Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol Clonmel 3.75 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bisoprolol Clonmel 3.75 mg
Each film-coated tablet contains 3.75 mg bisoprolol fumarate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Bisoprolol Clonmel 3.75 mg
Off white, round (8 mm in diameter), biconvex film-coated tablet, debossed with 'C' and score line on one side and '40' on other side.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bisoprolol Clonmel 1.25 mg, 2.5 mg, 3.75 mg and 7.5 mg film-coated tablets

- Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section 5.1).

4.2 Posology and method of administration

Posology

Treatment of stable chronic heart failure

Standard treatment of chronic heart failure (CHF) consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocker, diuretics, and when appropriate cardiac glycosides. Patients should be stable (without acute failure) when bisoprolol treatment is initiated.

It is recommended that the treating physician should be experienced in the management of chronic heart failure.

Transient worsening of heart failure, hypotension, or bradycardia may occur during the titration period and thereafter.

Titration phase
The treatment of stable chronic heart failure with bisoprolol requires a titration phase.

The treatment with bisoprolol is to be started with a gradual uptitration according to the following steps:

- 1.25 mg once daily for 1 week, if well tolerated increase to
- 2.5 mg once daily for 1 further week, if well tolerated increase to
- 3.75 mg once daily for 1 further week, if well tolerated increase to
- 5 mg once daily for the 4 following weeks, if well tolerated increase to
- 7.5 mg once daily for the 4 following weeks, if well tolerated increase to
- 10 mg once daily for the maintenance therapy

The maximum recommended dose is 10 mg once daily.

Close monitoring of vital signs (heart rate, blood pressure) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first day after initiating the therapy.

Treatment modification
If the maximum recommended dose is not well tolerated, gradual dose reduction may be considered.

In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation.

The reintroduction and/or uptitration of bisoprolol should always be considered when the patient becomes stable again.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patient's condition.

Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

Patients with hepatic or renal impairment
There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired hepatic or renal function. Uptitration of the dose in these populations should therefore be made with additional caution.

Elderly
No dosage adjustment is required.

Paediatric population
There is no paediatric experience with bisoprolol, therefore its use cannot be recommended in paediatric patients.

Method of administration
For oral use.
Bisoprolol tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed in order to avoid damage to the film-coating and thus preventing direct exposure to the bad-tasting active substance bisoprolol.

Bisoprolol Clonmel 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets can be divided into equal doses.

4.3 Contraindications

Bisoprolol is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- second or third degree AV block
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- untreated phaeochromocytoma (see section 4.4)
- metabolic acidosis

4.4 Special warnings and precautions for use

All indications
Especially in patients with ischaemic heart disease discontinuation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition (see section 4.2).

Bisoprolol must be used with caution in patients with hypertension or angina pectoris and associated heart failure.

Bisoprolol must be used with caution in:

- bronchospasm (bronchial asthma, obstructive airways diseases)
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) can be masked
- strict fasting
- ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment does not always yield the expected therapeutic effect
- first degree AV block
- Prinzmetal's angina: Cases of coronary vasospasm have been observed. Despite its high beta1-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina
- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy
- general anaesthesia. In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischaemia during induction and intubation, and 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 drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the 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

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with class I antiarrhythmic drugs and with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

Although cardioselective (beta1) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, bisoprolol may be used with caution. In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnoea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of $beta_2$-stimulants may have to be increased.

Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (e.g. bisoprolol) after carefully balancing the benefits against the risks.

In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockade.

Under treatment with bisoprolol the symptoms of a thyreotoxicosis may be masked.

<u>Additional warnings applicable to stable chronic heart failure only</u>
The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase (see section 4.2). The initiation and discontinuation of treatment with bisoprolol requires regular monitoring.

There is no therapeutic experience of bisoprolol treatment of heart failure in patients with the following diseases and conditions:

- insulin dependent diabetes mellitus (type I)
- severely impaired renal function
- severely impaired hepatic function
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended

Chronic heart failure only
Class I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

All indications
Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution

Hypertension and stable chronic angina pectoris only
Class I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

All indications
Calcium antagonists of the dihydropyridine type such as felodipine and amlodipine: 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.

Class-III antiarrhythmic drugs (e.g. amiodarone): effect on atrio-ventricular conduction time may be potentiated.

Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.

Parasympathomimetic drugs: concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Insulin and oral antidiabetic drugs: increase of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.

Anaesthetic agents: attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4.).

Digitalis glycosides: reduction of heart rate, increase of atrio-ventricular conduction time.

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.

Beta-Sympathomimetic agents (e.g. isoprenaline, dobutamine): combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.
Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered
Mefloquine: increased risk of bradycardia

Monoamine oxidase inhibitors (except MAO-B inhibitors): enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis.

4.6 Fertility, pregnancy and lactation

Pregnancy
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, intrauterine 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.
Bisoprolol should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental blood flow and the foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breast-feeding
It is not known whether this drug is excreted in human milk. Therefore, breast-feeding is not recommended during administration of bisoprolol.

4.7 Effects on ability to drive and use machines

In a study with coronary heart disease patients bisoprolol did not impair driving performance. However, due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

The following definitions apply to the frequency terminology used hereafter:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1 000 to < 1/100)
Rare (≥ 1/10 000 to < 1/1 000)
Very rare (< 1/10 000)
Not known (cannot be estimated from available data)

Psychiatric disorders
Uncommon: Sleep disorder, depression.
Rare: Nightmare, hallucination.

Nervous system disorders
Common: Dizziness, headache.
Rare: Syncope

Eye disorders
Rare: Reduced tear flow (to be considered if the patient uses lenses).
Very rare: Conjunctivitis.

Ear and labyrinth disorders
Rare: Hearing disorders.

Cardiac disorders
Very common: Bradycardia (in patients with chronic heart failure).
Common: Worsening of heart failure (in patients with chronic heart failure).
Uncommon: AV-conduction disturbances, worsening of pre-existing heart failure (in patients with hypertension or angina pectoris), bradycardia (in patients with hypertension or angina pectoris).

Vascular disorders
Common: Feeling of coldness or numbness in the extremities, hypotension.
Uncommon: Orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders
Uncommon: Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease.
Rare: Allergic rhinitis.

Gastrointestinal disorders
Common: Gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation.

Hepatobiliary disorders
Rare: Hepatitis.

Skin and subcutaneous tissue disorders
Rare: Hypersensitivity reactions (pruritus, flush, rash and angioedema).
Very rare: Alopecia. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash

Musculoskeletal and connective tissue disorders
Uncommon: Muscular weakness and cramps.

Reproductive system and breast disorders
Rare: Erectile dysfunction.

General disorders
Common: Asthenia (in patients with chronic heart failure), fatigue.
Uncommon: Asthenia (in patients with hypertension or angina pectoris).

Investigations
Rare: Increased triglycerides, increased liver enzymes (ALAT, ASAT).

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

Symptoms
With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general, the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2 000 mg) with bisoprolol have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension; all patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive. Therefore, it is mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme given in section 4.2.

Management
If overdose occurs, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is hardly dialysable. Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted.

Bradycardia: administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

Hypotension: intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.

AV block (second or third degree): patients should be carefully monitored and treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.

Acute worsening of heart failure: administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: administer bronchodilator therapy such as isoprenaline, $beta_2$-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: administer i.v. glucose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, beta blocking agents, selective
ATC Code: C07AB07

Mechanism of action
Bisoprolol is a highly $beta_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the $beta_2$-receptor of the smooth muscles of bronchi and vessels as well as to the $beta_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and $beta_2$-mediated metabolic effects. Its $beta_1$-selectivity extends beyond the therapeutic dose range.

Pharmacodynamic effect
As with other beta1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin activity.
In patients with angina, the blockade of beta1-receptors reduces heart action and thus reduces oxygen demand. Hence bisoprolol is effective in eliminating or reducing the symptoms.
In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

Clinical efficacy and safety
In total 2 647 patients were included in the CIBIS II trial. 83 % (n = 2 202) were in NYHA class III and 17 % (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction < 35 %, based on echocardiography). Total mortality was reduced from 17.3 % to 11.8 % (relative reduction 34 %). A decrease in sudden death (3.6 % vs 6.3 %, relative reduction 44 %) and a reduced number of heart failure episodes requiring hospital admission (12 % vs 17.6 %, relative reduction 36 %) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53 %), hypotension (0.23 %), and acute decompensation (4.97 %) were observed, but they were not more frequent than in the placebo-group (0 %, 0.3 % and 6.74 %). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1 010 patients aged ≥ 65 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction ≤ 35 %, who had not been treated previously with ACE inhibitors, beta-blockers, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either bisoprolol or enalapril.

There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months treatment. Non inferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at study end (32.4 % in the bisoprolol-first group vs. 33.1 % in the enalapril-first group, per-protocol population). The study shows that bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate disease.

5.2 Pharmacokinetic properties

Absorption
Bisoprolol is absorbed and has a biological availability of about 90 % after oral administration.

Distribution
The distribution volume is 3.5 l/kg. The plasma protein binding of bisoprolol is about 30 %.

Biotransformation and elimination

Bisoprolol is excreted from the body by two routes. 50 % is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50 % is excreted by the kidneys in an unmetabolised form. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24-hour effect after dosing once daily.

Linearity
The kinetics of bisoprolol are linear and independent of age.

Special population
Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency. The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied. In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64±21 ng/ml at a daily dose of 10 mg and the half-life is 17±5 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity. Like other beta-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/foetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Bisoprolol Clonmel 3.75 mg
Tablet core:
Cellulose, microcrystalline
Calcium hydrogen phosphate
Starch, pregelatinised (Starch 1500)
Crospovidone
Silica, colloidal anhydrous
Magnesium stearate

Film-coating:
Hypromellose (E464)
Titanium dioxide (E171)
Iron oxide yellow (E172)
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

oPA/Alu/PVC//Alu blisters containing 10, 20, 28, 30, 50, 56, 60, 90, 98 or 100 film-coated tablets or
oPA/Alu/PVC//Alu perforated unit dose blisters containing 10 x 1, 20 x 1, 30 x 1, 50 x 1, 90 x 1 or 100 x 1 film-coated tablets.

HDPE bottle (high density polyethylene with white masterbatch) with polypropylene closure containing 30, 100, 250, 500 or 1000 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/400/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th April 2025

10 DATE OF REVISION OF THE TEXT