Applicant: Teva Pharmaceuticals (Pty) Ltd	Product name: TEVACARD CO 2,5/6,25; 5/6,25; 10/6,25
TEVACARD CO 2,5/6,25: 47/7.1.3/1269 **TEVACARD CO 5/6,25:** 47/7.1.3/1270 **TEVACARD CO 10/6,25:** 47/7.1.3/1271	**Dosage form & strength:** Film-coated tablets contain 2,5; 5 or 10 mg bisoprolol fumarate and 6,25 mg hydrochlorothiazide respectively
Date of registration: 16 March 2021	

PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

TEVACARD CO 2,5/6,25 (film-coated tablets)

TEVACARD CO 5/6,25 (film-coated tablets)

TEVACARD CO 10/6,25 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

TEVACARD CO 2,5/6,25 contains 2,5 mg bisoprolol fumarate and 6,25 mg hydrochlorothiazide per film-coated tablet.

TEVACARD CO 5/6,25 contains 5 mg bisoprolol fumarate and 6,25 mg hydrochlorothiazide per film-coated tablet.

TEVACARD CO 10/6,25 contains 10 mg bisoprolol fumarate and 6,25 mg hydrochlorothiazide per film-coated tablet.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Film-coated tablets.

TEVACARD CO 2,5/6,25: Yellow, film-coated, round tablet, debossed with '2,5' on one side of the tablet and 'BH' on the other side of the tablet.

TEVACARD CO 5/6,25: Pink, film-coated, round tablet, debossed with '5' on one side of the tablet and 'BH' on the other side of the tablet.

TEVACARD CO 10/6,25: White, film-coated, round tablet, debossed with '10' on one side of the tablet

and 'BH' on the other side of the tablet.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

TEVACARD CO is indicated for the treatment of hypertension.

4.2 Posology and method of administration:

Antihypertensive therapy may be initiated with the lowest dose of **TEVACARD CO**, one 2,5 mg/6,25 mg tablet once daily. Subsequent dose adjustment may be carried out with **TEVACARD CO** tablets up to the maximum recommended dose of one 10 mg/6,25 mg tablet once daily, as appropriate.

If withdrawal of **TEVACARD CO** therapy is planned, it should be achieved gradually over a period of about 2 weeks.

Patients should be carefully observed.

Special populations:

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

Paediatric population:

There is no paediatric experience with **TEVACARD CO**.

Method of administration:

For oral use.

4.3 Contraindications:

- hypersensitivity to bisoprolol, hydrochlorothiazide, other thiazides, sulphonamides, or any of the excipients of **TEVACARD CO** listed in **section 6.1**

- acute heart failure or during episodes of heart failure decompensation requiring intravenous inotropic therapy
- cardiogenic shock
- second or third degree AV block
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- untreated phaeochromocytoma
- patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip
- severe renal impairment (creatinine clearance < 30 ml/min)
- severe hepatic impairment
- metabolic acidosis
- refractory hypokalaemia
- pregnancy or lactation (see **section 4.6**)
- safety and efficacy in children have not been established.

4.4 Special warnings and precautions for use:

Treatment with bisoprolol as contained in **TEVACARD CO** must not be withdrawn abruptly unless clearly indicated, since abrupt withdrawal of bisoprolol may lead to an acute deterioration of the patient's condition in particular in patients with ischaemic heart disease.

TEVACARD CO must be used with caution in patients with:

Liver disease:

Liver disease, thiazide diuretics and related products may trigger hepatic encephalopathy. Should this happen, diuretic therapy must be stopped immediately.

Asthma and chronic obstructive pulmonary disease:

Beta-blockers may be used only in mild forms of asthma or COPD, using a $beta_1$-selective adrenoceptor blocking medicine and a low starting dose. Pulmonary function testing is recommended before the start of therapy. Concomitant bronchodilating therapy is recommended in symptomatic patients. Occasionally, an increase in airway resistance may occur in patients with asthma or COPD, therefore the dose of $beta_2$-stimulants may have to be increased.

Acute respiratory toxicity:

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide as contained in **TEVACARD CO**. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, **TEVACARD CO** should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Cardiac failure:

Patients with compensated cardiac failure who require beta-blocker therapy may be administered bisoprolol as contained in **TEVACARD CO** using a very low starting dose, to be increased gradually with close medical monitoring.

First degree atrioventricular block:

Having negative dromotropic activity, beta-blockers should be used cautiously in patients with first degree atrioventricular block.

Prinzmetal's angina:

Beta-blockers may increase the frequency and length of vasospastic episodes in patients with Prinzmetal's angina. A $beta_1$-selective beta-blocker may be used in minor or mixed clinical presentations of Prinzmetal's angina if a vasodilator is used concurrently.

Peripheral arterial occlusive disease:

Beta-blockers may aggravate symptoms of peripheral arterial occlusive disease (PAOD) or Raynaud's syndrome. Such patients should preferably be prescribed a $beta_1$-selective beta-blocker.

Phaeochromocytoma:

In patients with phaeochromocytoma, **TEVACARD CO** must not be administered until after alpha-receptor blockade. Blood pressure should be closely monitored.

Elderly:

No dose adjustment is normally required. However, elderly patients should be closely monitored (see paragraph **Fluid and electrolyte balance**).

Diabetics:

Diabetic patients should be aware of the risk of hypoglycaemic episodes and of the increased need for careful home glucose monitoring in the initial phase of therapy. The warning signs of hypoglycaemia, particularly tachycardia, palpitations and sweating, may be masked.

Psoriasis:

There have been reports of beta-blockers being associated with worsening of psoriasis, thus patients with psoriasis should receive **TEVACARD CO** only if clearly needed.

Hypersensitivity reactions:

In patients at risk of severe anaphylactic reaction to whatever allergen, particularly when using iodine-containing contrast materials (see **section 4.5**) or during specific immunotherapy (desensitisation), beta-blockers may aggravate the anaphylactic reaction and cause unresponsiveness to the usual doses of epinephrine used to treat hypersensitivity reactions.

General anaesthesia:

In patients undergoing general anaesthesia, beta-blockade reduces the incidence of dysrhythmias and myocardial ischaemia during induction and intubation, and in the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other medicines, resulting in bradydysrhythmias, attenuation of reflex tachycardia and decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Hyperthyroidism:

Beta-blockers may mask the cardiovascular signs of hyperthyroidism.

Competitive athletes:

Competitive athletes should be aware that **TEVACARD CO** contains a substance that may give a positive reaction in doping tests.

Strict fasting:

TEVACARD CO must be used with caution in patients under strict fasting.

Combination with verapamil, diltiazem or bepridil:
Such combinations require a close clinical and electrocardiographical monitoring, notably in the elderly and at the beginning of the treatment (see **section 4.5**).
Fluid and electrolyte balance:
During long-term therapy with **TEVACARD CO**, periodic monitoring of serum electrolytes (especially potassium, sodium, calcium), creatinine and urea, serum lipids (cholesterol and triglycerides), uric acid as well as blood glucose is recommended.
Long-term, continuous administration of hydrochlorothiazide as contained in **TEVACARD CO** may lead to fluid and electrolyte disturbances, in particular hypokalaemia and hyponatraemia, also to hypomagnesaemia and hypochloraemia, and hypercalcaemia.
Plasma sodium:
Plasma sodium should be determined before and periodically during therapy. Any diuretic therapy may give rise to hyponatraemia, with serious consequences in some cases.
As hyponatraemia may initially be asymptomatic, periodic monitoring is indispensable and should be more frequent in high-risk populations, i.e. the elderly and patients with cirrhosis of the liver.
Plasma potassium:
Potassium loss resulting in hypokalaemia is the greatest risk associated with thiazide diuretics and related medicines.
The risk of hypokalaemia (< 3,5 mmol/L) should be anticipated in certain high-risk populations, i.e. the elderly and/or malnourished and/or taking multiple medicines, and patients with coronary artery disease or heart failure, where hypokalaemia increases the cardiotoxicity of digitalis glycosides and the risk of cardiac

dysrhythmia.

Also at risk are patients with long QT syndrome, either congenital or iatrogenic. Hypokalaemia (as well as bradycardia) facilitates the development of severe dysrhythmias, particularly torsades de pointes, which may be fatal.

More frequent plasma potassium monitoring is indicated in all of the above populations, starting within the week after initiation of therapy.

Plasma calcium:

Thiazide diuretics (e.g. **TEVACARD CO**) and related medicines may reduce urinary calcium excretion, resulting in mild, transient hypercalcaemia. Significant hypercalcaemia may be related to undiagnosed hyperparathyroidism. Therapy must be interrupted before performing parathyroid function tests.

Combination with lithium:

Due to the diuretic, this combination should be avoided (see **section 4.5**).

Blood glucose:

In diabetics, blood glucose must be monitored, especially in the presence of hypokalaemia.

Uric acid:

In patients with hyperuricaemia, the risk for attacks of gout may be increased. Dosage should be adjusted as a function of uric acid plasma concentrations.

Kidney function and diuretics:

Full benefit from thiazide diuretics can be derived only if kidney function is normal or almost normal (serum creatinine levels < 25 mg/L, or 220 µmol/L in adults).

Serum creatinine needs to be corrected for age, weight and gender, using Cockroft's formula, for instance:

* Cl_{Cr} = (140 – age) x weight/0,814 x serum creatinine

Where age is indicated in years, weight in kg, and serum creatinine in micromol/L.

The above formula gives Cl_{Cr} for elderly male subjects, and needs to be corrected for elderly female subjects by multiplying by 0,85.

Hypovolaemia secondary to diuretic-induced water and sodium loss at the start of therapy reduces glomerular filtration, which may result in blood urea nitrogen and serum creatinine increases.

This transient functional renal impairment is non-relevant in patients with normal kidney function but may worsen with pre-existing renal insufficiency.

Combination with other antihypertensive medicines:

It is advisable to reduce the dosage when this medicine is combined with another antihypertensive, at least in the initial phase of therapy.

Photosensitivity:

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

Non-melanoma skin cancer:

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

actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking **TEVACARD CO** should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. **TEVACARD CO** 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**).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma: Sulfonamide or sulfonamide derivative medicines can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of medicine initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue **TEVACARD CO** intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

4.5 Interaction with other medicines and other forms of interaction:

Combinations not recommended:

Lithium: **TEVACARD CO** may intensify the cardiotoxic and neurotoxic effect of lithium through a reduction of lithium excretion.

Calcium antagonists of the verapamil type and the diltiazem type: Negative effect on contractility and atrio-

ventricular conduction. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.
Centrally-acting antihypertensive medicines: Concomitant use of centrally-acting antihypertensive medicines may lead to a further reduction in heart rate and cardiac output and to vasodilatation. **Abrupt withdrawal, may increase the risk of 'rebound hypertension'.**
Combinations to be used with caution:
Calcium antagonists of the dihydropyridine type: Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.
Concomitant use with other antihypertensive medicines or with other medicines with blood pressure lowering potential may increase the risk of hypotension.
ACE inhibitors, Angiotensin II antagonists: Risk of significant fall in blood pressure and/or acute renal failure during initiation of ACE inhibitor therapy in patients with pre-existing sodium depletion (particularly in patients with renal artery stenosis). If prior diuretic therapy has produced sodium depletion, either stop the diuretic 3 days before starting ACE inhibitor therapy, or initiate ACE inhibitor therapy at a low dose.
Class-I antidysrhythmic medicines: Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.
Class-III antidysrhythmic medicines: Effect on atrio-ventricular conduction time may be potentiated.

Antidysrhythmic medicines that may induce torsade de pointes: Hypokalaemia may facilitate the occurrence of torsades de pointes.
Non-antidysrhythmic medicines that may induce torsade de pointes: Hypokalaemia may facilitate the occurrence of torsades de pointes
Parasympathomimetic medicines: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.
Insulin and oral antidiabetic medicines: Increase of blood sugar lowering effect. Blockade of beta-adrenoceptors may mask symptoms of hypoglycaemia.
Anaesthetic medicines: Attenuation of the reflex tachycardia and increase of the risk of hypotension.
Digitalis glycosides: Increase of atrio-ventricular conduction time, reduction in heart rate. If hypokalaemia and/or hypomagnesaemia develop during treatment with **TEVACARD CO** the myocardium may show increased sensitivity to cardiac glycosides, leading to an enhanced effect and adverse effects of the glycosides.
Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect. In patients developing hypovolaemia the concomitant administration of NSAIDs can trigger acute renal failure.
Beta-sympathomimetics: Combination with bisoprolol as contained in **TEVACARD CO** may reduce the effect of both medicines.

Sympathomimetics that activate both beta- and alpha-adrenoceptors: Combination with bisoprolol may lead to blood pressure increase. Such interactions are considered to be more likely with non-selective beta-blockers.
Potassium-wasting medicines may result in increased potassium losses.
Methyldopa: Haemolysis due to the formation of antibodies to hydrochlorothiazide has been described in isolated cases.
The effect of uric-acid-lowering medicines may be attenuated in concomitant administration of **TEVACARD CO**.
Cholestyramine, colestipol: Reduces the absorption of the hydrochlorothiazide component of **TEVACARD CO**.
Combinations to be considered:
Mefloquine: Increased risk of bradycardia.
Corticosteroids: Reduced antihypertensive effect.
4.6 Fertility, pregnancy and lactation:
Pregnancy: **TEVACARD CO** is contraindicated during pregnancy (see **section 4.3**). Administration to pregnant mothers shortly before giving birth or during labour may result in the new-born infant being born hypotonic, collapsed or hypoglycaemic.
Bisoprolol:

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intra-uterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, $beta_1$-selective adrenoceptor blockers are preferable.

Hydrochlorothiazide:

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise feto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women.

Breastfeeding:

TEVACARD CO is contraindicated in breastfeeding women. Hydrochlorothiazide can inhibit the milk production (see **section 4.3**).

4.7 Effects on ability to drive and use machines:

TEVACARD CO has no or negligible influence on the ability to drive and use machines. Depending on the individual patient's response to treatment with bisoprolol/hydrochlorothiazide the ability to drive and use

machines may be impaired. This should be considered particularly at the start of treatment as well as in conjunction with alcohol.

4.8 Undesirable effects:

Neoplasms benign, malignant and unspecified (incl cysts and polyps):	
Frequency unknown	Non-melanoma skin cancer (Basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders:	
Less frequent	Leucopenia, thrombocytopenia, agranulocytosis
Metabolism and nutrition disorders:	
Less frequent	Loss of appetite, hyperglycaemia, hyperuricaemia, disturbances of fluid and electrolyte balance (in particular hypokalaemia and hyponatraemia, also hypomagnesaemia and hypochloraemia as well as hypercalcaemia), metabolic alkalosis
Psychiatric disorders:	
Less frequent	Depression, sleep disorders, nightmares, hallucinations
Nervous system disorders:	
Frequent	Dizziness*, headache*
Eye disorders:	
Less frequent	Reduced tear flow (to be taken into consideration in patients wearing contact lenses), visual disturbances, conjunctivitis
Frequency unknown	Choroidal effusion
Ear and labyrinth disorders:	

Less frequent	Hearing disorders
Cardiac disorders:	
Less frequent	Bradycardia, atrioventricular conduction disturbances, worsening of pre-existing heart failure
Vascular disorders:	
Frequent	Feeling of coldness or numbness in extremities
Less frequent	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders:	
Less frequent	Bronchospasm in patients with bronchial asthma or history of obstructive airways disease, allergic rhinitis, acute respiratory distress syndrome (ARDS)
Gastrointestinal disorders:	
Frequent	Gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation
Less frequent	Abdominal complaints, pancreatitis
Hepato-biliary disorders:	
Less frequent	Hepatitis, jaundice
Skin and subcutaneous tissue disorders:	
Less frequent	Hypersensitivity reactions such as itching, flush, rash, photodermatitis, purpura, urticaria, anaphylactic reactions, toxic epidermic necrolysis (Lyell syndrome), alopecia, cutaneous lupus erythematosus. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash
Musculoskeletal and connective tissue disorders:	
Less frequent	Muscle weakness, muscle cramps
Reproductive system and breast disorders:	

Less frequent	Potency disorders
General disorders and administration site conditions:	
Frequent	Fatigue*
Less frequent	Asthenia, chest pain
Investigations:	
Less frequent	Increase in amylase, reversible increase of serum creatinine and urea, increased triglyceride and cholesterol levels, glucosuria, increase in liver enzymes (ASAT, ALAT)

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

Description of selected adverse reactions:

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

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare 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.

4.9 Overdose:

Symptoms:

The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia.

The clinical picture in acute or chronic overdose of hydrochlorothiazide is characterised by the extent of fluid and electrolyte loss. The most common signs are dizziness, nausea, somnolence, hypovolaemia, hypotension, hypokalaemia.
Management:
In general, if overdose occurs, discontinuation of **TEVACARD CO** and supportive and symptomatic treatment is recommended. Repeated activated charcoal is necessary in severe overdose.
Bradycardia: administer intravenous atropine (1-2 mg). Alternatively, dobutamine or isoprenaline (25 µg), may be required to reverse beta-blockade. Under some circumstances, transvenous pacemaker insertion may be necessary.
Hypotension: intravenous fluids and vasopressors should be administered.
Atrioventricular block (second or third degree): patients should be carefully monitored and treated with isoprenaline infusion or intravenous cardiac pacemaker insertion.
Acute worsening of heart failure: administer intravenous diuretics, inotropic medicines, vasodilating medicines.
Bronchospasm: administer bronchodilator therapy such as isoprenaline, beta$_2$-sympathomimetic medicines and/or aminophylline.
Hypoglycaemia: administer intravenous glucose.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 7 .1.3 Other hypotensives.

Pharmacotherapeutic group: Beta-blocking agents, selective, and thiazides

ATC code: C07B B07

TEVACARD CO is a combination of two antihypertensive medicines, bisoprolol and hydrochlorothiazide. Bisoprolol is a B_1-selective beta-adrenoceptor antagonist with low B_2-receptor affinity. It has no intrinsic sympathomimetic activity nor membrane-stabilising properties. It reduces blood pressure, and by blockade of the cardiac B_1-receptors, reduces the heart rate and depresses plasma renin levels.

Hydrochlorothiazide is a thiazide diuretic with antihypertensive activity. Its diuretic effect is due to inhibition of active Na+ transport from the renal tubules to the blood, affecting Na+ re-absorption.

5.2 Pharmacokinetic properties:

Bisoprolol:

Absorption:

Bisoprolol is rapidly absorbed after oral administration. T_{max} varies from 1-4 hours. Bioavailability is high (90 %) after an oral dose; hepatic extraction is very low; and absorption is not affected by the presence of food. The kinetics are linear for doses from 5-40 mg.

Distribution:

Plasma protein binding is 30 %, and the volume of distribution is high (approximately 3 L/kg).

Biotransformation:

50 % of a bisoprolol dose is metabolised in the liver. Bisoprolol metabolites are inactive.

Elimination:

The plasma elimination half-life is 10 to 12 hours, resulting in a duration of action of 24 hours. Renal clearance and hepatic clearance are approximately comparable, and half of a dose (50 % unchanged) as well as the metabolites are excreted in urine. The total clearance is approximately 15 L/h.

Hydrochlorothiazide:

Absorption:

The bioavailability of hydrochlorothiazide shows between-subject variability and ranges from 65 to 70 %. T_{max} varies from 1,5-5 hours (mean value ≈4 hrs). The plasma half-life is about 5 hours with a subsequent longer terminal phase; its biological half-life is up to about 15 hours.

Distribution:

Plasma protein binding is 40 %.

Elimination:

Hydrochlorothiazide is not metabolised and is excreted almost entirely unchanged by glomerular filtration and active tubular secretion. The terminal t½ of hydrochlorothiazide is approximately 8 hours.

The renal clearance of hydrochlorothiazide is reduced and the elimination half-life prolonged in patients with renal and/or cardiac insufficiency. The same applies to elderly subjects, who also show an increase in C_{max}.

Hydrochlorothiazide crosses the placental barrier and is excreted in human milk.

5.3 Preclinical safety data:

Bisoprolol or hydrochlorothiazide have not been found to be hazardous to humans according to the standard preclinical toxicity tests (long-term toxicity, mutagenicity, genotoxicity or carcinogenicity tests). Like other beta-blockers, bisoprolol at high doses has been found in animal experiments to cause toxic effects to the mother (decreased food intake and body weight gain), and to the embryo/fetus (increased late resorptions, reduced birth weight of the offspring, retardation of the physical development up to the end of lactation). However, bisoprolol as well as hydrochlorothiazide were not teratogenic. There was no increase in toxicity when both components were given in combination.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Tablet core:

Colloidal anhydrous silica

Calcium hydrogen phosphate, anhydrous

Magnesium stearate

Maize starch

Microcrystalline cellulose

Tablet coating:

All strengths:

Hypromellose

Macrogol 400

Polysorbate 80 (E433)

Titanium dioxide (E171)

2,5/6,25 mg: Iron oxide yellow, red and black E172

5/6,25 mg: Talc, iron oxide yellow, red and black E172

6.2 Incompatibilities:

Not relevant.

6.3 Shelf life:

2 years.

6.4 Special precautions for storage:

Store at or below 25 °C.

Keep the tablets in the blisters until required for use.

6.5 Nature and contents of container:

TEVACARD CO is packed into blisters made of Aluminium 20 µm and laminate: Polyamide 25 µm/Aluminium 45 µm/PVC 60 µm.

These blisters are further packed into a carton with a package leaflet, according to the approved pack size.

Blisters are packed in carton boxes containing: 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd,

Maxwell Office Park,

Magwa Crescent West,

Waterfall City,

Midrand,

Gauteng,

2090

8. REGISTRATION NUMBER:

TEVACARD CO 2,5/6,25: 47/7.1.3/1269

TEVACARD CO 5/6,25: 47/7.1.3/1270

TEVACARD CO 10/6,25: 47/7.1.3/1271

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

16 March 2021

10. DATE OF REVISION OF THE TEXT:

13 April 2023