SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains timolol maleate 10 mg and bendroflumethiazide 2.5 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, flat, oval-shaped tablets with a score mark on one side, and engraved on the other side with “V PRE”

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets are indicated for the treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Posology

The recommended dosage range is 1 to 4 tablets daily. The dosage can be taken in the morning or in two divided doses, morning and evening.
If blood pressure control is not achieved on 4 tablets daily, consideration should be given to titrating timolol and bendroflumethiazide separately or adding another agent with hypotensive activity.

Dosage in the elderly

Initiate treatment with 1 tablet daily and thereafter adjust according to response.

Paediatric population

The safety and efficacy of Timolol maleate/Bendroflumethiazide in children has not been established. No data are available.

Method of administration
Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets are for oral use

4.3 Contraindications

Hypersensitivity to timolol maleate and/or bendroflumethiazide or to any of the excipients listed in section 6.1.
Severe renal impairment or anuria.
Severe hepatic impairment.
Significant electrolyte disturbance including refractory hypokalaemia, hyponatraemia and hypercalcaemia, symptomatic hyperuricaemia and Addison`s disease.
Uncontrolled heart failure, bradycardia, cardiogenic shock, history of bronchospasm, bronchial asthma, chronic obstructive pulmonary disease, patients receiving adrenergic augmenting drugs (monoamine oxidase inhibitors and tricyclic antidepressants), sick sinus syndrome (including sino-atrial block), Prinzmetals angina, untreated phaeochromocytoma, second- or third-degree heart block, metabolic acidosis, hypotension and severe peripheral circulatory disturbances.
Anaesthesia with agents that produce myocardial depression, such as chloroform and ether.
Timolol maleate/Bendroflumethiazide is contraindicated in pregnancy.

4.4 Special warnings and precautions for use

Cardiovascular

The continued depression of sympathetic drive through beta-blockade may lead to cardiac failure. All patients should be observed for evidence of cardiac failure, and if it occurs, then treatment with beta blockers should be gradually withdrawn. If it is not possible to withdraw beta blocker treatment then digitalisation and diuretic therapy should be considered.

Beta blockers should not be used in patients with untreated congestive heart failure. This condition should first be stabilised.

Caution should be exercised in patients in patients with first-degree atrioventricular block or portal hypertension.

In patients with ischaemic heart disease, treatment should not be discontinued suddenly. The dosage should gradually be reduced, i.e. over 1-2 weeks. If necessary, replacement therapy should be initiated at the same time, to prevent exacerbation of angina pectoris.

Beta blockers may induce bradycardia. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dosage should be reduced.

In patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), beta blockers should be used with great caution as aggravation of these disorders may occur.

Metabolic/endocrine

Caution should be exercised in patients with diabetes mellitus, spontaneous hypoglycaemia, and impaired renal or hepatic function. Severe renal or hepatic impairment are contra-indicated (see section 4.3).

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

As all diuretics produce changes in fluid and electrolyte balance, caution should be exercised in patients with existing fluid and electrolyte imbalance. Electrolytes and fluids should be monitored, especially with high doses, long-term use or in renal impairment.

Thiazide diuretics should also be used with caution in patients with nephrotic syndrome, hyperaldosteronism and malnourishment.

Beta blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia. Beta-blockers could further increase the risk of severe hypoglycaemia when used concurrently with sulfonylureas. Diabetic patients should be advised to carefully monitor blood glucose levels. (see Section 4.5).

Thiazide diuretics can exacerbate gout and systemic lupus erythematosus.

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.

Other warnings

Beta blockers may unmask myasthenia gravis.

Psoriasis can be aggravated by beta blockers. Therefore patients with a history of psoriasis should take Timolol maleate/Bendroflumethiazide only after careful consideration.

Beta blockers may increase sensitivity to allergens and the seriousness of anaphylactic reactions.

The following statement will appear on the label of this product: `Do not take this medicine if you have a history of wheezing or asthma'.

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. Discontinuance of Timolol maleate/Bendroflumethiazide should be considered if any such reaction is not otherwise explicable, cessation of therapy with the beta-blocker should be gradual.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Timolol maleate/Bendroflumethiazide

The depressant effect of beta blocking drugs on myocardial contractility and on intracardiac conduction may be increased by concomitant use with other drugs having similar effects. Serious effects have been reported with verapamil, disopyramide, lignocaine and tocainide and may be anticipated with diltiazem, quinidine, amiodarone and any of the class 1 antiarrhythmic agents. Special care is necessary when any of these agents are given intravenously in patients who are receiving beta- blockers.

Concurrent administration of digitalis glycosides may increase the atrio-ventricular conduction time.

Beta blockers increase the risk of `rebound hypertension' when taken with clonidine. When clonidine is used in conjunction with non selective beta blockers such as timolol, treatment with clonidine should be continued for some time after treatment with the beta blocker has been discontinued.

Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines, dihydropyridine derivatives such as nifedipine or antihypertensive agents may increase the blood pressure lowering effect.

Concomitant use of beta blockers and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension. Therefore the anaesthetist should be informed when a patient is taking Timolol maleate/Bendroflumethiazide. The withdrawal of beta blocking drugs prior to surgery is not necessary in the majority of patients. If beta blockade is interrupted in preparation for surgery, therapy should be discontinued at least 24 hours beforehand. Continuation of beta blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypertension may be increased. Anaesthetic agents such as ether, cyclopropane and trichloroethylene should not be used whereas halothane, isoflurane, nitrous oxide, intravenous induction agents, muscle relaxants, narcotic analgesics and local anaesthetic agents are all compatible with beta adrenergic blockade. Local

anaesthetics with added vasoconstrictors, e.g. adrenaline, should be avoided. The patient may be protected against vagal reactions by intravenous administration of atropine.

The bioavailability of beta-blockers will be increased by co-administration with cimetidine or hydralazine and reduced with rifampicin.

Alcohol induces increased plasma levels of hepatically metabolised beta blockers such as timolol.

Some prostaglandin synthetase inhibiting drugs have been shown to impair the antihypertensive effect of beta blocking drugs.

Concomitant use of thiazide diuretics with drugs that increase the QT interval, such as astemizole, terfenadine, halofantrine, pimozide, and sotalol may increase the risk of arrhythmias.

There is an increased risk of hypokalaemia when thiazide diutretics are given with with other drugs causing hypokalaemia such as steroids and theophylline.

The antihypertensive effects of diuretics can be antagonised by drugs that cause fluid retention, such as corticosteroids, NSAIDs, or carbenoxolone.

Sympathomimetics such as isoprenaline and salbutamol may counteract the effect of beta blocking agents.

Effects of Timolol maleate/Bendroflumethiazide on other substances

The effect of sympathomimetic agents, e.g. isoprenaline, salbutamol, are reduced by concomitant use of beta blockers.

Beta blockers may intensify the blood sugar lowering effect of insulin and oral antidiabetic drugs. The concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia. (see Section 4.4).

Thiazide diuretics antagonise the hypoglycaemic effect of anti-diabetics.

As with other diuretics, Timolol maleate/Bendroflumethiazide should not be administered concurrently with lithium salts. Diuretics can reduce lithium clearance resulting in high serum levels of lithium. Increased toxicity has also been reported for other drugs, including allopurinol and tetracyclines, when given with thiazide diuretics.

Hypokalaemia caused by thiazide diuretics can increase the cardiac toxicity of digoxin and may also increase the cardiac toxicity of amiodarone, disopyramide and flecainide

4.6 Fertility, pregnancy and lactation

Timolol maleate/Bendroflumethiazide is contraindicated during pregnancy. (See section 4.3).Both constituents cross the placenta and appear in breast milk therefore breastfeeding is not recommended.

Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in foetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period.

4.7 Effects on ability to drive and use machines

None known. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

System Organ Class	**Rare** **≥ 1/10,000, < 1/1000**	**Frequency Not Known**
Blood and lymphatic system disorders		Blood dyscrasias (including thrombocytopenia, granulocytopenia, aplastic anaemia), haemolytic anaemia
Metabolism and nutrition disorders		Electrolyte depletion and dehydration; hypokalaemia; hyperglycaemia (in diabetic and other susceptible patients); hyperuricaemia; hypercalcaemia
Psychiatric disorders	Withdrawal syndrome (Abrupt withdrawal may precipitate angina in susceptible patients or cause rebound hypertension -see section 4.4.)	Hallucination; depression; disorientation; confusional state; nightmare; insomnia
Nervous system disorders		Coma (may be precipitated in hepatic cirrhosis); paraesthesia; dizziness; headache; sedation
Eye disorders	Dry eye	Aggravation of pre-existing myopia; visual impairment
Ear and labyrinth disorders		Vertigo
Cardiac disorders		Atrioventricular block; bradycardia; cardiac failure; cyanosis
Vascular disorders		Necrotising vasculitis; hypotension; Raynaud's phenomenon; increase of an existing intermittent claudication, peripheral coldness
Respiratory, thoracic and mediastinal disorders		Dyspnoea; bronchospasm (Bronchospasm is generally observed in patients with pre- existing asthma or obstructive airways disease.)
Gastrointestinal disorders	Retroperitoneal fibrosis	Acute pancreatitis; dyspepsia; vomiting; nausea; diarrhoea

Skin and subcutaneous tissue disorders	Allergic dermatitis; psoriasiform dermatitis; erythematous rash	Rash with associated photosensitivity
Musculoskeletal and connective tissue disorders	Arthralgia	Muscle pain
Renal and urinary disorders		Oliguria; glucosuria (in diabetic and other susceptible patients)
Reproductive system and breast disorders		Erectile dysfunction
General disorders and administration site conditions		Fatigue; weakness; thirst
Investigations		Increased blood urea (most pronounced in patients with renal disease and pre-existing retention of nitrogen); increased antinuclear antibody

Thiazide diuretics may cause excessive depletion of fluid and electrolytes during prolonged or intense use. Symptoms are muscle pain or fatigue, thirst and oliguria. With thiazide diuretics hypokalaemia is more severe in patients already depleted of potassium, as in renal or hepatic insufficiency.

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

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

Signs and symptoms of overdosage due to the beta blocker component of Timolol maleate/Bendroflumethiazide include severe hypotension, sinus bradycardia, atrioventricular block, acute cardiac failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma and occasionally hyperkalaemia.

Signs and symptoms of overdosage of the thiazide component include nausea, vomiting, diarrhoea, diuresis, dehydration, hypotension, dizziness, weakness and muscle cramps.

Treatment should include close monitoring of cardiovascular, respiratory and renal function, blood glucose and electrolytes. General measures should be taken to restore blood volume, maintain blood pressure and correct electrolyte imbalance.

Further absorption may be prevented by induction of vomiting, gastric lavage or administration of activated charcoal if ingestion is recent.

Cardiovascular complications should be treated symptomatically, which may require the use of sympathomimetic agents (e.g. noradrenaline, metariminol), atropine or inotropic agents (e.g. dopamine, dobutamine). Temporary pacing may be required for AV block. Glucagon can reverse the effects of excessive beta blockade. Intravenous B_2-stimulants, e.g. terbutaline, may be required to relieve bronchospasm.

Timolol cannot be effectively removed by haemodialysis.

There is no known specific antidote for bendroflumethiazide.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiovascular system, Beta blocking agents, non-selective and thiazides ATC code: C07BA06
Timolol maleate is a non-selective Beta-adrenoceptor antagonist with marked hypotensive activity.
Bendroflumethiazide is a thiazide diuretic, which has a moderate duration of activity.
It has been shown that beta-blocking agents used in combination with a thiazide diuretic potentiates the effects of this diuretic giving an enhanced antihypertensive effect. This may be due to the inhibition of renin release or concomitant regional haemodynamic changes. This means that a relatively lower dose of the beta-blocker is required.

5.2 Pharmacokinetic properties

Timolol maleate is well absorbed, extensively metabolised in the liver and eliminated through the kidney with a half-life of 2.5 to 5 hours (the biological half-life is somewhat longer). The beta-blocking effect of timolol is apparent within 30 minutes of administration and has been shown to last for up to 24 hours. It has low to moderate lipid solubility. Protein binding is reported to be low. It crosses the placenta and appears in breast milk.
Bendroflumethiazide has been reported to be completely absorbed from the gastro-intestinal tract and to have a plasma half-life of about 3 or 4 hours. It is highly bound to plasma protein. There is evidence that bendroflumethiazide is fairly extensively metabolised; about 30% is excreted unchanged in the urine. The diuretic effect of bendroflumethiazide is usually complete in 12-18 hours.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber, which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, pregelatinised starch, magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf life

The shelf life of Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets is three years.

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6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

Glass bottles of 30 tablets, 100 and 500 tablets.
Glass bottle of 14 tablets (sample pack).
Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Generics (U.K.) Limited T/A Viatris,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/1778

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/06/2015

10 DATE OF REVISION OF THE TEXT

13/04/2026