see section 4.3).
- **BISOPROLOL CO UNICORN** may reduce tear flow causing irritation of the eye in contact lens wearers.
- Caution should be exercised when transferring a patient from clonidine, as the withdrawal of clonidine may result in the release of large amounts of catecholamines that may give rise to a hypertensive crisis. If **BISOPROLOL CO UNICORN** is administered in these circumstances, the unopposed alpha-receptor stimulation may potentiate this effect. If **BISOPROLOL CO UNICORN** and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of **BISOPROLOL CO**

UNICORN as severe rebound hypertension may occur (see section 4.5). Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual (see section 4.2). Patients should be advised to limit the extent of their physical activity during the period that **BISOPROLOL CO UNICORN** is being discontinued.

- Patients with psoriasis should be given **BISOPROLOL CO UNICORN** with caution.
- Digitalisation of patients receiving long-term beta-blocker therapy, such as **BISOPROLOL CO UNICORN**, may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages, and of the individual patient's response (and notably pulse rate), is essential in this situation (see section 4.5).

Renal Insufficiency:

Hydrochlorothiazides, such as in **BISOPROLOL CO UNICORN,** should be used with caution in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. severe renal insufficiency).

Hepatic Disease:

Caution should be exercised when hydochlorothiazides (as in **BISOPROLOL CO UNICORN**) are used in patients with hepatic impairment or progressive liver disease, as minor alterations of fluid and electrolyte balance may precipitate hepatic coma in these patients.

Metabolic and Endocrine Effects:

Hydrochlorothiazide diuretics, as in **BISOPROLOL CO UNICORN**, may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.

Decreased urinary calcium excretion caused by hydrochlorothiazides may result in intermittent and a slightly raised serum calcium concentration. Should marked hypercalcaemia occur, it may be evidence of underlying hyperparathyroidism. **BISOPROLOL CO UNICORN** therapy should be discontinued before carrying out tests for parathyroid function (see section 4.5). Increased cholesterol and triglyceride levels may be a result of the hydrochlorothiazide diuretic (contained in **BISOPROLOL CO UNICORN**) therapy.

Hydrochlorothiazide diuretics may precipitate hyperuricaemia and/or gout in certain patients.

In patients receiving hydrochlorothiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of hydrochlorothiazides, as contained in **BISOPROLOL CO UNICORN**.

Ocular Effects:

Hydrochlorothiazide, such as in **BISOPROLOL CO UNICORN,** can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. The risk is greater in patients with a history of sulfonamide or penicillin allergy. Symptoms include active onset of decreased visual acuity or ocular pain and typically occur within hours to week of drug initiation. Primary treatment is discontinuation of **BISOPROLOL CO UNICORN** as rapidly as possible. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

Non-melanoma skin cancer:

An increased risk of nonmelanoma 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. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC. Patients taking **BISOPROLOL CO UNICORN** 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 the 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. **BISOPROLOL CO UNICORN** should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

- Calcium channel blockers, such as verapamil and diltiazem should not be given concomitantly with **BISOPROLOL CO UNICORN** (see section 4.5).
- **BISOPROLOL CO UNICORN**, containing bisoprolol, may potentiate the effect of other concomitantly administered antihypertensives. Centrally acting antihypertensives, such as methyldopa, may worsen heart failure by a decrease in central sympathetic tone.
- Strong inducers of the hepatic cytochrome P450 isoenzymes, CYP3A4 and CYP2D6, such as rifampicin and the barbiturates, may shorten the half-life of bisoprolol. An increase in the dose of **BISOPROLOL CO UNICORN**, however, is generally unnecessary with rifampicin.

- Strong inhibitors of the hepatic cytochrome P450 isoenzymes CYP3A4 and CYP2D6, such as cimetidine, erythromycin, fluoxetine and hydralazine may increase the half-life of bisoprolol. The pharmacokinetics of bisoprolol is not significantly influenced by cimetidine.
- Topical beta-blocker eye drops may add to the systemic side-effects of **BISOPROLOL CO UNICORN.**
- Concomitant use of **BISOPROLOL CO UNICORN** with hypoglycaemic agents, phenothiazines and various antidysrhythmic agents can have life-threatening consequences for example:
  - Profound hypoglycaemia with oral hypoglycaemic agents and insulin.
  - Impaired myocardial function with antidysrhythmic agents, such as lidocaine, quinidine, disopyramide, flecainide, and propafenone.
- Beta-adrenoceptor stimulating agents (such as dopamine, dobutamine and isoprenaline) may antagonise the effects of **BISOPROLOL CO UNICORN.**
- Alpha-adrenoceptor stimulants, such as pseudoephedrine and phenylephrine,

  As well as adrenergic neurone blocking agents, such as reserpine, may lead to life-threatening vasoconstriction in combination with **BISOPROLOL CO UNICORN.**
- **BISOPROLOL CO UNICORN** and digoxin may be used concomitantly for patients with congestive heart failure provided that the pulse rate and patient response is monitored (see section 4.5).
- **BISOPROLOL CO UNICORN,** containing thiazides, may increase the responsiveness to neuromuscular blockers, such as atracurium, and other competitive muscle relaxants.

- Potentiation of orthostatic hypotension caused by thiazides may occur with concurrent use of **BISOPROLOL CO UNICORN** with alcohol, barbiturates or narcotics.
- Concomitant use of a thiazide diuretic with corticosteroids or ACTH, may intensify electrolyte depletion and hypokalaemia.
- Thiazide diuretics may decrease response to pressor amines (e.g. adrenalin). This decrease in response is not sufficient to preclude the use of pressor amines.
- NSAIDs, such as indomethacin, may reduce the antihypertensive effects of beta-adrenergic blocking agents, such as **BISOPROLOL CO UNICORN**, possibly by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention.
- Severe hyponatraemia has occurred in patients taking trimethoprim or carbamazepine with **BISOPROLOL CO UNICORN**.

4.6 Fertility, pregnancy and lactation

Do not use **BISOPROLOL CO UNICORN** during pregnancy and lactation (see section 4.3).

Pregnancy

Administration of **BISOPROLOL CO UNICORN** to pregnant mothers shortly before birth or during labour may result in hypotonia, bradycardia, collapse or hypoglycaemia in the newborn (see section 4.3).

Breastfeeding

Hydrochlorothiazides cross the placental barrier and appear in cord blood. Hazards include foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which occur in the adult.

Hydrochlorothiazides appear in human milk. If **BISOPROLOL CO UNICORN** is deemed essential, the patient should stop breast-feeding.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or use machinery if dizziness or drowsiness is experienced.

4.8 Undesirable effects

Adverse reactions are more common in patients with renal decompensation.

Neoplasms benign and malignant (including cysts and polyps):

Hydrochlorothiazide:

Frequency unknown:

Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma).

Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide, as in **BISOPROLOL CO UNICORN**, and non-melanoma skin cancer has been observed (see section 4.5).

Blood and the lymphatic system disorders:

Bisoprolol:

Frequent: Thrombocytopenia.

Less frequent: Leukopenia.

Hydrochlorothiazide:

Less frequent: Thrombocytopenia.

The following has been reported but the frequency is unknown:

Leucopenia, aplastic anaemia, haemolytic anaemia, agranulocytosis.

Immune system disorders:

Bisoprolol:

Less frequent: Hypersensitivity (allergic) reactions.

Hydrochlorothiazide:

Less frequent: Anaphylactic reactions.

***Endocrine disorders*:**

Bisoprolol:

The following has been reported but the frequency is unknown:

Hypoglycaemia.

Hydrochlorothiazide:

Less frequent: Pancreatitis.

The following has been reported but the frequency is unknown:

Sialadenitis, hyperglycaemia.

***Metabolism and nutrition disorders*:**

Bisoprolol:

The following has been reported but the frequency is unknown:

Metabolic disturbances, increase in uric acid levels, hypercholesterolaemia.

Hydrochlorothiazide:

Frequent: Electrolyte imbalance including hyponatraemia.

Less frequent: Anorexia.

Psychiatric disorders:

Bisoprolol:

Less frequent: Anxiety, nervousness, mental depression, nightmares and vivid dreams.

The following has been reported but the frequency is unknown:

Psychosis, hallucinations.

***Nervous system disorders*:**

Bisoprolol:

Frequent: Drowsiness, unusual tiredness or weakness, sleep disorders or trouble sleeping.

Less frequent: Dizziness, mild headache, restlessness.

The following has been reported but the frequency is unknown:

Lassitude, paraesthesia.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Fever, restlessness.

***Eye disorders*:**

Bisoprolol:

Less frequent: Dry, sore eyes, reduced tear flow.

The following has been reported but the frequency is unknown:

Disturbances of vision.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Xanthopsia, transient blurred vision.

Ear and labyrinth disorders:

Bisoprolol:

The following has been reported but the frequency is unknown:

Transient hearing loss.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Vertigo.

***Cardiac disorders*:**

Bisoprolol:

Less frequent: Bradycardia and congestive heart failure, heart block, dysrhythmias.

***Vascular disorders*:**

Bisoprolol:

Less frequent: Fluid retention, reduced peripheral circulation, orthostatic hypotension.

The following has been reported but the frequency is unknown:

Paradoxical hypertension.

Exacerbation of peripheral vascular disease or the development of Raynaud's phenomenon.

Peripheral gangrene may be precipitated.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Necrotising vasculitis (cutaneous vasculitis).

***Respiratory, thoracic and mediastinal disorders*:**

Bisoprolol:

Less frequent: Allergic rhinitis, nasal congestion.

Bronchoconstriction or bronchospasm may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Respiratory distress including pneumonitis and pulmonary oedema.

***Gastrointestinal disorders*:**

Bisoprolol:

Less frequent: Nausea, vomiting, diarrhoea, constipation.

The following has been reported but the frequency is unknown:

Mass gain, stomatitis.

Hydrochlorothiazide:

Less frequent: Gastric irritation.

The following has been reported but the frequency is unknown:

Constipation.

***Hepato-biliary disorders*:**

Bisoprolol:

Less frequent: Hepatotoxicity.

The following has been reported but the frequency is unknown:

Raised liver enzymes.

Hydrochlorothiazide:

Less frequent: Jaundice (intrahepatic cholestatic jaundice).

***Skin and subcutaneous tissue disorders*:**

Bisoprolol:

Less frequent: Skin rash, psoriasiform eruption.

The following has been reported but the frequency is unknown:

Perspiration, alopecia.

Hydrochlorothiazide:

Less frequent: Photosensitivity.

The following has been reported but the frequency is unknown:

Purpura, urticaria. Activation of worsening psoriasis or inducing a psoriasis-like rash.

Musculoskeletal, connective tissue and bone disorders:

Bisoprolol:

Less frequent: Back pain or joint pain, chest pain.

The following has been reported but the frequency is unknown:

Muscle cramps, myopathy, skeletal muscle weakness.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Muscle spasm.

***Renal and urinary*:**

Hydrochlorothiazide:

Less frequent: Hyperuricaemia.

The following has been reported but the frequency is unknown:

Renal failure, renal dysfunction and interstitial nephritis, glycosuria.

***Reproductive system and breast disorders*:**

Bisoprolol:

Frequent: Decreased sexual ability.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **BISOPROLOL CO UNICORN** is important. It allows continued monitoring of the benefit/risk balance of **BISOPROLOL CO UNICORN**. Health care providers are asked to report any

suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/Publications/Index/8.

Adverse reactions must also be reported to Unicorn Pharmaceuticals (Pty) Ltd to vigilance@unicornpharma.co.za

4.9 Overdose

Bisoprolol:

Overdosage may produce bradycardia, severe hypotension and/or third- degree AV-block. Bronchospasm and heart failure may be produced.

Cases of overdose should be observed for at least 4 hours, as apnoea and cardiovascular collapse may appear suddenly.

Repeated activated charcoal may be necessary in overdose.

I.V. atropine may be used to treat severe bradycardia. If the response is inadequate, glucagon may be given intravenously. Alternatively, dobutamine may be required to reverse beta-blockade. Cardiac pacing may be required for severe bradycardia. Bronchospasm should be treated with I.V. aminophylline or inhaled or I.V. $beta_2$-adrenergic agonist, e.g. salbutamol.

Hydrochlorothiazide:

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digoxin has been used concomitantly, hypokalaemia may accentuate cardiac dysrhythmias.

5. PHARMACOLOGICAL PROPERTIES

PHARMACOLOGICAL CLASSIFICATION:

A. 7.1.3 Other hypotensives

5.1 Pharmacodynamic properties

BISOPROLOL CO UNICORN is a combination of bisoprolol and hydrochlorothiazide.

Bisoprolol is a selective β_1-adrenoceptor antagonist devoid of intrinsic sympathomimetic and membrane-stabilising activity.

Hydrochlorothiazide is a thiazide diuretic. It affects the distal renal tubular mechanism of electrolyte re-absorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effects of the thiazides is unknown.

Non-melanoma skin cancer: Based on available data from epidemiological studies, a cumulative dose-dependent association between hydrochlorothiazide (HCTZ) and non-melanoma skin cancer (NMSC) has been observed. One study included a population comprised of 71 533 cases of basal cell carcinoma (BCC) and of 8 629 cases of squamous cell carcinoma (SCC) matched to 1 430 833 and 172 462 population controls, respectively.

High HCTZ use (≥ 50 000 mg cumulative) was associated with an adjusted odds ratio (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.

A 50 000 mg cumulative dose corresponds to 12,5 mg HCTZ taken daily for about 11 years.

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 section 4.5).

Incidence rates of NMSC depend on skin phenotypes and other factors leading to different baseline risks and varying incidence rates in different countries. Estimated incidence rates vary across different regions in Europe and are estimated at rates of around 1 to 34 cases per 100 000 inhabitants per year for SCC and 30 to 150 per 100 000 inhabitants per year for BCC. Based on the results of the two Danish epidemiological studies, this risk may increase approximately 4 to 7,7-fold for SCC and 1,3-fold for BCC depending on the cumulative dose of HCTZ.

5.2 Pharmacokinetic properties

Bisoprolol:

Bisoprolol is well absorbed following oral administration with a resultant bioavailability of about 90 %. Bisoprolol undergoes minimal hepatic first-pass metabolism. About 50 % of a dose is metabolised in the liver and the remainder is excreted unchanged via the kidneys. The plasma elimination half-life is approximately 10 to 12 hours and the duration of action is about 24 hours.

Hydrochlorothiazide:

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney.

The plasma half-life has been observed to vary between 5,6 and 14,8 hours after 24 hour observation. It is reported to have a bioavailability of about 65 – 70 %. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, corn starch, crospovidone, dibasic calcium phosphate,

magnesium stearate, microcrystalline cellulose and pregelatinised starch.

The following colourants are also included: iron oxide red (5/6,25 tablet only) and opadry white.

6.2 Incompatibilities

No incompatibilities.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

Clear PVC/PVDC/Aluminium foil blisters containing 10 tablets each.

Three blister strips with a package insert are placed in an outer carton.

6.6 Special precautions for disposal and other handling

No special precautions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd.

Corner Searle and Pontac Streets,

Cape Town,

8001

South Africa

8. REGISTRATION NUMBER(S)

BISOPROLOL CO UNICORN 5/6,25: 46/7.1.3/0387

BISOPROLOL CO UNICORN 10/6,25: 46/7.1.3/0388

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 March 2015

10. DATE OF REVISION OF THE TEXT

September 2021

Proposed Professional Information for

BISOPROLOL CO UNICORN 5/6,25 TABLETS

BISOPROLOL CO UNICORN 10/6,25 TABLETS

SCHEDULING STATUS:

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BISOPROLOL CO UNICORN film-coated tablets are sugar free.

3. PHARMACEUTICAL FORM

BISOPROLOL CO UNICORN 5/6,25: Pink-coloured, film-coated, round tablets debossed with “5” on one side and plain on the other side.

BISOPROLOL CO UNICORN 10/6,25: White to off-white-coloured, film-coated, round tablets debossed with “10” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BISOPROLOL CO UNICORN is indicated for the treatment of hypertension in patients who have been stabilised on the individual components given in the same proportions.

4.2 Posology and method of administration

Adults*:* Antihypertensive therapy may be initiated with the lowest dose of bisoprolol/hydrochlorothiazide 2,5/6,25 mg, taking one tablet once daily. Another formulation should be used. Subsequent dose adjustment may be carried out with **BISOPROLOL CO UNICORN** tablets up to the maximum recommended dose of one 10/6,25 mg tablet once daily as appropriate.

Withdrawal of **BISOPROLOL CO UNICORN** therapy should be achieved gradually over a period of about two weeks. Patients should be carefully monitored.

A daily dose of 10 mg bisoprolol should not be exceeded in patients with mild to moderate renal or hepatic impairment.

Special populations

Elderly:

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

Children:

Efficacy and safety in children less than 12 years have not been established (see section 4.5).

4.3 Contraindications

- Hypersensitivity to bisoprolol or to any of the ingredients of **BISOPROLOL CO UNICORN.**
- Hypersensitivity to hydrochlorothiazide or other sulphonamide derived medicines.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.
- Second and third-degree heart block and bradycardia (less than 50 beats per minute).
- Pregnancy and lactation (see section 4.6).
- Uncontrolled cardiac failure.
- Cardiogenic shock.
- Severe hypotension (systolic blood pressure of less than 100 mmHg).
- Metabolic acidosis.
- Sinus bradycardia (less than 50 beats per minute).
- Phaeochromocytoma.
- Hyperthyroidism, as clinical manifestations may be masked.
- Bronchospasm or asthma, or patients with a history of bronchitis or chronic respiratory diseases.
- Late stage peripheral vascular diseases and Raynaud's phenomenon.
- Addison’s disease.
- Severe renal impairment (creatinine clearance < 30 ml/minute).

- Severe hepatic impairment, in which encephalopathy may be precipitated (see section 4.5).
- Porphyria.

4.4 Special warnings and precautions for use

- Safety and efficacy in children have not been established.
- If the decision is made to withdraw **BISOPROLOL CO UNICORN** before anaesthesia, at least 48 hours should be allowed to elapse between the last dose and surgery. If **BISOPROLOL CO UNICORN** is to be continued, care should be taken when using anaesthetics such as ether, cyclopropane and trichloroethylene. Atropine (1 – 2 mg I.V.) may be used to correct vagal dominance. The patient must be maintained on the usual dosage perioperatively to avoid aggravation of angina pectoris or hypertension.
- Particular caution should be taken in diabetes mellitus, as symptoms and signs of hypoglycaemia, such as tachycardia, may be masked by **BISOPROLOL CO UNICORN**, and response to hypoglycaemia is diminished. **BISOPROLOL CO UNICORN** may also delay recovery of insulin-induced hypoglycaemia.
- A potentially life-threatening reaction may occur between **BISOPROLOL CO UNICORN** and quinidine. The thiazide induced K^+ depletion worsens the quinidine-induced torsades des pointes and the bisoprolol aggravates these effects further.
- Tachycardic responses, due to hypovolaemia or blood loss, may be obscured during or after surgery. Particular caution should be taken in this regard.
- The dosage of **BISOPROLOL CO UNICORN** should be adjusted in patients with renal impairment (see section 4.2).

- Care should be taken in prescribing **BISOPROLOL CO UNICORN** together with Class 1 antidysrhythmic agents such as disopyramide, myocardial depressants, and inhibitors of AV conduction, such as calcium antagonists.

  BISOPROLOL CO UNICORN should be used with caution in combination with verapamil in patients with impaired ventricular function. This combination should not be given to patients with conduction abnormalities. Neither medicine should be administered within 48 hours of discontinuing the other.

  The intravenous administration of calcium antagonists and antidysrhythmic agents should be avoided during therapy with **BISOPROLOL CO UNICORN.**
- Patients with phaeochromocytoma who are receiving **BISOPROLOL CO UNICORN** require pre-treatment with an alpha-adrenergic blocker (see section 4.3).
- **BISOPROLOL CO UNICORN** may increase sensitivity towards allergens and the incidence of anaphylactic reactions. Treatment of anaphylaxis with epinephrine (adrenaline) does not always have the expected effect.
- Exacerbation of peripheral vascular disease or the development of Raynaud's phenomenon may occur with the use of **BISOPROLOL CO UNICORN** due to unopposed arteriolar alpha-sympathomimetic activation. Peripheral gangrene may be precipitated (see section 4.3).
- **BISOPROLOL CO UNICORN** may reduce tear flow causing irritation of the eye in contact lens wearers.
- Caution should be exercised when transferring a patient from clonidine, as the withdrawal of clonidine may result in the release of large amounts of catecholamines that may give rise to a hypertensive crisis. If **BISOPROLOL CO UNICORN** is administered in these

circumstances, the unopposed alpha-receptor stimulation may potentiate this effect. If **BISOPROLOL CO UNICORN** and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of **BISOPROLOL CO UNICORN** as severe rebound hypertension may occur (see section 4.5). Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual (see section 4.2). Patients should be advised to limit the extent of their physical activity during the period that **BISOPROLOL CO UNICORN** is being discontinued.

- Patients with psoriasis should be given **BISOPROLOL CO UNICORN** with caution.
- Digitalisation of patients receiving long-term beta-blocker therapy, such as **BISOPROLOL CO UNICORN**, may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages, and of the individual patient's response (and notably pulse rate), is essential in this situation (see section 4.5).

Renal Insufficiency:

Hydrochlorothiazides, such as in **BISOPROLOL CO UNICORN,** should be used with caution in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. severe renal insufficiency).

Hepatic Disease:

Caution should be exercised when hydochlorothiazides (as in **BISOPROLOL CO UNICORN**) are used in patients with hepatic impairment or progressive liver disease, as minor alterations of fluid and electrolyte balance may precipitate hepatic coma in these patients.

Metabolic and Endocrine Effects:

Hydrochlorothiazide diuretics, as in **BISOPROLOL CO UNICORN**, may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.

Decreased urinary calcium excretion caused by hydrochlorothiazides may result in intermittent and a slightly raised serum calcium concentration. Should marked hypercalcaemia occur, it may be evidence of underlying hyperparathyroidism. **BISOPROLOL CO UNICORN** therapy should be discontinued before carrying out tests for parathyroid function (see section 4.5). Increased cholesterol and triglyceride levels may be a result of the hydrochlorothiazide diuretic (contained in **BISOPROLOL CO UNICORN**) therapy.

Hydrochlorothiazide diuretics may precipitate hyperuricaemia and/or gout in certain patients.

In patients receiving hydrochlorothiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of hydrochlorothiazides, as contained in **BISOPROLOL CO UNICORN**.

Ocular Effects:

Hydrochlorothiazide, such as in **BISOPROLOL CO UNICORN,** can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. The risk is greater in patients with a history of sulfonamide or penicillin allergy. Symptoms include active

onset of decreased visual acuity or ocular pain and typically occur within hours to week of drug initiation. Primary treatment is discontinuation of **BISOPROLOL CO UNICORN** as rapidly as possible. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

Non-melanoma skin cancer:

An increased risk of nonmelanoma 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. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC. Patients taking **BISOPROLOL CO UNICORN** 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 the 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. **BISOPROLOL CO UNICORN** should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

- Calcium channel blockers, such as verapamil and diltiazem should not be given concomitantly with **BISOPROLOL CO UNICORN** (see section 4.5).

- **BISOPROLOL CO UNICORN**, containing bisoprolol, may potentiate the effect of other concomitantly administered antihypertensives. Centrally acting antihypertensives, such as methyldopa, may worsen heart failure by a decrease in central sympathetic tone.
- Strong inducers of the hepatic cytochrome P450 isoenzymes, CYP3A4 and CYP2D6, such as rifampicin and the barbiturates, may shorten the half-life of bisoprolol. An increase in the dose of **BISOPROLOL CO UNICORN**, however, is generally unnecessary with rifampicin.
- Strong inhibitors of the hepatic cytochrome P450 isoenzymes CYP3A4 and CYP2D6, such as cimetidine, erythromycin, fluoxetine and hydralazine may increase the half-life of bisoprolol. The pharmacokinetics of bisoprolol is not significantly influenced by cimetidine.
- Topical beta-blocker eye drops may add to the systemic side-effects of **BISOPROLOL CO UNICORN.**
- Concomitant use of **BISOPROLOL CO UNICORN** with hypoglycaemic agents, phenothiazines and various antidysrhythmic agents can have life-threatening consequences for example:
    - Profound hypoglycaemia with oral hypoglycaemic agents and insulin.
    - Impaired myocardial function with antidysrhythmic agents, such as lidocaine, quinidine, disopyramide, flecainide, and propafenone.
- Beta-adrenoceptor stimulating agents (such as dopamine, dobutamine and isoprenaline) may antagonise the effects of **BISOPROLOL CO UNICORN.**
- Alpha-adrenoceptor stimulants, such as pseudoephedrine and phenylephrine,

As well as adrenergic neurone blocking agents, such as reserpine, may lead to life-threatening vasoconstriction in combination with **BISOPROLOL CO UNICORN.**

- **BISOPROLOL CO UNICORN** and digoxin may be used concomitantly for patients with congestive heart failure provided that the pulse rate and patient response is monitored (see section 4.5).
- **BISOPROLOL CO UNICORN,** containing thiazides, may increase the responsiveness to neuromuscular blockers, such as atracurium, and other competitive muscle relaxants.
- Potentiation of orthostatic hypotension caused by thiazides may occur with concurrent use of **BISOPROLOL CO UNICORN** with alcohol, barbiturates or narcotics.
- Concomitant use of a thiazide diuretic with corticosteroids or ACTH, may intensify electrolyte depletion and hypokalaemia.
- Thiazide diuretics may decrease response to pressor amines (e.g. adrenalin). This decrease in response is not sufficient to preclude the use of pressor amines.
- NSAIDs, such as indomethacin, may reduce the antihypertensive effects of beta-adrenergic blocking agents, such as **BISOPROLOL CO UNICORN**, possibly by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention.
- Severe hyponatraemia has occurred in patients taking trimethoprim or carbamazepine with **BISOPROLOL CO UNICORN**.

4.6 Fertility, pregnancy and lactation

Do not use **BISOPROLOL CO UNICORN** during pregnancy and lactation (see section 4.3).

Pregnancy

Administration of **BISOPROLOL CO UNICORN** to pregnant mothers shortly before birth or during labour may result in hypotonia, bradycardia, collapse or hypoglycaemia in the newborn (see section 4.3).

Breastfeeding

Hydrochlorothiazides cross the placental barrier and appear in cord blood. Hazards include foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which occur in the adult.

Hydrochlorothiazides appear in human milk. If **BISOPROLOL CO UNICORN** is deemed essential, the patient should stop breast-feeding.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or use machinery if dizziness or drowsiness is experienced.

4.8 Undesirable effects

Adverse reactions are more common in patients with renal decompensation.

Neoplasms benign and malignant (including cysts and polyps):

Hydrochlorothiazide:

Frequency unknown:

Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma).

Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide, as in **BISOPROLOL CO UNICORN**, and non-melanoma skin cancer has been observed (see section 4.5).

Blood and the lymphatic system disorders:

Bisoprolol:

Frequent: Thrombocytopenia.

Less frequent: Leukopenia.

Hydrochlorothiazide:

Less frequent: Thrombocytopenia.

The following has been reported but the frequency is unknown:

Leucopenia, aplastic anaemia, haemolytic anaemia, agranulocytosis.

Immune system disorders:

Bisoprolol:

Less frequent: Hypersensitivity (allergic) reactions.

Hydrochlorothiazide:

Less frequent: Anaphylactic reactions.

***Endocrine disorders*:**

Bisoprolol:

The following has been reported but the frequency is unknown:

Hypoglycaemia.

Hydrochlorothiazide:

Less frequent: Pancreatitis.

The following has been reported but the frequency is unknown:

Sialadenitis, hyperglycaemia.

***Metabolism and nutrition disorders*:**

Bisoprolol:

The following has been reported but the frequency is unknown:

Metabolic disturbances, increase in uric acid levels, hypercholesterolaemia.

Hydrochlorothiazide:

Frequent: Electrolyte imbalance including hyponatraemia.

Less frequent: Anorexia.

Psychiatric disorders:

Bisoprolol:

Less frequent: Anxiety, nervousness, mental depression, nightmares and vivid dreams.

The following has been reported but the frequency is unknown:

Psychosis, hallucinations.

***Nervous system disorders*:**

Bisoprolol:

Frequent: Drowsiness, unusual tiredness or weakness, sleep disorders or trouble sleeping.

Less frequent: Dizziness, mild headache, restlessness.

The following has been reported but the frequency is unknown:

Lassitude, paraesthesia.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Fever, restlessness.

***Eye disorders*:**

Bisoprolol:

Less frequent: Dry, sore eyes, reduced tear flow.

The following has been reported but the frequency is unknown:

Disturbances of vision.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Xanthopsia, transient blurred vision.

Ear and labyrinth disorders:

Bisoprolol:

The following has been reported but the frequency is unknown:

Transient hearing loss.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Vertigo.

***Cardiac disorders*:**

Bisoprolol:

Less frequent: Bradycardia and congestive heart failure, heart block, dysrhythmias.

***Vascular disorders*:**

Bisoprolol:

Less frequent: Fluid retention, reduced peripheral circulation, orthostatic hypotension.

The following has been reported but the frequency is unknown:

Paradoxical hypertension.

Exacerbation of peripheral vascular disease or the development of Raynaud's phenomenon. Peripheral gangrene may be precipitated.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Necrotising vasculitis (cutaneous vasculitis).

***Respiratory, thoracic and mediastinal disorders*:**

Bisoprolol:

Less frequent: Allergic rhinitis, nasal congestion.

Bronchoconstriction or bronchospasm may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Respiratory distress including pneumonitis and pulmonary oedema.

***Gastrointestinal disorders*:**

Bisoprolol:

Less frequent: Nausea, vomiting, diarrhoea, constipation.

The following has been reported but the frequency is unknown:

Mass gain, stomatitis.

Hydrochlorothiazide:

Less frequent: Gastric irritation.

The following has been reported but the frequency is unknown:

Constipation.

***Hepato-biliary disorders*:**

Bisoprolol:

Less frequent: Hepatotoxicity.

The following has been reported but the frequency is unknown:

Raised liver enzymes.

Hydrochlorothiazide:

Less frequent: Jaundice (intrahepatic cholestatic jaundice).

***Skin and subcutaneous tissue disorders*:**

Bisoprolol:

Less frequent: Skin rash, psoriasiform eruption.

The following has been reported but the frequency is unknown:

Perspiration, alopecia.

Hydrochlorothiazide:

Less frequent: Photosensitivity.

The following has been reported but the frequency is unknown:

Purpura, urticaria. Activation of worsening psoriasis or inducing a psoriasis-like rash.

Musculoskeletal, connective tissue and bone disorders:

Bisoprolol:

Less frequent: Back pain or joint pain, chest pain.

The following has been reported but the frequency is unknown:

Muscle cramps, myopathy, skeletal muscle weakness.

Hydrochlorothiazide:

The following has been reported but the frequency is unknown:

Muscle spasm.

***Renal and urinary*:**

Hydrochlorothiazide:

Less frequent: Hyperuricaemia.

The following has been reported but the frequency is unknown:

Renal failure, renal dysfunction and interstitial nephritis, glycosuria.

***Reproductive system and breast disorders*:**

Bisoprolol:

Frequent: Decreased sexual ability.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **BISOPROLOL CO UNICORN** is important. It allows continued monitoring of the benefit/risk balance of **BISOPROLOL CO UNICORN**. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Adverse reactions must also be reported to Unicorn Pharmaceuticals (Pty) Ltd to vigilance@unicornpharma.co.za

4.9 Overdose

Bisoprolol:

Overdosage may produce bradycardia, severe hypotension and/or third- degree AV-block. Bronchospasm and heart failure may be produced.

Cases of overdose should be observed for at least 4 hours, as apnoea and cardiovascular collapse may appear suddenly.

Repeated activated charcoal may be necessary in overdose.

I.V. atropine may be used to treat severe bradycardia. If the response is inadequate, glucagon may be given intravenously. Alternatively, dobutamine may be required to reverse beta-blockade. Cardiac pacing may be required for severe bradycardia. Bronchospasm should be treated with I.V. aminophylline or inhaled or I.V. $beta_2$-adrenergic agonist, e.g. salbutamol.

Hydrochlorothiazide:

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digoxin has been used concomitantly, hypokalaemia may accentuate cardiac dysrhythmias.

5. PHARMACOLOGICAL PROPERTIES

PHARMACOLOGICAL CLASSIFICATION:

A. 7.1.3 Other hypotensives

5.1 Pharmacodynamic properties

BISOPROLOL CO UNICORN is a combination of bisoprolol and hydrochlorothiazide.

Bisoprolol is a selective β_1-adrenoceptor antagonist devoid of intrinsic sympathomimetic and membrane-stabilising activity.

Hydrochlorothiazide is a thiazide diuretic. It affects the distal renal tubular mechanism of electrolyte re-absorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effects of the thiazides is unknown.

Non-melanoma skin cancer: Based on available data from epidemiological studies, a cumulative dose-dependent association between hydrochlorothiazide (HCTZ) and non-melanoma skin cancer (NMSC) has been observed. One study included a population

comprised of 71 533 cases of basal cell carcinoma (BCC) and of 8 629 cases of squamous cell carcinoma (SCC) matched to 1 430 833 and 172 462 population controls, respectively.
High HCTZ use (≥ 50 000 mg cumulative) was associated with an adjusted odds ratio (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.
A 50 000 mg cumulative dose corresponds to 12,5 mg HCTZ taken daily for about 11 years.

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 section 4.5).

Incidence rates of NMSC depend on skin phenotypes and other factors leading to different baseline risks and varying incidence rates in different countries. Estimated incidence rates vary across different regions in Europe and are estimated at rates of around 1 to 34 cases per 100 000 inhabitants per year for SCC and 30 to 150 per 100 000 inhabitants per year for BCC. Based on the results of the two Danish epidemiological studies, this risk may increase approximately 4 to 7,7-fold for SCC and 1,3-fold for BCC depending on the cumulative dose of HCTZ.

5.2 Pharmacokinetic properties

Bisoprolol:

Bisoprolol is well absorbed following oral administration with a resultant bioavailability of about 90 %. Bisoprolol undergoes minimal hepatic first-pass metabolism. About 50 % of a dose is metabolised in the liver and the remainder is excreted unchanged via the kidneys. The plasma elimination half-life is approximately 10 to 12 hours and the duration of action is about 24 hours.

Hydrochlorothiazide:

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney.

The plasma half-life has been observed to vary between 5,6 and 14,8 hours after 24 hour observation. It is reported to have a bioavailability of about 65 – 70 %. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, corn starch, crospovidone, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and pregelatinised starch.

The following colourants are also included: iron oxide red (5/6,25 tablet only) and opadry white.

6.2 Incompatibilities

No incompatibilities.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

Clear PVC/PVDC/Aluminium foil blisters containing 10 tablets each.

Three blister strips with a package insert are placed in an outer carton.

6.6 Special precautions for disposal and other handling

No special precautions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd.

Corner Searle and Pontac Streets,

Woodstock, Cape Town,

8001

South Africa

8. REGISTRATION NUMBER(S)

BISOPROLOL CO UNICORN 5/6,25: 46/7.1.3/0387

BISOPROLOL CO UNICORN 10/6,25: 46/7.1.3/0388

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 March 2015

10. DATE OF REVISION OF THE TEXT

September 2021