Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prestim 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 single score line on one face and engraved on the other side with "V PRE".

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prestim tablets are indicated for the treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Posology

The recommended dosage range is one to four 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 four tablets daily, consideration should be given to titrating timolol and bendroflumethiazide separately or adding another hypotensive agent.

Dosage in the elderly:
Initiate treatment with 1 tablet daily and thereafter adjust according to response.

Patients with hepatic and renal impairment:
When Prestim is administered to patients with hepatic or renal impairment, the dosage may require adjustment (see section 4.4, Special warnings and precautions for use).

Paediatric population:
The safety and efficacy of Prestim in children has not been established. No data are available.

Method of administration
Prestim tablets are for oral administration.

4.3 Contraindications

- Hypersensitivity to timolol maleate and/or bendroflumethiazide to any of the excipients (listed in section 6.1)
- History of bronchospasm, bronchial asthma, chronic obstructive pulmonary disease
- Severe renal failure or anuria
- Severe hepatic impairment
- Uncontrolled heart failure, bradycardia, cardiogenic shock, second or third-degree heart block.
- Use in patients who have received verapamil intravenously within 48 hours
- Concurrent use with lithium salts (see section 4.5, Interaction with other medicinal products and other forms of interaction)
- Sick sinus syndrome (including sino-atrial block)
- Prinzmetal 's angina

● Severe peripheral circulatory diseases
● Untreated phaeochromocytoma
● Hypotension
● Metabolic acidosis
● Anaesthesia with agents that produce myocardial depression such as chloroform and ether
● Symptomatic hyperuricaemia, significant electrolyte disturbance including hypokalaemia, hyponatraemia, hypercalcaemia, Addison's disease
● Use in the presence of digitalis intoxication
● Use in patients receiving adrenergic augmenting drugs (monoamine oxidase inhibitors and tricyclic antidepressants)
● 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 withdraw. 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 with first-degree antrioventricular 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 the disorder may occur.

Metabolic/Endocrine

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

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 higher doses, long-term use or in renal impairment.

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

Thiazide diuretics can exacerbate gout and systemic lupus erythematosus.

Beta-blockers may mask the symptoms of thyrotoxicosis and hypoglycaemia.

Other warnings

Beta blockers may unmask myasthenia gravis.

Psoriasis can be aggravated by beta blockers. Therefore, patients with a history of psoriasis should take Prestim 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 Prestim should be considered if any such reaction is not otherwise explicable, cessation of therapy with the beta-blocker should be gradual.

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.

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.

4.5 Interaction with other medicinal products and other forms of interactions

Effects of other medicinal products on Prestim
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.

Anaesthesia
The anaesthesiologist should be informed when the patient is receiving a beta blocking agent. Concomitant use of beta blockers and anaesthetics may attenuate reflex tachycardia and increase risk of hypotension.

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. The patient may be protected against vagal reactions by intravenous administration of atropine.

Other

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 diuretics are given with other drugs causing hypokalaemia such as steroids and theophylline.

The antihypertensive effects of diuretics can be antagonized 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 drugs.

Effects of Prestim 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.

Thiazide diuretics antagonize the hypoglycaemic effect of anti-diabetics.

As with other diuretics, Prestim 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 increase the cardiac toxicity of aminodarone, disopyramide and flecainide.

Caution is recommended when administering to patients with catecholamine depleting drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy

Prestim is contraindicated during pregnancy (section section 4.3).

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.

Lactation
Both constituents cross the placenta and appear in breast milk therefore breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

Prestim has no known influence on the ability to drive or operate machines. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur (see section 4.8, Undesirable effects).

4.8 Undesirable effects

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.

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		Atrioventicular 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

Description of selected adverse reactions
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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Signs and symptoms of overdosage due to the beta blocker component of Prestim 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 B2-stimulants, e.g. terbutaline, may be required to relieve bronchospasm.

Timolol cannot be effectively removed y haemodialysis.

There is no known specific antidote for bedroflumethiazide.

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 presciber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Maize starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber glass bottles of 30 tablets and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36
Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2010/034/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 February 1997
Date of last renewal: 09 February 2007

10 DATE OF REVISION OF THE TEXT

November 2020