Public Assessment Report

Decentralised Procedure

Bisoprolol Fumarate 5mg film-coated tablets
Bisoprolol Fumarate 10mg film-coated tablets

Procedure Nos:
UK/H/3771/001-2/DC
UK/H/3772/001-2/DC
UK/H/3972/001-2/DC

UK Licence Nos:
PL 17871/0055-8
PL 17871/0083-4

Jenson Pharmaceutical Services Limited
LAY SUMMARY

On 19 November 2010, the MHRA granted Jenson Pharmaceutical Services Limited Marketing Authorisations for medicines called Bisoprolol fumarate 5 mg and 10 mg film-coated tablets.

These medicines are only available on prescription from your doctor.

Bisoprolol fumarate is used in the treatment of high blood pressure (hypertension) and angina pectoris (chest pain caused by blockages in the arteries that supply the heart muscle) and chronic stable angina pectoris.

The active ingredient bisoprolol fumarate belongs to a family of medicines called beta-blockers. Beta-blockers protect the heart against too much activity.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Bisoprolol fumarate 5 mg and 10 mg film-coated tablets outweigh the risks, and Marketing Authorisations were granted.
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## Module 1
### Information about the initial procedure

| **Product Names**       | Bisoprolol fumarate 5 mg film-coated tablets  
                          | Bisoprolol fumarate 10 mg film-coated tablets |
|-------------------------|------------------------------------------------|
| **Type of Application** | Generic, Article 10.1                           |
| **Active Substance**    | Bisoprolol fumarate                             |
| **Form**                | Film-coated tablets                             |
| **Strength**            | 5 mg and 10 mg                                  |
| **MA Holder**           | Jenson Pharmaceutical Services Ltd,  
                          | Carradine House, 237 Regent’s Park Road  
                          | London N3 3LF, UK            |
| **Reference Member State (RMS)** | UK                                           |
| **Concerned Member States (CMS)** | UK/H/3771/01-02/DC: Belgium, Bulgaria, Czech Republic, Denmark, Spain, Finland, Ireland, Iceland, Norway, Portugal and Sweden.  
                                 | UK/H/3772/01-02/DC: Belgium  
                                 | UK/H/3972/01-02/DC: Belgium and Luxembourg |
| **Procedure Number**    | UK/H/3771/01-2/DC  
                          | UK/H/3772/01-2/DC  
                          | UK/H/3972/01-02/DC          |
| **Timetable**           | Day 210 – 20 October 2010                      |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol fumarate 5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg of bisoprolol fumarate

Excipient(s):
Each tablet contains:
0.069 mg tartrazine (E102)
30 mg lactose (anhydrous)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Pale yellow, oval, biconvex film coated tablets with side notches; ‘BL & 4’ engraved on either side of the scoreline on one face of the tablet; ‘M’ engraved on the other face of the tablet.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of hypertension.
Treatment of chronic stable angina pectoris.

4.2 Posology and method of administration
Administration
For oral use

Bisoprolol fumarate tablets are taken in the morning with or without food. They are swallowed with some liquid and not to be chewed.

Adults
_Treatment of hypertension and chronic stable angina pectoris_

The dosage should be individually adjusted. It is recommended to start with 5 mg per day. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day.

Patients with renal impairment
In patients with severe renal impairment (creatinine clearance < 20 ml/min) the dose should not exceed 10 mg once daily. This dosage may eventually be divided into halves.

Patients with severe liver impairment
No dosage adjustment is required, however careful monitoring is advised.

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

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

Discontinuation of treatment
Treatment should not be stopped abruptly (see section 4.4). The dosage should be diminished slowly by a weekly halving of the dose.
4.3 Contraindications
Bisoprolol is contraindicated in patients with:

- hypersensitivity to bisoprolol or to any of the excipients.
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- second or third degree AV block (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- late stages of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- untreated phaeochromocytoma (see section 4.4)
- metabolic acidosis

4.4 Special warnings and precautions for use

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

Tablet contains lactose (anhydrous) - patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Tablet contains tartrazine (E102) - may cause allergic reactions.

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

Bisoprolol must be used with caution in:

- diabetes mellitus showing large fluctuations in blood glucose values. Symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) can be masked,
- strict fasting,
- ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment may not always yield the expected therapeutic effect,
- First degree AV block,
- Prinzmetal's angina,
- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.

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

The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol.

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

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 of 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 bradycarrhythmias, attenuation of reflex tachycardia, and 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.

In bronchial asthma or other chronic obstructive pulmonary diseases, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of the airway
resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

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.

- Centrally acting antihypertensive drugs (e.g. clonidine, methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may further decrease 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:

- 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.

- Calcium antagonists of the dihydropyridine type (e.g. felodipine and amlodipine): Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

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

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

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

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

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

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

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

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

- Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.

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

Combinations to be considered:

- Mefloquine: increased risk of bradycardia.

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

- Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug-metabolizing enzymes. Normally no dosage adjustment is necessary.

- Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

4.6 Pregnancy and lactation

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, β-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the fetus and newborn infant. If treatment with β-adrenoceptor blockers is necessary, β1-selective adrenoceptor blockers are preferable.
Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment is considered necessary, monitoring of the uteroplacental blood flow and fetal growth is recommended. In case of harmful effects on pregnancy or the fetus consideration of alternative treatment is recommended. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Lactation
There are no data on the excretion of bisoprolol in human breast milk or the safety of bisoprolol exposure in infants. Therefore, breastfeeding is not recommended during administration of bisoprolol.

4.7 Effects on ability to drive and use machines
In a study of coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patients response to treatment an effect on the ability to drive a vehicle or to use machines cannot be excluded.. This should be considered particularly at the start of treatment and upon change of medication or in conjunction with alcohol.

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

Investigations:
Rare: increased triglycerides, increased liver enzymes (ALT, AST)

Cardiac disorders:
Uncommon: AV-conduction disturbances, worsening of pre-existing heart failure, bradycardia.

Nervous system disorders:
Common: dizziness*, headache*.
Rare: syncope.

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

Ear and labyrinth disorders:
Rare: hearing disorders.

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

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

Skin and subcutaneous tissue disorders:
Rare: hypersensitivity reactions such as itching, flush, rash.
Very rare: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia.

Musculoskeletal and connective tissue disorders:
Uncommon: muscular weakness, muscle cramps.

Vascular disorders:
Common: feeling of coldness or numbness in the extremities, hypotension especially in patients with heart failure.
4.9 Overdose

The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

In general, if overdose occurs, discontinuation of bisoprolol treatment and supportive and symptomatic treatment is recommended.

Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures may be considered when clinically warranted.

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

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

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or temporary pacing.

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

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Limited data suggest that bisoprolol is hardly dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective, ATC code: C07 AB07

Bisoprolol is a highly beta₁-selective-adrenoceptor blocking agent, lacking intrinsic sympathomimetic and without relevant membrane stabilising activity. It only shows low affinity to the beta₂-receptor of the smooth muscles of bronchi and vessels as well as to the beta₂-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta₂-mediated metabolic effects. Its beta₁-selectivity extends beyond the therapeutic dose range.
Bisoprolol is used for the treatment of hypertension and angina pectoris. As with other Beta₁-blocking agents, the method of acting in hypertension is unclear. However, it is known that Bisoprolol reduces plasma renin activity markedly.

Antianginal mechanism: Bisoprolol by inhibiting the cardiac beta receptors inhibits the response given to sympathetic activation. That results in the decrease of heart rate and contractility this way decreasing the oxygen demand of the cardiac muscle.

Bisoprolol is also used for the treatment of heart failure.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

5.2 Pharmacokinetic properties

Bisoprolol is absorbed almost completely from the gastrointestinal tract. Together with the very small first pass effect in the liver, this results in a high bioavailability of approximately 90%. The plasma protein binding of bisopropol is about 30 %. The distribution volume is 3.5 l/kg. The total clearance is approximately 15 l/h.

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.

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 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.

In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64±21 ng/ml at a daily dose of 10 mg and the half life is 17±5 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity.

Like other beta-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/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

Tablet
Cellulose microcrystalline
Lactose anhydrous
Colloidal anhydrous silica
Magnesium stearate
Sodium lauril sulfate
Iron oxide yellow (E172)
Croscarmellose sodium

Film coat
Titanium dioxide (E171)
Polydextrose FCC (E1200)
Hypermellose (E464)
Macrogol
Tartrazine (E102)
Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.
6.3 **Shelf life**
Blister: 21 months
Bottle: 24 months

6.4 **Special precautions for storage**
Blister: Store below 30°C. Store in the original packaging in order to protect from moisture.
Bottle: Store below 30°C. Store in the original packaging in order to protect from moisture. Use within 30 days of opening. Once open keep bottle tightly closed.

6.5 **Nature and contents of container**
PVC/Al blister packs. Blister pack comprises of clear transparent PVC film with backing of aluminium foil coated with heat seal lacquer containing 14, 28, 30, 50, 56, 60, 84, 98, 100 and 500 film-coated tablets.

White HDPE bottles with white opaque polypropylene cap containing 14, 28, 30, 50, 56, 60, 84, 98, 100 and 500 film-coated tablets.

Bottle contains a perforated HDPE canister holding silica gel and activated carbon desiccant.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
Any unused product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
Jenson Pharmaceutical Services Ltd, Carradine House, 237 Regent’s Park Road, London, N3 3LF, United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 17871/0055
PL 17871/0056
PL 17871/0083

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
19/11/2010

10 **DATE OF REVISION OF THE TEXT**
19/11/2010
NAME OF THE MEDICINAL PRODUCT

Bisoprolol fumarate 10 mg film-coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of bisoprolol fumarate

Excipient(s):

Each tablet contains:

0.042 mg sunset yellow (E110)
30 mg lactose (anhydrous)

For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM

Film-coated tablet

Pale orange to light orange, oval, biconvex film coated tablets with side notches; ‘BL & 6’ engraved on either side of the scoreline on one face of the tablet; ‘M’ engraved on the other face of the tablet.

The tablet can be divided into equal halves.

CLINICAL PARTICULARS

Therapeutic indications

Treatment of hypertension.

Treatment of chronic stable angina pectoris.

Posology and method of administration

Administration

For oral use

Bisoprolol fumarate tablets are taken in the morning with or without food. They are swallowed with some liquid and not to be chewed.

Adults

Treatment of hypertension and chronic stable angina pectoris

The dosage should be individually adjusted. It is recommended to start with 5 mg per day. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day.

Patients with renal impairment

In patients with severe renal impairment (creatinine clearance < 20 ml/min) the dose should not exceed 10 mg once daily. This dosage may eventually be divided into halves.

Patients with severe liver impairment

No dosage adjustment is required, however careful monitoring is advised.

Elderly

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

Children

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

Discontinuation of treatment

Treatment should not be stopped abruptly (see section 4.4). The dosage should be diminished slowly by a weekly halving of the dose.

Contraindications

Bisoprolol is contraindicated in patients with:

- hypersensitivity to bisoprolol or to any of the excipients.
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- second or third degree AV block (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- late stages of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- untreated phaeochromocytoma (see section 4.4)
- metabolic acidosis

4.4 Special warnings and precautions for use

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

Tablet contains lactose (anhydrous) - patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

Tablet contains sunset yellow (E110) - may cause allergic reactions.

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

Bisoprolol must be used with caution in:
- diabetes mellitus showing large fluctuations in blood glucose values. Symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) can be masked,
- strict fasting,
- ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment may not always yield the expected therapeutic effect,
- First degree AV block,
- Prinzmetal's angina,
- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.

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

The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol.

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

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 of 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 reflex tachycardia, and 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.

In bronchial asthma or other chronic obstructive pulmonary diseases, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.
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.
- Centrally acting antihypertensive drugs (e.g. clonidine, methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may further decrease 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:
- 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.
- Calcium antagonists of the dihydropyridine type (e.g. felodipine and amlodipine): Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.
- Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.
- Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.
- Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
- Insulin and oral antidiabetic drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.
- Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4).
- Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.
- Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.
- Beta-sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.
- Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.
- Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered:
- Mefloquine: increased risk of bradycardia.
- Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis.
- Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug-metabolizing enzymes. Normally no dosage adjustment is necessary.
- Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

4.6 Pregnancy and lactation
Pregnancy
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, β-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the fetus and newborn infant. If treatment with β-adrenoceptor blockers is necessary, β1-selective adrenoceptor blockers are preferable.

Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment is considered necessary, monitoring of the uteroplacental blood flow and fetal growth is recommended. In case of harmful effects on pregnancy or the fetus consideration of alternative treatment is recommended. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.
Lactation
There are no data on the excretion of bisoprolol in human breast milk or the safety of bisoprolol exposure in infants. Therefore, breastfeeding is not recommended during administration of bisoprolol.

4.7 Effects on ability to drive and use machines
In a study of coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patients response to treatment an effect on the ability to drive a vehicle or to use machines cannot be excluded.. This should be considered particularly at the start of treatment and upon change of medication or in conjunction with alcohol.

4.8 Undesirable effects
The following definitions apply to the frequency terminology used hereafter:
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Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
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Investigations:
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Cardiac disorders:
Uncommon: AV-conduction disturbances, worsening of pre-existing heart failure, bradycardia.

Nervous system disorders:
Common: dizziness*, headache*.
Rare: syncope.

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

Ear and labyrinth disorders:
Rare: hearing disorders.

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

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

Skin and subcutaneous tissue disorders:
Rare: hypersensitivity reactions such as itching, flush, rash.
Very rare: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia.

Musculoskeletal and connective tissue disorders:
Uncommon: muscular weakness, muscle cramps.

Vascular disorders:
Common: feeling of coldness or numbness in the extremities, hypotension especially in patients with heart failure.

General disorders:
Common: fatigue*.
Uncommon: asthenia.

Hepatobiliary disorders:
Rare: hepatitis.
Reproductive system and breast disorders:
Rare: potency disorders.

Psychiatric disorders:
Uncommon: sleep disorders, depression.
Rare: nightmares, hallucinations.

*These symptoms especially occur at the beginning of the therapy. They are generally mild and often disappear within 1 to 2 weeks.

4.9 Overdose
The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

In general, if overdose occurs, discontinuation of bisoprolol treatment and supportive and symptomatic treatment is recommended.

Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures may be considered when clinically warranted.

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

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

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or temporary pacing.

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

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Limited data suggest that bisoprolol is hardly dialysable.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Beta blocking agents, selective, ATC code: C07 AB07

Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic sympathomimetic and without relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

Bisoprolol is used for the treatment of hypertension and angina pectoris. As with other Beta1-blocking agents, the method of acting in hypertension is unclear. However, it is known that Bisoprolol reduces plasma renin activity markedly.

Antiangular mechanism: Bisoprolol by inhibiting the cardiac beta receptors inhibits the response given to sympathetic activation. That results in the decrease of heart rate and contractility this way decreasing the oxygen demand of the cardiac muscle.

Bisoprolol is also used for the treatment of heart failure.
In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

5.2 Pharmacokinetic properties

Bisoprolol is absorbed almost completely from the gastrointestinal tract. Together with the very small first pass effect in the liver, this results in a high bioavailability of approximately 90%. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. The total clearance is approximately 15 l/h.

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.

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 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.

In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64±21 ng/ml at a daily dose of 10 mg and the half life is 17±5 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity.

Like other beta-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/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

Tablet
Cellulose microcrystalline
Lactose anhydrous
Colloidal anhydrous silica
Magnesium stearate
Sodium lauril sulfate
Iron oxide red (E172)
Crocarmellose sodium

Film coat
Titanium dioxide (E171)
Polydextrose FCC (E1200)
Hypromellose (E464)
Macrogol
Iron oxide yellow (E172)
Sunset yellow (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister: 21 months
Bottle: 24 months

6.4 Special precautions for storage

Blister: Store below 30°C. Store in the original packaging in order to protect from moisture.
Bottle: Store below 30°C. Store in the original packaging in order to protect from moisture. Use within 30 days of opening. Once open keep bottle tightly closed.
6.5 **Nature and contents of container**
PVC/Al blister packs. Blister pack comprises of clear transparent PVC film with backing of aluminium foil coated with heat seal lacquer containing 14, 28, 30, 50, 56, 60, 84, 98, 100 and 500 film-coated tablets.

White HDPE bottles with white opaque polypropylene cap containing 14, 28, 30, 50, 56, 60, 84, 98, 100 and 500 film-coated tablets. Bottle contains a perforated HDPE canister holding silica gel and activated carbon desiccant.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
Any unused product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
Jenson Pharmaceutical Services Ltd, Carradine House, 237 Regent’s Park Road, London, N3 3LF, United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 17871/0057
PL 17871/0058
PL 17871/0084

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
19/11/2010

10 **DATE OF REVISION OF THE TEXT**
19/11/2010
Module 3
Patient Information Leaflet

The below text was approved for these products at the end of the decentralised procedure. The MA holder is required to submit mock-ups of the leaflet to the relevant regulatory authorities before marketing any pack size in a particular member state.
Bisoprolol fumarate 5 mg and 10 mg film-coated tablets UK/H/3771-2 and 3972/001-2/DC

PACKAGE LEAFLET: INFORMATION FOR THE USER

BISOPROLOL FUMARATE 5 mg or 10 mg FILM-COATED TABLETS
(bisoprolol fumarate)

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, 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 gets 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 is and what it is used for.
2. Before you take Bisoprolol Tablets.
3. How to take Bisoprolol Tablets.
4. Possible side effects.
5. How to store Bisoprolol Tablets.
6. Further information.

1. WHAT BISOPROLOL IS AND WHAT IT IS USED FOR

Bisoprolol belongs to a family of medicines called beta-blockers. Beta-blockers protect the heart against too much activity.

Bisoprolol is used to treat:
- high blood pressure (hypertension)
- angina pectoris (chest pain caused by blockages in the arteries that supply the heart muscle).

2. BEFORE YOU TAKE BISOPROLOL TABLETS

Do not take Bisoprolol Tablets if you:
- are allergic (hypersensitive) to the bisoprolol or any of the other ingredients of Bisoprolol Tablets
- have severe asthma or severe chronic lung disease
- have a slow or irregular heart rate (less than 60 beats per minute). Ask your doctor if you are not sure
- have very low blood pressure
- have severe blood circulation problems (which may cause your fingers and toes to tingle or turn pale or blue)
- have heart failure that suddenly becomes worse and/or that may require hospital treatment
- have excess acid in the blood, a condition known as metabolic acidosis
- have untreated phaeochromocytoma, a rare tumour of the adrenal gland

Take special care with Bisoprolol Tablets - Tell your doctor before you start to take this medicine if you:
- have asthma or chronic lung disease
- have diabetes. Bisoprolol can hide the symptoms of low blood sugar
- are fasting from solid food
- are treated for hypersensitivity (allergic) reactions. Bisoprolol may make your allergy worse or more difficult to treat.
- have any heart problems
- have any liver or kidney problems
- have any problems with the circulation in your limbs
are going to be given a general anaesthetic during an operation – tell your doctor that you are taking bisoprolol

- are taking verapamil or diltiazem, medicines used to treat heart conditions. Concomitant use is not recommended, see also “taking other medicines”
- have (or have had) psoriasis (a recurring skin rash)
- have phaeochromocytoma (a rare tumour of the adrenal gland). Your doctor will need to treat this before prescribing bisoprolol for you
- have a thyroid problem. The tablets can hide symptoms of an overactive thyroid.

**Taking other medicines - Tell your doctor if you are already taking or using any of the following as they may interact with your medicine:**

- medicines for controlling the blood pressure or medicines for heart problems (such as amiodarone, amlozopine, clonidine, digitalis glycosides, diltiazem, disopyramide, felodipine, flecaïnide, lidocaine, methyldopa, moxonidine, phenytoin, propafenone, quinidine, rilmenidine, verapamil)
- medicines for depression e.g. imipramine, amitriptyline, moclobemide
- medicines to treat mental illness e.g. phenothiazines such as levomepromazine
- medicines used for anaesthesia during an operation (see also “Take special care with Bisoprolol Tablets”)
- medicines used to treat epilepsy e.g. barbiturates such as phenobarbital
- certain painkillers (for instance acetyl salicylic acid, diclofenac, indomethacin, ibuprofen, naproxen)
- medicines for asthma or medicines used for a blocked nose
- medicines used for certain eye disorders such as glaucoma (increased pressure in the eye) or used to widen the pupil of the eye
- certain medicines to treat clinical shock (e.g. adrenaline, dobutamine, noradrenaline)
- mefloquine, a medicine for malaria
- all these drugs as well as bisoprolol may influence the blood pressure and/or heart function.
- rifampicin for the treatment of infections
- medicines to treat severe headaches or migraines (ergotamine derivatives).

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Taking Bisoprolol Tablets with food and drink**

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

**Pregnancy and breast-feeding**

Bisoprolol can be harmful to the pregnancy and/or to the child (increased possibility of premature birth, miscarriage, retarded growth, low blood glucose level and reduced heart rate of the child). Therefore **do not** use this medicinal product during pregnancy.

It is unknown if Bisoprolol is excreted in the breast milk. Breast-feeding during the use of this medicinal product is therefore **not** recommended.

Ask your doctor or pharmacist for advice before taking any medicinal product.

**Driving and using machines**

The use of Bisoprolol may sometimes result in dizziness or fatigue (see ‘Possible side-effects’). If you suffer from these side effects, **do not** operate vehicles and/or machines. These side-effects are likely to happen at the start of treatment, or with a change in the amount of Bisoprolol you take.
Important information about some of the ingredients of Bisoprolol Tablets

5 mg, and 10 mg tablet:
Lactose- If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

5 mg tablet only:
Tartrazine (E102)- May cause allergic reactions.

10 mg tablet only:
Sunset Yellow (E110)- May cause allergic reactions.

3. HOW TO TAKE BISOPROLOL TABLETS

Always take Bisoprolol Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- Swallow the tablets with a glass of water.
- The tablets should not be chewed.

Adults
Your doctor will start the treatment with the lowest possible dose (5 mg). Your doctor will monitor you closely at the start of treatment. Your doctor will increase your dose to obtain the best possible dosage for you.
The maximum recommended dose is 20 mg once per day.

Patients with kidney disease
Patients with severe kidney disease should not exceed 10 mg of bisoprolol once daily. Please consult your doctor before starting to use this medicine.

Patients with liver disease
Patients with severe liver disease should not exceed 10 mg of bisoprolol once daily. Please consult your doctor before starting to use this medicine.

Children
The use of Bisoprolol is not recommended as there is insufficient experience with the use of this medicinal product in children.

Elderly patients
In general an adjustment of the dose is not needed. It is recommended to start with the lowest possible dose.

If you notice that the Bisoprolol dose is too strong or does not work well enough, please consult your doctor or pharmacist.

If you take more Bisoprolol Tablets than you should
If you take more Bisoprolol Tablets than you should contact your doctor or casualty department immediately. Take the container and any remaining tablets with you.

If you forget to take Bisoprolol Tablets
If you forget to take a dose of Bisoprolol Tablets do not take a double dose to make up for the forgotten dose. Take the next dose on time. If you miss several doses, contact your doctor.

If you stop taking Bisoprolol Tablets
If you suddenly stop taking Bisoprolol Tablets you are likely to suffer from side effects. Your doctor will reduce your dose slowly over 2 weeks.

If you have any further questions on the use of this product, please ask your doctor or pharmacist.
4. **POSSIBLE SIDE EFFECTS**

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

The following side effects are important and will require immediate action if you experience them. You should stop taking Bisoprolol tablets and see your doctor immediately if the following symptoms occur:

Uncommon side effects (affecting fewer than 1 in 100 people):
- worsening of heart failure causing increased breathlessness and/or retention of fluid.

Frequency not stated:
- worsening of symptoms of blockage of the main blood vessels to the legs, especially at the start of treatment.

The following side-effects have also been reported:

**Common side effects** (affecting fewer than 1 in 10 people):
- cold hands and/or feet
- numbness of hands and/or feet
- low blood pressure
- feeling sick, vomiting, diarrhoea, constipation
- tiredness*
- dizziness*
- headache*.

**Uncommon side effects** (affecting fewer than 1 in 100 people)
- slow heart beat
- worsening of irregular heart beat
- sleep disorders
- depression
- breathing problems in patients with asthma or chronic lung disease
- muscle weakness, muscle cramps
- feeling weak.

**Rare side effects** (affecting fewer than 1 in 1,000 people)
- changes in blood test results
- reduced tear flow (can be a problem if you wear contact lenses)
- hearing disorders
- blocked, runny nose
- inflammation of the liver (hepatitis) causing abdominal pain, loss of appetite and sometimes jaundice with yellowing of the whites of the eyes and skin and dark urine
- hypersensitivity reactions such as itching, redness and skin rash
- reduced sexual performance
- nightmares
- hallucinations
- fainting.

**Very rare side effects** (affecting fewer than 1 in 10,000 people):
- inflammation of the eye (conjunctivitis)
- aggravation of the skin condition psoriasis or the appearance of a similar dry, scaly rash
- hair loss.

* these symptoms are especially occur at the beginning of treatment, or if your dosage changes. They are generally mild and often disappear within 1 to 2 weeks.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE BISOPROLOL TABLETS

Keep out of the reach and sight of children. Do not use Bisoprolol Tablets after the expiry date which is stated on the carton and the bottle or blister after EXP. The expiry date refers to the last day of that month. Blister: Store below 30°C. Store in the original packaging in order to protect from moisture. Bottle: Store below 30°C. Store in the original packaging in order to protect from moisture. Use within 30 days of opening. Once open keep bottle tightly closed. 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

What Bisoprolol film-coated tablets contain:
Each film-coated tablet contains either 5 mg or 10 mg of the active ingredient bisoprolol fumarate.

The other ingredients are: Tablet: Cellulose microcrystalline, lactose anhydrous, colloidal anhydrous silica, magnesium stearate, sodium lauril sulfate, croscarmellose sodium, iron oxide yellow (E172) (5 mg tablets only), iron oxide red (E172) (10 mg tablets only). Film coat: Titanium dioxide (E171), polydextrose (E1200), hypromellose (E464), macrogol, iron oxide yellow (E172) (10 mg tablets only), tartrazine (E102) (5 mg tablets only), indigo carmine (E132) (5 mg tablet only), sunset yellow (E110) (10 mg tablet only).

What Bisoprolol Tablets looks like and contents of the pack

Film-coated tablet

5 mg tablet: Pale yellow, oval, biconvex film-coated tablets with side notches; ‘BL & 4’ engraved on either side of the scoreline on one face of the tablet; ‘M’ engraved on the other face of the tablet.

10 mg tablet: Pale orange to light orange, oval, biconvex film-coated tablets with side notches; ‘BL & 6’ engraved on either side of the scoreline on one face of the tablet; ‘M’ engraved on the other face of the tablet.

Bisoprolol Tablets are packed in blister packs containing 14, 28, 30, 50, 56, 60, 84, 98, 100 and 500 film-coated tablets. Bisoprolol Tablets are packed in bottles containing 14, 28, 30, 50, 56, 60, 84, 98, 100 and 500 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:

[To be completed nationally]

Manufacturer:

[To be completed nationally]
This medicinal product is authorised in the Member States of the EEA under the following names:

For Procedure UK/H/3771/001-002/DC

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<td>Bulgaria</td>
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<td>Czech Republic</td>
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This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>
Module 4
Labelling

The below text was approved for these products at the end of the decentralised procedure. The MA holder is required to submit mock-ups of the labelling to the relevant regulatory authorities before marketing any pack size in a particular member state.

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

#### CARDBOARD CARTON

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td><strong>5 mg tablet only:</strong></td>
</tr>
<tr>
<td>Bisoprolol fumarate 5 mg film-coated tablets</td>
</tr>
<tr>
<td>bisoprolol fumarate</td>
</tr>
<tr>
<td><strong>10 mg tablet only:</strong></td>
</tr>
<tr>
<td>Bisoprolol fumarate 10 mg film-coated tablets</td>
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<td>bisoprolol fumarate</td>
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<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE (S)</th>
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</thead>
<tbody>
<tr>
<td><strong>5 mg tablet only:</strong></td>
</tr>
<tr>
<td>Each tablet contains 5 mg of bisoprolol fumarate</td>
</tr>
<tr>
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<tr>
<td>Each tablet contains 10 mg of bisoprolol fumarate</td>
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<tr>
<th>3. LIST OF EXCIPIENTS</th>
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<tr>
<td><strong>5 mg tablet only:</strong></td>
</tr>
<tr>
<td>Also contains: Tartrazine (E102), Lactose. See leaflet for further information.</td>
</tr>
<tr>
<td><strong>10 mg tablet only</strong></td>
</tr>
<tr>
<td>Also contains: Sunset Yellow (E110), Lactose. See leaflet for further information.</td>
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<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
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<tr>
<td>Film coated tablets</td>
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<tr>
<td>14 film-coated tablets.</td>
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5. METHOD AND ROUTE (S) OF ADMINISTRATION

For oral use. 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

Bottle carton:
Store below 30°C. Store in the original packaging in order to protect from moisture. Use within 30 days of opening. Once open keep bottle tightly closed.

Blister carton:
Store below 30°C. Store in the original packaging in order to protect from moisture.

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

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

5 mg tablet only:
Bisoprolol fumarate #5 mg tablets

10 mg tablet only:
Bisoprolol fumarate #10 mg tablets
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

HDPE BOTTLE WITH LDPE SCREW CAP

1. NAME OF THE MEDICINAL PRODUCT

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<td>100 film-coated tablets.</td>
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<tr>
<td>500 film-coated tablets.</td>
</tr>
</tbody>
</table>

5. METHOD AND ROUTE (S) OF ADMINISTRATION

For oral use. 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

Store below 30°C. Store in the original packaging in order to protect from moisture. Use within 30 days of opening. Once open keep bottle tightly closed.

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

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER (S)

[To be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

5 mg tablet only:
Bisoprolol fumarate #5 mg tablets

10 mg tablet only:
Bisoprolol fumarate #10 mg tablets
Bisoprolol fumarate 5 mg and 10 mg film-coated tablets UK/H/3771-2 and 3972/001-2/DC

### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### PVC/ALUMINIUM BLISTER

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>5 mg tablet only:</td>
</tr>
<tr>
<td>Bisoprolol fumarate 5 mg film-coated tablets</td>
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<tr>
<td>Bisoprolol fumarate</td>
</tr>
<tr>
<td>10 mg tablet only:</td>
</tr>
<tr>
<td>Bisoprolol fumarate 10 mg film-coated tablets</td>
</tr>
<tr>
<td>Bisoprolol fumarate</td>
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<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<tr>
<td>[To be completed nationally]</td>
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<tr>
<th>3. EXPIRY DATE</th>
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<td>EXP:</td>
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<th>4. BATCH NUMBER</th>
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<tbody>
<tr>
<td>Batch:</td>
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</table>

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<tr>
<th>5. OTHER</th>
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</table>
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Bisoprolol fumarate 5 mg and 10 mg film-coated tablets (PL 17871/0055-8 and PL 17871/0083-4; UK/H/3771-2/DC and UK/H/3972/001-2/DC) could be approved. The products are prescription-only medicines (POM) used in the treatment of hypertension and chronic stable angina pectoris.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Belgium, Bulgaria, Czech Republic, Denmark, Spain, Finland, Ireland, Iceland, Norway, Portugal, Sweden and Luxembourg as Concerned Member States (CMS). The applications were submitted under Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Concor film-coated tablets (Merck Pharma GmbH, Germany) which were first licensed in the EU in January 1986. The corresponding reference products in the UK are Cardicor 5 mg and 10 mg film-coated tablets (E Merck Limited, UK) which were first authorised in the UK in 1999.

The active ingredient bisoprolol fumarate is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic sympathomimetic and relevant membrane stabilising activity. It only shows low affinity to the beta-2 receptor of the smooth muscles of bronchi and blood vessels as well as to the beta-2 receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to affect airway resistance and beta-2-mediated metabolic effects.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

One single-dose, bioequivalence study was submitted to support these applications, comparing the test products Bisoprolol fumarate 10 mg film-coated tablets (Jenson Pharmaceutical Services Limited, UK) and the reference product Cardicor 10 mg film-coated tablets (E Merck Limited, UK).

The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP). With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. 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, 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 and CMS considered that the applications could be approved at the end of procedure (Day 210) on 20 October 2010. After a subsequent national phase, licences were granted in the UK on 19 November 2010.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Bisoprolol fumarate 5 mg film-coated tablets  
Bisoprolol fumarate 10 mg film-coated tablets |
<table>
<thead>
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<th></th>
<th></th>
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</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>C07AB07: beta-blocking agents, selective</td>
</tr>
</tbody>
</table>
| Pharmaceutical form and strength(s)             | Film-coated tablets  
5 mg and 10 mg                                                     |
| Reference numbers for the Decentralised Procedure | UK/H/3771/01-02/DC  
UK/H/3772/01-02/DC  
UK/H/3972/01-02/DC |
| Reference Member State (RMS)                     | United Kingdom                                                   |
| Concerned Member States (CMS)                    | UK/H/3771/01-02/DC:  
Belgium, Bulgaria, Czech Republic, Denmark,  
Spain, Finland, Ireland, Iceland, Norway,  
Portugal and Sweden.  
UK/H/3772/01-02/DC:  
Belgium  
UK/H/3972/01-02/DC:  
Belgium, and Luxembourg |
| Marketing Authorisation Number(s)                | PL 17871/0055-8,  
PL 17871/0083-4                                                   |
| Name and address of the authorisation holder     | Jenson Pharmaceutical Services Ltd  
Carradine House, 237 Regent’s Park Road,  
London N3 3LF, UK                                                  |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Bisoprolol fumarate
Other name: Bisoprolol hemifumarate
Chemical names: \((R,S)-(4-[2-(1-
\text{Methyl}
\text{ethoxy})\text{ethoxy}]-3\text{phenox}y)-3[[1\text{methyl}
\text{ethyl}]\text{amino}]\text{propan-2-ol fumarate}
2\text{propanol},1\-(4-(2-(1-\text{Methyl-ethoxy})\text{ethoxy})\text{methyl})\text{phenox}y)-3-((1-
\text{methyl}
\text{ethyl})\text{amino})\ (±),(E)-2\text{butenedioate (2:1 salt}}\)
\((±)-1-[(\alpha-(2-\text{Isopropoxyethoxy})\text{-p-tolyl})\text{oxy}]3-\text{(Isopropylamino)-2-propanol}
\text{fumarate (2:1 salt}})\.

Structure:

Molecular formula: \((C_{18}H_{31}NO_4)_2C_4H_4O_4\)
Molecular Mass: 767.0
Appearance: A white or almost white hygroscopic powder, very soluble in water and freely soluble on methanol.

Bisoprolol fumarate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance bisoprolol fumarate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients in the tablet core, namely cellulose microcrystalline, lactose anhydrous, colloidal anhydrous silica, magnesium stearate, sodium lauril sulfate, croscarmellose sodium, iron oxide yellow (E172) (5 mg tablets only) and iron oxide red (E172) (10 mg tablets only). The tablet coating is composed of titanium dioxide (E171), polydextrose (E1200), hypromellose (E464), macrogol, iron oxide yellow (E172) (10 mg tablets only), tartrazine (E102) (5 mg tablets only), indigo carmine (E132) (5 mg tablet only) and sunset yellow (E110) (10 mg tablet only).

All excipients comply with their respective European Pharmacopoeia monograph with the exception of polydextrose (E1200), iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172), tartrazine (E102), indigo carmine (E132) and sunset yellow (E110). These are controlled to suitable in-house specifications and are in compliance with current EEC directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients.
With the exception of lactose anhydrous and magnesium stearate, none of the excipients contain materials of animal or human origin. The supplier of lactose anhydrous has confirmed that the milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material of any kind is used during the production of lactose anhydrous. Magnesium stearate may be sourced from animal or vegetable origin. The supplier of magnesium stearate sourced from animal origins has provided certificates of suitability from the European Directorate for the Quality of Medicines (EDQM) to show that it is manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

Pharmaceutical Development
The objective of the development programme was to produce safe, efficacious products containing 5 mg and 10 mg bisoprolol fumarate that could be considered generic medicinal products of Cardicor 5 mg and 10 mg film-coated tablets (E Merck Limited, UK). Suitable pharmaceutical development data have been provided for these applications.

Comparative in-vitro dissolution and impurity profiles have been provided for these products and the reference products Cardicor 5 mg and10 mg film-coated tablets (E Merck Limited, UK).

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The tablets are packaged in either:
1. polvinylchloride/aluminium blisters strips in pack sizes of 14, 28, 30, 50, 56, 60, 84, 98, 100 and 500 film-coated tablets.
2. white high-density polyethylene (HDPE) bottles, with white polypropylene caps and a perforated HDPE canister holding silica gel and activated carbon desiccant, in pack sizes of 14, 28, 30, 50, 56, 60, 84, 98, 100 and 500 film-coated tablets.

Not all pack sizes may be marketed. However, the marketing authorisation holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before marketing any pack size.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.
Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, the following shelf-lives/storage conditions have been accepted:
- 21 months for product packaged in blister packs, with the storage conditions, “Store below 30°C. Store in the original packaging in order to protect from moisture.”
- 24 months for product packaged in the HPDE bottles, with the storage conditions “Store below 30°C. Store in the original packaging in order to protect from moisture. Use within 30 days of opening. Once open keep bottle tightly closed.”

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet 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 contains.

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 aspects of the dossiers.

Conclusion
The grant of marketing authorisations is recommended.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of bisoprolol fumarate are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ non-clinical pharmacology, pharmacokinetics and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with products that are already marketed, thus no increase in environmental burden is anticipated, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of Marketing Authorisations is recommended.
III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, single-dose, open-label, two-treatment, two-sequence, two-period, crossover study comparing the pharmacokinetics of the test product Bisoprolol fumarate 10 mg film-coated tablets (Jenson Pharmaceutical Services Limited, UK) and the reference product Cardicor 10 mg film-coated tablets (E Merck Limited, UK).

The subjects were given a 10 mg dose of bisoprolol fumarate with 240 ml of water after about a 10-hour fast. Subjects were not permitted water for one hour before and after administration. Subjects were kept seated or ambulant for 2 hours after dosing. Blood samples were collected before and up to 48 hours after each administration. The washout period between the treatment arms was at least 7 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (geometric mean, ratio and confidence intervals [CI]) of bisoprolol fumarate</th>
<th>Bisoprolol fumarate 10 mg (Test)</th>
<th>Cardicor 10 mg (Reference)</th>
<th>Test/Ref Ratio(%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀₋ₜ (hr·ng/mL)</td>
<td>499.9106</td>
<td>510.4079</td>
<td>97.94</td>
<td>94.66-101.34</td>
</tr>
<tr>
<td>AUC₀₋∞ (hr·ng/mL)</td>
<td>511.5385</td>
<td>523.0537</td>
<td>97.80</td>
<td>94.42-101.30</td>
</tr>
<tr>
<td>Cₘₐₓ (ng/mL)</td>
<td>37.3253</td>
<td>37.3374</td>
<td>97.97</td>
<td>97.53-102.47</td>
</tr>
</tbody>
</table>

AUC₀₋ₜ: area under the plasma concentration-time curve from time zero to t hours
AUC₀₋∞: area under the plasma concentration-time curve from time zero to infinity
Cₘₐₓ: maximum plasma concentration

The 90% confidence intervals of the test/reference ratio of geometric means for AUC₀₋ₜ, AUC₀₋∞ and Cₘₐₓ lie within the acceptable limits. Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 5 mg and 10 mg strength products meet all the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions from the bioequivalence study with the 10 mg tablet strength can be extrapolated to the 5 mg strength.

Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications. As the pharmacodynamic profile of bisoprolol fumarate is already well-known, this is considered to be satisfactory.

Efficacy and Safety

No new efficacy data have been submitted for these applications. As the efficacy of bisoprolol fumarate is already well-known, this is considered to be satisfactory.

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none are required for this type of applications. No new or unexpected safety issues were raised by the bioequivalence data.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL),
Labels
The SmPCs, PIL and labels are clinically acceptable. The SmPCs are consistent with those
for the originator products. The PIL is consistent with the details in the SmPCs and in-line
with the current guidelines. The labelling is in-line with the current guidelines.

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 dossiers.

Pharmacovigilance System and Risk Management Plan
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.

Suitable justification has been provided for not submitting a risk management plan for these
products.

Conclusion
The grant of marketing authorisations is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Bisoprolol fumarate 5 mg and 10 mg film-coated 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
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 10 mg strength tablets and the reference product. As the 5 mg and 10 mg strength of the product meet all the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions from the bioequivalence study with the 10 mg tablet strength can be extrapolated to the 5 mg tablet strength.

SAFETY
The safety profile of bisoprolol fumarate is well-known. No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that these products are generic medicinal products of the reference products, Cardicor 5 mg and 10 mg film-coated tablets (E Merck Limited, UK). 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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