SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Timolol/Amiloride/Hydrochlorothiazide 10 mg/2.5 mg/25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg hydrochlorothiazide, 2.5 mg amiloride hydrochloride and 10 mg timolol maleate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Light-blue coloured, square, compressed tablets with rounded corners; one side flat with bevelled edges and scored, the other side convex and imprinted ‘17’.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate hypertension.

4.2 Posology and method of administration

1 to 2 tablets once a day, taken orally.

Use in the elderly: Timolol/amiloride/hydrochlorothiazide has been shown to be as well tolerated in the elderly as in younger patients. The recommended starting dose is 1 tablet daily.

Children: Because the safety and efficacy has not been established in children, it is not recommended for paediatric use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with bronchial asthma or with a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second- or third-degree AV block, overt cardiac failure, right ventricular failure secondary to pulmonary hypertension, significant cardiomegaly and cardiogenic shock.
- Hyperkalaemia (plasma potassium over 5.5 mmol/l).
- Anuria, acute and chronic renal insufficiency, severe progressive renal disease, and diabetic nephropathy.
- Patients with blood urea over 10 mmol/l or serum creatinine over 130 µmol/l or diabetes mellitus should not receive Timolol/Amiloride/Hydrochlorothiazide without careful and frequent serum urea and serum electrolyte monitoring.
- Anaesthetic agents causing myocardial depression, hypersensitivity to any component of the medicinal product or other sulphonamide-derived drugs.
- Use with other potassium-conserving agents. Use with potassium-rich foods and potassium supplements except in severe and/or refractory cases of hypokalaemia when careful monitoring of the serum potassium level is necessary.
- The packaging carries the warning: 'Do not take this medicine if you have a history of wheezing or asthma'.
- See also *Children*, under section 4.2, section 4.4and section 4.6.

4.4 Special warnings and precautions for use

Congestive cardiac failure: Care should be exercised before and during treatment of patients with cardiomegaly or history of cardiac failure.

Cardiac arrhythmias: patients at risk of congestive heart failure should be carefully observed for bradycardia, AV block and respiratory distress. If congestive cardiac failure persists, Timolol/Amiloride/Hydrochlorothiazide should be withdrawn. Beta-adrenergic blocking agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow are observed, consideration should be given to discontinuing these agents.

Exacerbation of ischaemic heart disease following abrupt withdrawal: exacerbation of angina and, in some cases, myocardial infarction has occurred after abrupt withdrawal of beta-blocker therapy. Therefore, it is recommended that if Timolol/Amiloride/Hydrochlorothiazide is to be withdrawn, dosage should be gradually reduced.

Elective or emergency surgery: Timolol/Amiloride/Hydrochlorothiazide should also be gradually withdrawn prior to elective surgery of anginal patients. Agonists such as isoprenaline, dopamine, dobutamine or norepinephrine (noradrenaline) may be used to counter the effects of beta-blockade in emergency surgery.

Renal and hepatic disease and electrolyte disturbances: This product should be used with caution in patients with renal or hepatic disease and in those patients in whom fluid and electrolyte balance is critical. When creatinine clearance falls below 30 ml/min, thiazide diuretics are ineffective. Azotaemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotaemia and oliguria occur during treatment of renal disease, the diuretic should be discontinued.

Metabolic or respiratory acidosis: acid-base balance should be monitored frequently in severely ill patients at risk of respiratory or metabolic acidosis.

Electrolyte and fluid balance: Hyponatraemia, hypochloraemic alkalosis, hypokalaemia, hyperkalaemia or hypomagnesaemia may occur. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, seizures, confusion, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastro-intestinal disturbances such as nausea and vomiting. Serum and urine electrolyte determinations should be made in patients vomiting excessively or receiving parenteral fluids. Dilutional hyponatraemia may occur in oedematous patients in hot weather, which calls for appropriate therapy. Hypochloraemia requires specific treatment only under exceptional circumstances. If hyperkalaemia occurs, Timolol/Amiloride/Hydrochlorothiazide should be discontinued immediately and, if necessary, active measures taken to reduce the plasma potassium level.

Diabetes mellitus, hypoglycaemia: Timolol/Amiloride/Hydrochlorothiazide should be given with caution to diabetic patients and to patients subject to spontaneous hypoglycaemia, as the symptoms and signs of acute hypoglycaemia may be masked. To minimise the risk of hyperkalaemia in diabetic or suspected diabetic patients, the status of the renal function should be known before initiating therapy with this product. Therapy should be discontinued at least three days prior to glucose tolerance testing. Thiazide therapy may impair glucose tolerance. Dosage adjustments of antidiabetic agents, including insulin, may be required.

Skin and sensitivity reactions: there have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Withdrawal should be gradual. Sensitivity reactions to this medicinal product may occur with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus reactions have been reported with thiazide diuretics.

Risk from anaphylactic reaction: While taking ß-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens,

either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine (adrenaline) used to treat anaphylactic reactions.

Metabolic and endocrine: beta-adrenergic blocking agents may mask the signs of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm. Hypercalcaemia and hypophosphataemia have been reported with thiazide diuretics.

Timolol/Amiloride/Hydrochlorothiazide should be discontinued in patients prior to testing for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy. Hyperuricaemia or acute gout may be precipitated in some patients.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma: Sulfonamide or sulfonamide derivative drugs 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 drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug 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

Musculoskeletal: beta-blockers have been reported to induce myasthenic symptoms such as diplopia, ptosis, and generalised weakness.

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 HCTZ 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. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Timolol/Amiloride/Hydrochlorothiazide may potentiate other antihypertensive agents, such as reserpine or guanethidine. The antihypertensive effect of beta-blockers may be reduced by NSAIDs. NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of diuretics. The effect of this product may be enhanced in the post-sympathectomy patient.

Oral calcium antagonists may be combined with Timolol/Amiloride/Hydrochlorothiazide only when heart function is normal. When the heart function is impaired, combination of beta-blockers with dihydropyridine derivatives such as nifedipine may lead to hypotension; and combination with verapamil or diltiazem may cause AV conduction disturbances or left ventricular failure. Intravenous calcium antagonists and Timolol/Amiloride/Hydrochlorothiazide should only be used together with caution. Concomitant beta-blockers and digitalis with either diltiazem or verapamil may further prolong the AV conduction time.

Potentiated systemic ß-blockade (e.g. decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

ß-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, ß-adrenergic blocking agents should be withdrawn several days before the gradual withdraw of clonidine. If replacing clonidine by ß-blocker therapy, the introduction of ß-adrenergic blocking agents should be delayed for several days after clonidine administration has stopped.

Concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) and potassium-sparing agents, including amiloride hydrochloride, may cause hyperkalaemia and renal failure particularly in elderly patients. Therefore, when amiloride hydrochloride is used concomitantly with NSAIDs, renal function and serum potassium levels should be carefully monitored.

When amiloride hydrochloride is administered concomitantly with an angiotensin-converting enzyme inhibitor, an angiotensin II receptor antagonist, cyclosporin or tacrolimus, the risk of hyperkalaemia may be increased. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

When given concomitantly, the following drugs may interact with thiazide diuretics: *Alcohol, barbiturates or narcotics*: co-administration may potentiate orthostatic hypotension.

Oral and parenteral antidiabetic drugs may require adjustment of dosage with concurrent use.

Cholestyramine and colestipol resins: absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastro-intestinal tract by up to 85 and 43 percent respectively. When cholestyramine is

given 4 hours after the hydrochlorothiazide, the absorption is reduced by 30 to 35 percent.

Corticosteroids or ACTH may intensify any thiazide-induced electrolyte depletion, particularly hypokalaemia.

Pressor amines such as epinephrine (adrenaline) may show decreased arterial responsiveness when used with Timolol/Amiloride/Hydrochlorothiazide, but this reaction is not enough to preclude their therapeutic usefulness.

Non-depolarising muscle relaxants such as tubocurarine may possibly interact with Timolol/Amiloride/Hydrochlorothiazide' to increase muscle relaxation.

Lithium should not generally be given with diuretics, because they reduce its renal clearance and add a high risk of lithium toxicity.

Drug/laboratory test interactions: because thiazides may affect calcium metabolism, Timolol/Amiloride/Hydrochlorothiazide may interfere with tests for parathyroid function (see 'Special warnings and precautions for use').

4.6 Fertility, pregnancy and lactation

Pregnancy
Timolol/Amiloride/Hydrochlorothiazide is not recommended for use during pregnancy. The use of any drug in women of child-bearing age requires that the anticipated benefit be weighed against possible hazards, which include foetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

There is a 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 foeto-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 preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding
Thiazides and timolol appear in breast milk, but it is not known whether amiloride is also excreted. If the use of this medicinal product is deemed essential, the mother should stop breast-feeding.

Hydrochlorothiazide is excreted in human milk in small amounts.
Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Timolol/Amiloride/Hydrochlorothiazide 10 mg/2.5 mg/25 mg Tablets during breast-feeding is not recommended. If Timolol/Amiloride/Hydrochlorothiazide 10 mg/2.5 mg/25 mg Tablets is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

Timolol/Amiloride/Hydrochlorothiazide is usually well tolerated, with significant side effects only infrequently reported.

Most common effects experienced are dizziness, asthenia, fatigue, and bradycardia.

Other clinical adverse reactions with Timolol/Amiloride/Hydrochlorothiazide reported are:

Body as a whole: headache.

Cardiovascular: peripheral vascular disorder (cold extremities), hypotension, syncope, arrhythmia, angina pectoris.

Respiratory: dyspnoea, wheezing.

Digestive: nausea, dyspepsia, constipation, diarrhoea, vomiting, GI pain, anorexia, thirst, dry mouth, stomatitis.

Urogenital: impotence.

Nervous: vertigo, paraesthesiae, tremors.

Integumentary: sweating.

Musculoskeletal: muscle cramps.

Psychiatric: insomnia, nervousness, depression, somnolence, abnormal dreaming, sleep disturbance.

Special senses: visual disturbances.

Additional side effects that have been reported with the individual components which should be considered as potential adverse effects of Timolol/Amiloride/Hydrochlorothiazide.

Amiloride-related effects

Body as a whole: weakness, back pain, chest pain, neck/shoulder ache, pain in extremities.

Digestive: abnormal liver function, activation of probable pre-existing peptic ulcer, jaundice, abdominal pain, GI bleeding, flatulence.

Integumentary: alopecia, rash, pruritus.

Haematological: aplastic anaemia, neutropenia.

Metabolic: elevated serum potassium levels (>5.5 mmol/l), hyponatraemia.

Cardiovascular: one patient with partial heart block developed complete heart block; palpitation, orthostatic hypotension.

Psychiatric: decreased libido, mental confusion.

Respiratory: cough.

Nervous: encephalopathy.

Special senses: tinnitus, increased intra-ocular pressure, nasal congestion.

Musculoskeletal: joint pain.

Urogenital: polyuria, urinary frequency, bladder spasm, dysuria.

Hydrochlorothiazide-related effects

Body as a whole: anaphylactic reaction, fever.

Cardiovascular: necrotising angiitis (vasculitis, cutaneous vasculitis).

Digestive: jaundice (intrahepatic cholestatic jaundice), pancreatitis, cramping, gastric irritation.

Integumentary: photosensitivity, toxic epidermal necrolysis, urticaria.

Endocrine/metabolic: glycosuria, hypoglycaemia, hyperglycaemia, hyperuricaemia, electrolyte imbalance, including hypokalaemia and hyponatraemia, sialadenitis.

Psychiatric: restlessness.

Eye disorders: choroidal effusion (frequency not known)

Renal: renal dysfunction, interstitial nephritis, renal failure.

Respiratory: respiratory distresses including, pneumonitis, pulmonary oedema.

Special senses: transient blurred vision, xanthopsia.

Haematological: agranulocytosis, aplastic anaemia, haemolytic anaemia, leucopenia, purpura, thrombocytopenia.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps):
Not known (cannot be estimated from the available data): Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

Timolol maleate-related effects

Body as a whole: chest pain, extremity pain, decreased exercise tolerance, weight loss.

Cardiovascular: cardiac arrest, cerebral vascular accident, palpitation, second- or third-degree AV block, sino-atrial block, oedema and pulmonary oedema, cardiac failure, Raynaud's phenomenon, claudication, worsening of arterial insufficiency and angina pectoris, vasodilatation.

Digestive: diarrhoea, hepatomegaly.

Endocrine: hypoglycaemia, hyperglycaemia.

Integumentary: rash, pruritus, skin irritation, increased pigmentation, exfoliative dermatitis (one case).

Musculoskeletal: arthralgia.

Nervous system: local weakness.

Psychiatric: diminished concentration, hallucination, decreased libido.

Haematological: non-thrombocytopenic purpura.

Respiratory: bronchial spasm, rales, cough.

Special senses: tinnitus, visual disturbances, diplopia, ptosis, eye irritation, dry eyes.

Urogenital: micturition difficulties.

Clinical laboratory tests: Clinically important changes in standard laboratory tests associated with timolol maleate are rare. Slight increases in blood urea, serum

potassium and serum uric acid, and slight decreases in haemoglobin and haematocrit occurred but were not progressive or associated with clinical manifestations.

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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

No specific data are available regarding symptoms or the treatment of overdosage with Timolol/Amiloride/Hydrochlorothiazide, and no antidote is available. Little is known about dialysability of its components; a study of patients with renal failure showed that timolol did not readily dialyse. Treatment is symptomatic and supportive.

Therapy Timolol/Amiloride/Hydrochlorothiazide should be stopped and emesis and/or gastric lavage induced.

Hydrochlorothiazide and amiloride hydrochloride: The signs and symptoms most likely are dehydration and electrolyte imbalance. If hyperkalaemia occurs, active measures should be taken to reduce plasma potassium levels.

Timolol maleate: The most common signs and symptoms to be expected following overdosage with a beta-adrenergic receptor blocking agent are symptomatic bradycardia, hypotension, bronchospasm, acute cardiac failure and heart block.

If overdosage occurs, the following measures are recommended:

1. *Gastric lavage*.

2. *For symptomatic bradycardia*: atropine sulphate, 0.25 to 2 mg intravenously, should be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline hydrochloride should be administered cautiously. In refractory cases, the use of a cardiac pacemaker may be considered.

3. *For hypotension*: a sympathomimetic pressor agent such as dopamine, dobutamine or noradrenaline should be used. In refractory cases, the use of glucagon has been reported to be useful.

4. *For bronchospasm*: isoprenaline hydrochloride should be used. Additional therapy with aminophylline may be considered.

5. *For acute cardiac failure*: conventional therapy with digitalis, diuretics, and oxygen should be instituted immediately. In refractory cases, the use of intravenous aminophylline is suggested. This may be followed, if necessary, by glucagon which has been reported useful.

6. *For heart block*: isoprenaline hydrochloride or a transvenous cardiac pacemaker should be used.

The components of Timolol/Amiloride/Hydrochlorothiazide have, respectively, plasma half-lives of:

hydrochlorothiazide at 5.6 hours with a longer terminal phase; amiloride at about 6 hours; and timolol at about 4 hours.

5.1 Pharmacodynamic properties

In the doses studied, Timolol/Amiloride/Hydrochlorothiazide was more effective in reducing blood pressure than was timolol maleate alone or a combination of hydrochlorothiazide and amiloride hydrochloride.

Timolol/Amiloride/Hydrochlorothiazide was shown to be well tolerated, and effective in lowering blood pressure in a large proportion of the patients studied.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted 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. 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 also section 4.4).

5.2 Pharmacokinetic properties

The three components have similar dosage schedules, and study data have shown that the bioavailabilities of each component are the same when given singly as when the three agents are given together in the combination tablet.

Amiloride hydrochloride is not bound to plasma proteins and has a half-life of about 6-9 hours. It is excreted unchanged by the kidneys.

Hydrochlorothiazide has been estimated to have a plasma half-life of about 5.6 hours with a subsequent longer terminal phase; its biological half-life is up to about 15 hours. It is excreted unchanged in the urine.

Peak plasma concentrations of timolol maleate occur about 1 to 2 hours after a dose, with a plasma half-life of about 4 hours. It is extensively metabolised in the liver, the metabolites being excreted in the urine together with some unchanged timolol. Protein binding is reported to be low.

5.3 Preclinical safety data

No further information provided.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients:

Indigo Carmine E132

Microcrystalline Cellulose E460

Pregelatinised Maize Starch

Magnesium Stearate E572

6.2 Incompatibilities

None known

6.3 Shelf life

Opacified PVC blister packs of 28 tablets - 36 months.

Amber glass bottles, with Ropp or Jay-Cap seals, of 100 tablets - 36 months.

Aluminium/polyethylene strips of 14 tablets - 60 months.

6.4 Special precautions for storage

Store in a dry place below 25°C, protected from light.

6.5 Nature and contents of container

Opacified PVC blisters lidded with aluminium foil, in packs of 28 tablets.
Amber glass bottles, with Ropp or Jay-Cap seals, in packs of 100 tablets.
Aluminium/polyethylene strip packaging in packs of 14 tablets.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

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TW20 8RN
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8 MARKETING AUTHORISATION NUMBER(S)

PL 17736/0123

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