

NEW ZEALAND DATA SHEET

BISOPROLOL MYLAN



1. Product Name

Bisoprolol Mylan, 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg, film coated tablet.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg or 10 mg of bisoprolol fumarate.

Bisoprolol Mylan tablets contain lactose. For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Bisoprolol Mylan 1.25 mg – White oval biconvex film-coated tablets debossed with 'BLM' on one side and '1.25' on the other side.

Bisoprolol Mylan 2.5 mg – Grey, oval, biconvex film coated tablets with side notches and debossed with 'BL & M' on either side of the scoreline on one side and '2.5' on the other side.

Bisoprolol Mylan 3.75 mg – Cream, oval, biconvex film coated tablets with side notches and debossed with 'BL & M' on either side of the scoreline on one side and '3.75' on the other side.

Bisoprolol Mylan 5 mg – Pale yellow, oval, biconvex film coated tablets with side notches and debossed with 'BL & M' on either side of the scoreline on one side and '5' on the other side.

Bisoprolol Mylan 7.5 mg – Yellow, oval, biconvex film coated tablets with side notches and debossed with 'BL & M' on either side of the scoreline on one side and '7.5' on the other side.

Bisoprolol Mylan 10 mg – Pale orange to light orange, oval, biconvex film coated tablets with side notches and debossed with 'BL & M' on either side of the scoreline on one side and '10' on the other side.

The 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg tablets can be divided into equal halves.

Do not halve 1.25 mg tablet. Dose equivalence when the tablet is divided has not been established.

4. Clinical Particulars

4.1 *Therapeutic indications*

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

Treatment of chronic, stable angina pectoris.

Treatment of essential hypertension.

4.2 Dose and method of administration

Dose

Stable chronic heart failure

Standard treatment of 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 a further week, if well tolerated increase to
- 3.75 mg once daily for a 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 the 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.

Special populations

Renal or liver impairment

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

Elderly

No dosage adjustment is required. It is recommended to start with the lowest possible dose.

Children

There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

Hypertension and angina pectoris

The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day. In patients with ischemic heart disease, it is recommended that withdrawal of treatment should be gradually over 1-2 weeks. In some patients 5 mg per day may be adequate.

Special population

Renal or liver impairment

In patients with final stage impairment of renal function (creatinine clearance < 20 ml/min) or liver function, the dose should not exceed 10 mg bisoprolol once daily.

Elderly

No dosage adjustment is normally required, but 5 mg per day may be adequate in some patients; as for other adults, dosage may have to be reduced in cases of severe renal or hepatic dysfunction.

Children under 12 years and adolescents

Bisoprolol is not recommended for use in children due to a lack of experience in children.

Method of administration

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.

4.3 Contraindications

Bisoprolol is contraindicated in chronic heart failure patients with:

- Acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- Cardiogenic shock
- Second or third degree AV block (without a pacemaker)
- Sick sinus syndrome
- Sinoatrial block
- Bradycardia with less than 60 beats/min before the start of therapy
- Hypotension (systolic blood pressure less than 100 mm Hg)
- Severe bronchial asthma or severe chronic obstructive pulmonary disease
- Late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- Untreated phaeochromocytoma
- Metabolic acidosis
- Hypersensitivity to bisoprolol or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 can be masked
- Strict fasting
- Ongoing desensitisation therapy
- First degree AV block
- Prinzmetal's angina

- Peripheral arterial occlusive disease (intensification of complaints may happen especially during the start of therapy)
- General anaesthesia.

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia 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.

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.

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.

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 beta₂-stimulants may have to be increased.

As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenaline treatment does not always give the expected therapeutic effect.

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 thyrotoxicosis may be masked.

The initiation of treatment with bisoprolol necessitates regular monitoring. For the posology and method of administration please refer to section 4.2.

The cessation of therapy with bisoprolol should not be done abruptly unless clearly indicated. For further information please refer to section 4.2.

4.5 Interaction with other medicines and other forms of interaction

Combinations not recommended

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.

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.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonidine, rilmenidine): Concomitant use of centrally acting antihypertensive medicinal products 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

Calcium antagonists such as dihydropyridine derivatives with negative inotropic effect (e.g., nifedipine). Nifedipine decrease myocardial contractility by affecting the amount of calcium. Its concomitant use in patients on beta-blocker treatment may increase the risk of hypotension and reduction of the ventricular pump function with possible development of heart failure in patients with latent cardiac insufficiency. The negative inotropism of nifedipine may precipitate or exacerbate heart failure.

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 medicinal products (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 medicinal products: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Insulin and oral antidiabetic medicinal products: Intensification 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 (see 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.

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

Sympathomimetics that activate both β - and α -adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the α -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 β -blockers. Higher doses of adrenaline may be necessary for treatment of allergic reactions.

Concomitant use with antihypertensive agents as well as with other medicinal products with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Moxisylyate: Possibly causes severe postural hypertension.

Combinations to be considered

Mefloquine: increased risk of bradycardia.

Monoamineoxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of beta-blocking agents but also risk of hypertensive crisis.

4.6 Fertility, pregnancy and lactation

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/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 fetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, beta₁-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 fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus 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, breastfeeding is not recommended during administration of bisoprolol.

Fertility

No data available.

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 terminologies have been used in order to classify the occurrence of undesirable effects:

Very common ($\geq 1/10$)

Common ($\geq 1/100$, to $< 1/10$)

Uncommon ($\geq 1/1,000$, to $< 1/100$)

Rare ($\geq 1/10,000$, to $< 1/1,000$)

Very rare ($\leq 1/10,000$)

Cardiac disorders

Very common: bradycardia.

Common: worsening of heart failure.

Uncommon: AV-conduction disturbances.

Investigations

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

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 impairment.

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.

Skin and subcutaneous tissue disorders

Rare: hypersensitivity reactions (itching, flush, rash).

Very rare: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia.

Musculoskeletal and connective tissue disorders

Uncommon: muscular weakness and cramps.

Vascular disorders

Common: Feeling of coldness or numbness in the extremities, hypotension.

Uncommon: orthostatic hypotension.

General disorders

Common: asthenia, fatigue.

Hepatobiliary disorders

Rare: hepatitis.

Reproductive system and breast disorders

Rare: Potency disorders.

Psychiatric disorders

Uncommon: sleep disorders, depression.

Rare: nightmares, hallucinations.

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 professionals are asked to report any suspected adverse reactions

<https://nzphvc.otago.ac.nz/reporting/>

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 overdose of a beta-blocking agent are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000 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 pharmacological actions and recommendations for other beta-blocking agents, the following general measures should be considered when clinically warranted.

Bradycardia: Atropine should be administered intravenously. 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: bronchodilator therapy such as isoprenaline, beta₂-sympathomimetic medicinal products and/or aminophylline should be administered.

Hypoglycaemia: i.v. glucose should be administered.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective, ATC code: C07AB07

Mechanism of action

Bisoprolol is a highly beta₁-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the beta₂-receptor of the smooth muscles of bronchi and vessels as well as to the beta₂-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta₂-mediated metabolic effects. Its beta₁-selectivity extends beyond the therapeutic dose range.

Clinical efficacy and safety

In total 2647 patients were included in the CIBIS II trial. 83% (n = 2202) 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 1010 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 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.

Bisoprolol is also used for the treatment of hypertension and angina. As with other β_1 -blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin levels.

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. Hence bisoprolol is effective in eliminating or reducing the symptoms.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation/elimination

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. 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. 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.

Linearity/non-linearity

The kinetics of bisoprolol are linear and independent of age.

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-blocking agents, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal 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*

In addition to the drug substance, Bisoprolol Mylan tablets also contain microcrystalline cellulose, lactose anhydrous, silica (colloidal anhydrous), magnesium stearate, sodium lauryl sulphate and croscarmellose sodium, titanium dioxide, polydextrose, hypromellose, and macrogol.

The 2.5 mg tablet also contains iron oxide yellow, iron oxide red and iron oxide black.

The 3.75 mg tablet also contains iron oxide yellow.

The 5 mg tablet also contains iron oxide yellow and iron oxide black.

The 7.5 mg tablet also contains iron oxide yellow and iron oxide red.

The 10 mg tablet also contains iron oxide yellow, iron oxide red and Sunset Yellow FCF.

Bisoprolol Mylan is gluten-free.

6.2 *Incompatibilities*

Not applicable.

6.3 *Shelf life*

18 months (1.25 mg, 2.5mg)

24 months (3.75 mg, 5 mg, 7.5 mg, 10 mg)

6.4 *Special precautions for storage*

Store below 25°C. Protect from moisture.

6.5 *Nature and contents of container*

PVC-Aluminium blister. Pack sizes of 30 or 90 film-coated tablets.

HDPE bottle with polypropylene child resistant closure and desiccant. Pack size of 30 film-coated tablets.

Not all pack types and sizes may be marketed.

6.6 *Special precautions for disposal*

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

16 November 2017

10. Date of Revision of the Text

27 April 2020

Section	Summary of changes
6.3	Updated shelf-life.