Public Assessment Report

Decentralised Procedure

BISOPROLOL ORION 2.5 MG, 5 MG AND 10 MG TABLETS

BISOPROLOL FUMARATE

UK/H/4320/001-3/DC

UK Licence No: PL 27925/0063-5

ORION CORPORATION
LAY SUMMARY

On 10\textsuperscript{th} March 2011, the UK granted Orion Corporation Marketing Authorisations (licences) for Bisoprolol Orion 2.5 mg, 5 mg and 10 mg tablets (PL 27925/0063-5; UK/H/4320/001-3/DC).

Bisoprolol Orion 2.5 mg, 5 mg and 10 mg tablets contain the active ingredient, bisoprolol fumarate. Bisoprolol fumarate belongs to a group of medicines called beta-blockers.

Bisoprolol Orion 2.5 mg, 5 mg and 10 mg tablets are used to treat:
- Stable chronic heart failure. It is used in combination with other medicines suitable for this condition (such as ACE-inhibitors, diuretics, and heart glycosides).
- Coronary heart disease and chest pain (angina pectoris) caused by shortage of oxygen in the heart muscle.
- High blood pressure (hypertension).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Bisoprolol Orion 2.5 mg, 5 mg and 10 mg tablets outweigh the risks; hence these Marketing Authorisations have been granted.
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Module 6: Steps taken after initial procedure  Not applicable
# Module 1

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<th><strong>Product Name</strong></th>
<th>Bisoprolol Orion 2.5 mg, 5 mg and 10 mg tablets</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10.1</td>
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<tr>
<td><strong>Active Substance</strong></td>
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<td><strong>Form</strong></td>
<td>Tablets</td>
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<tr>
<td><strong>Strength</strong></td>
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<td>Orion Corporation</td>
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<td>FI-02200 Espoo</td>
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<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
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<td><strong>Concerned Member States (CMS)</strong></td>
<td>The Czech Republic (CZ), Denmark (DK), Finland (FI), Norway (NO), Sweden (SE) and the Slovak Republic (SK)</td>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/4320/001-3/DC</td>
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<td><strong>End of Procedure</strong></td>
<td>Day 180 – 8th February 2011</td>
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</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol Orion 2.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2.5 mg bisoprolol fumarate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
2.5 mg: White to off white round biconvex tablet with a break line on one side
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- 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).
- Treatment of chronic, stable angina pectoris.
- Treatment of essential hypertension.

4.2 Posology and method of administration
Route of Administration: Oral use

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 fumarate requires a titration phase.
The treatment with bisoprolol fumarate 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 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 fumarate is generally a long-term treatment.

Administration
Bisoprolol Fumarate Tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

Renal or liver impairment:
There is no information regarding pharmacokinetics of bisoprolol fumarate in patients with chronic heart failure and with impaired liver or renal function. Up titration 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 and adolescents:
Bisoprolol Fumarate is not recommended for use in children and adolescents due to a lack of experience in 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.

Renal or hepatic 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 and adolescents:
Bisoprolol Fumarate is not recommended for use in children and adolescents due to a lack of experience in children.

4.3 Contraindications
- hypersensitivity to bisoprolol or to any of the excipients
- untreated, acute, or uncompensated heart failure, requiring intravenous inotropic support (see 4.4)
- cardiogenic shock
- Atrio-ventricular block of second or third degree (without a pacemaker)
- sick sinus syndrome
- sino-atrial 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 (see 4.4)
- metabolic acidosis
4.4 Special warnings and precautions for use
- Bisoprolol Fumarate must be used with caution in:
  - stable chronic heart failure (Bisoprolol indicated for treatment after initial titration phase)
  - 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
  - AV block of first degree
  - prinzmetal's angina
  - peripheral arterial occlusive disease (intensification of complaints might 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 bradycardia and 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 fumarate treatment of heart failure in patients with the following diseases and conditions:
- insulin dependent diabetes mellitus (type I)
- severely impaired renal function (serum creatinine>300 micromol/l)
- severely impaired liver function
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

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

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-blocking agents, bisoprolol fumarate 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-blocking agents (e.g. bisoprolol fumarate) after carefully balancing the benefits against the risks.

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

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

The initiation of treatment with bisoprolol fumarate necessitates regular monitoring. For the posology and method of administration please refer to section 4.2. The cessation of therapy with bisoprolol fumarate should not be done abruptly unless clearly indicated. For further information please refer to section 4.2.
4.5 Interaction with other medicinal products 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, moxonodine, 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 (eg, 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.

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 (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.

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.

Moxisylyte: 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 Pregnancy and lactation
Pregnancy:
Bisoprolol Fumarate 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 reactions (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.

Lactation:
It is not known whether this drug is excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol fumarate.

4.7 Effects on ability to drive and use machines
Bisoprolol Fumarate Tablets has negligible influence on the ability to drive and use machines. In a study with coronary heart disease patients bisoprolol fumarate 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:

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td>Sleep disorders, depression</td>
<td>Nightmares, hallucinations</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Dizziness, headache</td>
<td></td>
<td>Syncope</td>
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<tr>
<td>Eye disorders</td>
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<td>Reduced tear flow (to be considered if the patient uses lenses)</td>
<td>Conjunctivitis</td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
<td>Hearing impairment</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Bradycardia</td>
<td>Worsening of heart failure</td>
<td>AV-conduction disturbances</td>
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<tr>
<td>Vascular disorders</td>
<td></td>
<td>Feeling of coldness or numbness in the extremities, hypotension</td>
<td>Orthostatic hypotension</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<td></td>
<td>Bronchospasm in patients with bronchial asthma or a history of</td>
<td>Allergic rhinitis</td>
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</tbody>
</table>
### Overdose

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 up titration according to the scheme given in section 4.2.

If overdose occurs, bisoprolol fumarate 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-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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Bisoprolol fumarate 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 fumarate 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.

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 already used for the treatment of hypertension and angina. As with other β1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma rennin levels.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol fumarate 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

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. 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.
The kinetics of bisoprolol are linear and independent of age.

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-blocking agents, bisoprolol fumarate 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
Cellulose, Microcrystalline Silica, Colloidal Anhydrous Croscarmellose sodium Sodium Starch glycolate (Type A) Magnesium Stearate

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
Blister of white PVC/PVDC/Aluminium Pack sizes of 20, 21, 28, 30, 50, 56, 60, 90 and 100. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Orion Corporation Orionintie 1 FI-02200 Espoo Finland

8 MARKETING AUTHORISATION NUMBER(S)
PL 27925/0063

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/03/2011

10 DATE OF REVISION OF THE TEXT
10/03/2011

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol Orion 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg bisoprolol fumarate
For a full list of excipients, see section 6.1.

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Tablet
5 mg: White to off white round biconvex tablet with a break line on one side
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4 CLINICAL PARTICULARS
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• 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).
• Treatment of chronic, stable angina pectoris.
• Treatment of essential hypertension.

4.2 Posology and method of administration
Route of Administration: Oral use

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 fumarate requires a titration phase.
The treatment with bisoprolol fumarate is to be started with a gradual uptitration according to the
following steps:

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- 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 period. Symptoms may already occur within the first day after
initiating the therapy.

Treatment modification
If the maximum recommended dose is 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 fumarate is generally a long-term treatment.

**Administration**

Bisoprolol Fumarate Tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

**Renal or liver impairment:**

There is no information regarding pharmacokinetics of bisoprolol fumarate in patients with chronic heart failure and with impaired liver or renal function. Up titration 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 and adolescents:**

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

**Renal or hepatic 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 and adolescents:**

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

### 4.3 Contraindications

- hypersensitivity to bisoprolol or to any of the excipients
- untreated, acute, or uncompensated heart failure, requiring intravenous inotropic support (see 4.4)
- cardiogenic shock
- Atrio-ventricular block of second or third degree (without a pacemaker)
- sick sinus syndrome
- sino-atrial 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 (see 4.4)
- metabolic acidosis

### 4.4 Special warnings and precautions for use

- Bisoprolol Fumarate must be used with caution in:
- stable chronic heart failure (Bisoprolol indicated for treatment after initial titration phase)
- 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
- AV block of first degree
- prinzmetal's angina
- peripheral arterial occlusive disease (intensification of complaints might 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 bradycardias, 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 fumarate treatment of heart failure in patients with the following diseases and conditions:

- insulin dependent diabetes mellitus (type I)
- severely impaired renal function (serum creatinine>300 micromol/l)
- severely impaired liver function
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

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

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-blocking agents, bisoprolol fumarate 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-blocking agents (e.g. bisoprolol fumarate) after carefully balancing the benefits against the risks.

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

4.5 Interaction with other medicinal products and other forms of interaction

Combination 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 atrophicventricular 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, moxonodine, 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, vasodilatation). 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 (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.

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.

Moxisylate: 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 Pregnancy and lactation
Pregnancy:
Bisoprolol Fumarate has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenoeceptor blockers reduce placental perfusion, which has been
associated with growth retardation, intrauterine death, abortion or early labour. Adverse reactions (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.

**Lactation:**
It is not known whether this drug is excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol fumarate.

**4.7 Effects on ability to drive and use machines**
Bisoprolol Fumarate Tablets has negligible influence on the ability to drive and use machines. In a study with coronary heart disease patients bisoprolol fumarate 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:

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<tr>
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<td>Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease</td>
<td>Allergic rhinitis</td>
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<tr>
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<td>Gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation</td>
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4.9 Overdose

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 up titration according to the scheme given in section 4.2.

If overdose occurs, bisoprolol fumarate 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-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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Bisoprolol fumarate 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 fumarate 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.

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 already used for the treatment of hypertension and angina. As with other beta-blockers, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma rennin levels.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol fumarate 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
Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. 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.

The kinetics of bisoprolol are linear and independent of age.

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-blocking agents, bisoprolol fumarate 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
Cellulose, Microcrystalline
Silica, Colloidal Anhydrous
Croscarmellose sodium
Sodium Starch glycolate (Type A)
Magnesium Stearate

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
Blister of white PVC/PVDC/Aluminium
Pack sizes of 20, 21, 28, 30, 50, 56, 60, 90 and 100.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER(S)
PL 27925/0064

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/03/2011

10 DATE OF REVISION OF THE TEXT
10/03/2011
1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol Orion 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg bisoprolol fumarate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
10 mg: White to off white round biconvex tablet with a break line on one side
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
• 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).
• Treatment of chronic, stable angina pectoris.
• Treatment of essential hypertension.

4.2 Posology and method of administration
Route of Administration: Oral use

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 fumarate requires a titration phase.
The treatment with bisoprolol fumarate 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 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 fumarate is generally a long-term treatment.

**Administration**
Bisoprolol Fumarate Tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

**Renal or liver impairment:**
There is no information regarding pharmacokinetics of bisoprolol fumarate in patients with chronic heart failure and with impaired liver or renal function. Up titration 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 and adolescents:**
Bisoprolol Fumarate is not recommended for use in children and adolescents due to a lack of experience in 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.

**Renal or hepatic 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 and adolescents:**
Bisoprolol Fumarate is not recommended for use in children and adolescents due to a lack of experience in children.

### 4.3 Contraindications
- hypersensitivity to bisoprolol or to any of the excipients
- untreated, acute, or uncompensated heart failure, requiring intravenous inotropic support (see 4.4)
- cardiogenic shock
- Atrio-ventricular block of second or third degree (without a pacemaker)
- sick sinus syndrome
- sino-atrial 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 (see 4.4)
- metabolic acidosis

### 4.4 Special warnings and precautions for use
- Bisoprolol Fumarate must be used with caution in:
- stable chronic heart failure (Bisoprolol indicated for treatment after initial titration phase)
- 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
- AV block of first degree
- prinzmetal's angina
- peripheral arterial occlusive disease (intensification of complaints might 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 fumarate treatment of heart failure in patients with the following diseases and conditions:

- insulin dependent diabetes mellitus (type I)
- severely impaired renal function (serum creatinine > 300 micromol/l)
- severely impaired liver function
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

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

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-blocking agents, bisoprolol fumarate 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-blocking agents (e.g. bisoprolol fumarate) after carefully balancing the benefits against the risks.

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

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

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

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

4.5 Interaction with other medicinal products 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, moxonodine, 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.

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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.

Moxisylyte: 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 Pregnancy and lactation

Pregnancy:
Bisoprolol Fumarate 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 reactions (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.

Lactation:
It is not known whether this drug is excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol fumarate.

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<td></td>
<td>Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease</td>
<td></td>
<td>Allergic rhinitis</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Gastrointestinal complaints such as nausea, vomiting,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorder</td>
<td>Symptom/Effect</td>
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<td>--------------------------------------------------------------------------------</td>
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<tr>
<td>Hepatobiliary disorders</td>
<td>diarrhoea, constipation</td>
<td></td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Hepatitis</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Hypersensitivity reactions (itching, flush, rash)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia</td>
<td></td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscular weakness and cramps</td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td>Potency disorders</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia, fatigue</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Investigations</td>
<td>Increased triglycerides, increased liver enzymes (ALAT, ASAT)</td>
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</tbody>
</table>

**4.9 Overdose**

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 up titration according to the scheme given in section 4.2.

If overdose occurs, bisoprolol fumarate 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-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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective, ATC Code: C07AB07
Bisoprolol fumarate 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 fumarate 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.

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 already used for the treatment of hypertension and angina. As with other β1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma rennin levels.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol fumarate 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

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. 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.

The kinetics of bisoprolol are linear and independent of age.

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-blocking agents, bisoprolol fumarate 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
Cellulose, Microcrystalline
Silica, Colloidal Anhydrous
Croscarmellose sodium
Sodium Starch glycolate (Type A)
Magnesium Stearate

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
Blister of white PVC/PVDC/Aluminium
Pack sizes of 20, 21, 28, 30, 50, 56, 60, 90 and 100.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORITY
Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8 MARKETING AUTHORITY NUMBER(S)
PL 27925/0065

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
10/03/2011

10 DATE OF REVISION OF THE TEXT
10/03/2011
Module 3
Product Information Leaflets

The Patient Information Leaflets (PILs) below are the leaflets for PL 27925/0063-5. Please note that there are no mock-ups available. The marketing authorisation holder has stated that it is not intending to market the products and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PILs for review to the regulatory authority before marketing the products.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Bisoprolol Orion 2.5 mg Tablets
Bisoprolol Orion 5 mg Tablets
Bisoprolol Orion 10 mg Tablets

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What [Bisoprolol Orion] Tablets are and what they are used for.
2. Before you take [Bisoprolol Orion] Tablets
3. How to take [Bisoprolol Orion] Tablets
4. Possible side effects
5. How to store [Bisoprolol Orion] Tablets
6. Further Information.

1. What Bisoprolol Orion Tablets are and what they are used for

The active substance in this medicine is Bisoprolol fumarate. [Bisoprolol Orion] belongs to a group of medicines called beta-blockers. These medicines work by affecting the body’s response to some nerve impulses, especially in the heart. As a result, bisoprolol slows down the heart rate and makes the heart more efficient at pumping blood around the body. Heart failure occurs when the heart muscle is weak and unable to pump enough blood to supply the body’s needs.

Bisoprolol is used:
- To treat stable chronic heart failure. It is used in combination with other medicines suitable for this condition (such as ACE-inhibitors, diuretics, and heart glycosides).
- In treatment of coronary heart disease and chest pain (angina pectoris) caused by shortage of oxygen in the heart muscle.
- In treatment of high blood pressure (hypertension).

2. Before you take Bisoprolol Orion Tablets

Do not take [Bisoprolol Orion] Tablets:

Do not take Bisoprolol Orion Tablets if one of the following conditions applies to you:
- allergic (hypersensitive) to bisoprolol fumarate or any of the other ingredients of [Bisoprolol Orion] tablets.
- severe asthma or severe chronic lung disease
- severe blood circulation problems in your limbs (such as Raynaud’s syndrome), which may cause your fingers and toes to tingle or turn pale or blue
- untreated phaeochromocytoma, which is a rare tumour of the adrenal gland
- metabolic acidosis, which is a condition when there is too much acid in the blood.

Do not take [Bisoprolol Orion] Tablets if you have one of the following heart problems:
- acute heart failure
- worsening heart failure requiring injection of medicines into a vein, that increase the force of contraction of the heart
- slow heart rate
- low blood pressure
- certain heart conditions causing a very slow heart rate or irregular heartbeat
- cardiogenic shock, which is an acute serious heart condition causing low blood pressure and circulatory failure.
Take special care with [Bisoprolol Orion] Tablets:
If you have any of the following conditions tell your doctor before taking this medicine; he or she may want to take special care (for example give additional treatment or perform more frequent checks):
- diabetes
- strict fasting
- certain heart diseases such as disturbances in heart rhythm, or severe chest pain at rest (Prinzmetal’s angina)
- kidney or liver problems
- less severe blood circulation problems in your limbs
- less severe asthma or chronic lung disease
- history of a scaly skin rash (psoriasis)
- tumour of the adrenal gland (phaeochromocytoma)
- thyroid disorder.

In addition, tell your doctor if you are going to have:
- desensitization therapy (for example for the prevention of hay fever), because Bisoprolol may make it more likely that you experience an allergic reaction, or such reaction may be more severe
- anaesthesia (for example for surgery), because this medicine may influence how your body reacts to this situation

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Do not take the following medicines with Bisoprolol Orion without special advice from your doctor:
- Certain medicines used to treat irregular or abnormal heartbeat (Class I antiarrhythmic medicines such as quinidine, disopyramide, lidocaine, phenytoin; flecainide, propafenone)
- Certain medicines used to treat high blood pressure, angina pectoris or irregular heartbeat (calcium antagonists such as verapamil and diltiazem)
- Certain medicines used to treat high blood pressure such as clonidine, methyl dopa, moxonodine, rilmenidine. However, do not stop taking these medicines without checking with your doctor first.

Check with your doctor before taking the following medicines with [Bisoprolol Orion]: your doctor may need to check your condition more frequently:
- Certain medicines used to treat high blood pressure or angina or abnormal heart beat (dihydropyridine-derivative calcium antagonists such as nifedipine)
- Certain medicines used to treat high blood pressure or angina pectoris (dihydropyridine-type calcium antagonists such as felodipine and amiodipine)
- Certain medicines used to treat irregular or abnormal heartbeat (Class III antiarrhythmic medicines such as amiodarone)
- Beta-blocking agents applied locally (such as timolol eye drops for glaucoma treatment)
- Certain medicines used to treat for example Alzheimer’s disease or glaucoma (parasympathomimetics such as tacrine or carbachol) or medicines that are used to treat acute heart problems (sympathomimetics such as isoprenaline and dobutamine)
- Antidiabetic medicines including insulin
- Anaesthetic agents (for example during surgery)
- Digitals, used to treat heart failure
- Non-steroidal anti-inflammatory medicines (NSAIDs) used to treat arthritis, pain or inflammation (for example ibuprofen or diclofenac)
- Any medicine, which can lower blood pressure as a desired or undesired effect such as antihypertensives, certain medicines for depression (tricyclic antidepressants such as imipramine or amitriptyline), certain medicines used to treat epilepsy or during anaesthesia (barbiturates such as phenobarbital), or certain medicines to treat mental illness characterized by a loss of contact with reality (phenothiazines such as levomepromazine)
- Moxisylylate, used for treatment Raynauds disease (poor circulation which makes toes and fingers numb and pale)
- Mefloquine, used for prevention or treatment of malaria
- Depression treatment medicines called monoamine oxidase inhibitors (except MAO-B inhibitors) such as moclobemide.

Taking [Bisoprolol Orion] Tablets with food and drink:
[Bisoprolol Orion] Tablets should be taken in the morning, before, with or after breakfast. They should be swallowed whole with liquid and should not be chewed or crushed.
Avoid drinking excessive alcohol, since it may increase the blood pressure-lowering effect of Bisoprolol. Avoid drinking alcohol altogether, if it makes you more dizzy or more light-headed than usual.

Pregnancy and breast-feeding:
There is a risk that use of [Bisoprolol Orion] during pregnancy may harm the baby. If you are pregnant or planning to become pregnant, tell your doctor. He or she will decide whether you can take this medicine during
pregnancy. It is not known whether bisoprolol passes into human breast milk. Therefore, breastfeeding is not recommended during therapy with Bisoprolol Orion.

Driving and using machines:
Your ability to drive or use machinery may be affected depending on how well you tolerate the medicine. Please be especially cautious at the start of treatment, when the dose is increased or the medication is changed, as well as in combination with alcohol.

3. How to take Bisoprolol Orion tablets

Always take Bisoprolol Orion tablets exactly as your doctor has told you. You should check with your doctor or your pharmacist if you are not sure. Bisoprolol Orion Tablets should be taken in the morning, before, with or after breakfast. Swallow the tablet/s whole with some water and do not chew or crush them.

This treatment should be initiated by a specialist in cardiology or internal medicine.

Children and adolescents: Bisoprolol Orion Tablets are not recommended for use in children.

Stable chronic heart failure
Adults including the elderly: Treatment with bisoprolol must be started at a low dose and increased gradually. Your doctor will decide how to increase the dose, and this will normally be done in the following way:
• 1.25 mg bisoprolol once daily for one week
• 2.5 mg bisoprolol once daily for one week
• 3.75 mg bisoprolol once daily for one week
• 5 mg bisoprolol once daily for four weeks
• 7.5 mg bisoprolol once daily for four weeks
• 10 mg bisoprolol once daily for maintenance (on-going) therapy.

The maximum recommended daily dose is 10 mg bisoprolol.
Depending on how well you tolerate the medicine, your doctor may also decide to lengthen the time between dose increases. If your condition gets worse or you no longer tolerate the drug, it may be necessary to reduce the dose again or to interrupt treatment. In some patients a maintenance dose lower than 10 mg bisoprolol may be sufficient. Your doctor will tell you what to do. If you have to stop treatment entirely, your doctor will usually advise you to reduce the dose gradually, as otherwise your condition may become worse.

Renal or liver disease: The dosage should be increased very gradually and cautiously in patients with severe kidney or liver problems

Hypertension and angina
Adults and the elderly: The usual dose for adults is one tablet (10 mg) daily. Your doctor may decide to increase or decrease this dose.

Renal or liver disease: The dosage should not exceed 10 mg once daily in patients with severe kidney or liver problems.

If you take more [Bisoprolol Orion] Tablets than you should:
Contact your doctor or local emergency ward immediately. Take this leaflet and any tablets you still have with you. Your doctor will decide what measures are necessary. Symptoms of an overdose may include slowed heart rate, severe difficulty in breathing feeling dizzy, or trembling (due to decreased blood sugar).

For Spain only: En caso de sobredosis o ingestión accidental, consulte inmediatamente a su médico o farmacéutico o llame al Servicio de Información Toxicológica, teléfono 91 562 04 20 indicando el medicamento y la cantidad ingerida.

If you forget to take [Bisoprolol Orion] Tablets:
If you forget to take a dose, take it as soon as you remember it unless it is nearly time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking [Bisoprolol Orion] Tablets:
Do not stop treatment suddenly or change the recommended dose without talking to your doctor first. If you need to stop treatment, it must be done gradually, to avoid side effects.
If you have any further questions on the use of this product, ask you doctor or pharmacist.
4. Possible side effects

Like all medicines, Bisoprolol Orion Tablets can cause side effects, although not everybody gets them.

To prevent serious reactions, speak to a doctor immediately if a side effect is severe, occurred suddenly or gets worse rapidly. The most serious side effects are related to the heart function:

- slowing of heart rate (affects more than 1 person in 10)
- worsening of heart failure (affects less than 1 person in 10)
- slow or irregular heartbeat (affects less than 1 person in 100)

If you feel dizzy or weak, or have breathing difficulties please contact your doctor as soon as possible.

Further side effects are listed below according to how frequently they may occur:

<table>
<thead>
<tr>
<th>Very common:</th>
<th>affects more than 1 user in 10</th>
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<tbody>
<tr>
<td>Common:</td>
<td>affects 1 to 10 users in 100</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>affects 1 to 10 users in 1,000</td>
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<tr>
<td>Rare:</td>
<td>affects 1 to 10 users in 10,000</td>
</tr>
<tr>
<td>Very rare:</td>
<td>affects less than 1 user in 10,000</td>
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</tbody>
</table>

Common (affects less than 1 person in 10):
- tiredness, feeling weak, dizziness, headache
- feeling of coldness or numbness in hands or feet
- low blood pressure
- stomach or intestine problems such as nausea, vomiting, diarrhoea, or constipation.

Uncommon (affects less than 1 person in 100):
- sleep disturbances
- depression
- dizziness when standing up
- breathing problems in patients with asthma or chronic lung disease
- muscle weakness, muscle cramps.

Rare (affects less than 1 person in 1,000):
- hearing problems
- allergic runny nose
- reduced tear flow
- inflammation of the liver which can cause yellowing of the skin or whites of the eyes
- certain blood test results for liver function or fat levels differing from normal
- allergy-like reactions such as itching, flush, rash
- impaired erection
- nightmares, hallucinations.

Very rare (affects less than 1 person in 10,000):
- irritation and redness of the eye (conjunctivitis)
- hair loss
- appearance or worsening of scaly skin rash (psoriasis); psoriasis-like rash.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Bisoprolol Orion tablets

Keep out of the reach and sight of children
Do not use Bisoprolol Orion Tablets after the expiry date which is stated on the blister and the carton. The expiry date refers to the last day of that month. This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
6. Further Information

The active substance is bisoprolol fumarate

**What Bisoprolol Orion Tablets contain**

The active substance is bisoprolol fumarate

- Each 2.5 mg tablet contains 2.5 mg bisoprolol fumarate.
- Each 5 mg tablet contains 5 mg bisoprolol fumarate.
- Each 10 mg tablet contains 10 mg bisoprolol fumarate.

The other ingredients are cellulose, microcrystalline, silica colloidal anhydrous, croscarmellose sodium, sodium starch glycolate (type A) and magnesium stearate.

**What Bisoprolol Orion Tablets look like and contents of the pack:**

- 2.5 mg: White to off white round biconvex tablets with a break line on one side.
- 5 mg: White to off white round biconvex tablets with a break line on one side.
- 10 mg: White to off white round biconvex tablets with a break line on one side.

Bisoprolol Orion 2.5 mg, 5 mg and 10 mg Tablets only. The tablet can be divided into equal halves.

Pack sizes of 20, 21, 28, 30, 50, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

**Manufacturer:**

Chanelle Medical, Loughrea, Co Galway, Ireland

This medicinal product is authorised in the Member States of the EEA under the following names:

This leaflet was last approved in: MMYYYY
Module 4
Labelling

The labelling below is for PL 27925/0063-5. Please note that there are no mock-ups available. The marketing authorisation holder has stated that it is not intending to market the products and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK labelling for review to the regulatory authority before marketing the products.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol Orion 2.5 mg Tablets
Bisoprolol Orion 5 mg Tablets
Bisoprolol Orion 10 mg Tablets
bisoprolol fumarate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg bisoprolol (as bisoprolol fumarate)
Each tablet contains 5 mg bisoprolol (as bisoprolol fumarate)
Each tablet contains 10 mg bisoprolol (as bisoprolol fumarate)

3. LIST OF EXCIPIENTS

See Package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet
20 tablets
21 tablets
28 tablets
30 tablets
50 tablets
56 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY


8. EXPIRY DATE

EXP:
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

bisoprolol orion 2.5 mg
bisoprolol orion 5 mg
bisoprolol orion 10 mg
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<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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<tr>
<td>Bisoprolol Orion 5 mg</td>
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<td>Bisoprolol Orion 10 mg</td>
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<td>bisoprolol fumarate</td>
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<th>5. OTHER</th>
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Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, The Czech Republic (CZ), Denmark (DK), Finland (FI), Norway (NO), Sweden (SE), the Slovak Republic (SK) and the UK considered that the applications for Bisoprolol Orion 2.5 mg, 5 mg and 10 mg tablets could be approved. Bisoprolol Orion 2.5 mg, 5 mg and 10 mg tablets are prescription only medicines (POM) and are indicated for the treatment of:

- Stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.
- Chronic, stable angina pectoris.
- Essential hypertension.

These applications for Bisoprolol Orion 2.5 mg, 5 mg and 10 mg tablets were submitted according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Emcor tablets (containing 10 mg bisoprolol fumarate), first authorised in UK on 11\textsuperscript{th} February 1988 to E. Merck Limited (PL 00493/0127).

The UK reference products are Cardicor 2.5 mg, 5 mg and 10 mg film coated tablets (PL 00493/0180, PL 00493/0182 and PL 00493/0184), first authorised to E. Merck Limited on 24\textsuperscript{th} December 1999.

Bisoprolol is a highly beta\textsubscript{1}-selective adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. Bisoprolol is a racemic mixture with the levorotatory form S(-) enantiomer possessing 30 to 80 times the greater $\beta$ blocking activity than the dextrorotatory form. Bisoprolol is absorbed and has a biological availability of about 90\% after oral administration. The kinetics of bisoprolol are linear and independent of age.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for these applications as the pharmacology of bisoprolol fumarate is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory justification has been provided for non-submission of a Risk Management Plan has been provided.
## ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Bisoprolol Orion 2.5 mg, 5 mg and 10 mg tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Bisoprolol fumarate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Beta blocking agents, selective</td>
</tr>
<tr>
<td>Pharmacological preparation (ATC Code)</td>
<td>(C07AB07)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>2.5 mg, 5 mg and 10 mg tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/4320/001-3/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>The Czech Republic (CZ), Denmark (DK),</td>
</tr>
<tr>
<td></td>
<td>Finland (FI), Norway (NO), Sweden (SE) and</td>
</tr>
<tr>
<td></td>
<td>the Slovak Republic (SK)</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 27925/0063-5</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Orion Corporation</td>
</tr>
<tr>
<td></td>
<td>Orionintie 1</td>
</tr>
<tr>
<td></td>
<td>FI-02200 Espoo</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Bisoprolol fumarate

Chemical names:
- (+)-1-(4-((2-(1-Methyl-ethoxy)ethoxy)methyl)phenoxy)-3-((1-methylethyl)amino)-2-propanol(E)-2-butenedioate (2:1) salt.
- (±)-1-[[α-(2-Isopropoxyethoxy)-p-tolyl]oxy]-3-(Isopropylamino)-2-propanolfumarate(2:1) salt.

Structural formula:

![Structural formula of Bisoprolol fumarate](image)

Molecular formula: \((\text{C}_{18}\text{H}_{31}\text{NO}_{4})_2\text{C}_4\text{H}_4\text{O}_4\)

Appearance: White or almost white powder.


Molecular weight: 767.0

Bisoprolol fumarate complies with its European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data has been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Suitable Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.
Adequate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, sodium starch glycolate (Type A) and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin. The supplier has confirmed that the magnesium stearate contained in this product is sourced from vegetable origin.

Pharmaceutical Development

The objective of the development programme was to produce safe, efficacious products containing bisoprolol fumarate that could be considered generic medicinal products of Cardicor 2.5 mg, 5 mg and 10 mg film coated tablets (E. Merck Limited).

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

The reference product used in the bioequivalence study is Cardicor 10 mg film coated tablets, licensed in the UK.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot-scale batches of each strength have been provided and are satisfactory.

The applicant has committed to perform process validation on future production-scale batches.

Finished Product Specification

The finished product specifications are acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System

These products are packaged in blisters composed of white polyvinyl chloride (PVC), polyvinylidene chloride (PVDC) and aluminium. The products come in pack sizes of 20, 21, 28, 30, 50, 56, 60, 90 and 100 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.
Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 3 years with no special storage instructions. This is satisfactory.

Summary of Product Characteristics (SmPCs), Patient Information Leaflets (PILs), Labels
The SmPCs, PILs and labelling are pharmaceutically acceptable. The UK approved PIL and label text are included in modules 3 and 4 of this report. The Marketing Authorisation Holder has stated that it is not intending to market the products and, thus, no UK-specific documents have been submitted. The Marketing Authorisation Holder has committed to submit the UK PILs and labelling for review to the regulatory authority before marketing the products.

User testing results of the PIL for these products have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of bisoprolol fumarate are well-known. As bisoprolol fumarate is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory justification has been provided for non-submission of an Environmental Risk Assessment.

It is recommended that Marketing Authorisations are granted for these applications.
III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required.

Pharmacokinetics

A comparative, randomised, single-dose, two-way, crossover study to compare the pharmacokinetics of the test product Bisoprolol Orion (bisoprolol fumarate) 10 mg tablets versus the reference product Cardicor (bisoprolol fumarate) 10 mg tablets (E. Merck Limited, UK) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 72 hours post dose. There was a washout period of 7 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for bisoprolol fumarate are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-\infty}$(ng.h/mL)</th>
<th>$\text{AUC}_{0-t}$(ng.h/mL)</th>
<th>$\text{C}_{\text{max}}$(ng/ml)</th>
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<tbody>
<tr>
<td>Test (T)</td>
<td>504.33±116.85</td>
<td>521.97±124.43</td>
<td>34.99±7.57</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>476.94±85.85</td>
<td>491.47±91.22</td>
<td>31.94±5.87</td>
</tr>
<tr>
<td>T/R Ratio</td>
<td>104.96 (100.63 – 109.47)</td>
<td>105.44 (101.17 – 109.90)</td>
<td>108.81 (103.21 – 114.70)</td>
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</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for $\text{AUC}_{0-t}$ and $\text{C}_{\text{max}}$ for bisoprolol fumarate lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

As the product ranges meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) for a biowaiver for the lower strengths, the results and conclusions of the bioequivalence study on the 10 mg strength can be extrapolated to Bisoprolol Orion 2.5 mg and 5 mg tablets.

EFFICACY
No new efficacy data were submitted with these applications and none were required.

SAFETY
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with these applications and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.
SUMMARY OF PRODUCT CHARACTERISTICS (SmPCS), PATIENT INFORMATION LEAFLETS (PILS) AND LABELLING
The SmPCS, PILs and labelling are medically satisfactory and consistent with those for the reference products, where appropriate.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA FORM
The MAA Forms are medically satisfactory.

CONCLUSIONS
It is recommended that Marketing Authorisations are granted for these applications.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Bisoprolol Orion 2.5 mg, 5 mg and 10 mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Bisoprolol Orion 10 mg tablets and the reference product Cardicor 10 mg tablets. These bioequivalence results and conclusions can be extrapolated to Bisoprolol Orion 2.5 mg and 5 mg tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PILs and labelling are satisfactory and consistent with that for the reference products.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with bisoprolol fumarate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
### Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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