Public Assessment Report

Decentralised Procedure

Bisoprolol and Aspirin 5mg/75mg and 10mg/75mg Capsules
Acetylsalicylic acid and bisoprolol fumarate

UK/H/3451/01-02/DC

UK licence no: PL 32226/0009-10

Applicant: ASA Pharma PLC
LAY SUMMARY

On the 2\textsuperscript{nd} November 2010 the MHRA granted ASA Pharma PLC Marketing Authorisations (licences) for the medicinal products Bisoprolol and Aspirin 5mg/75mg and 10/75mg Capsules. These medicines are only available on prescription from your doctor.

Bisoprolol and Aspirin 5mg/75mg and 10/75mg Capsules contain two active ingredients, bisoprolol and acetylsalicylic acid. Bisoprolol belongs to a group of drugs called beta blockers and is used to reduce blood pressure. Acetylsalicylic acid is a pain killer which also has the effect of preventing the development of blood clots. Acetylsalicylic acid is also known as Aspirin.

Bisoprolol and Aspirin 5mg/75mg and 10/75mg Capsules are used in the treatment of high blood pressure in patients at risk of heart disease who were previously treated with the individual ingredients.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Bisoprolol and Aspirin 5mg/75mg and 10/75mg Capsules outweigh the risks, hence Marketing Authorisations have been granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure ................................................................. Page 4
Module 2: Summary of Product Characteristics .............................................................. Page 5
Module 3: Product Information Leaflet .............................................................................. Page 19
Module 4: Labelling ........................................................................................................ Page 23
Module 5: Scientific Discussion ....................................................................................... Page 25

I. Introduction
II. Quality aspects
III. Non-clinical aspects
IV. Clinical aspects
V. Overall conclusion and Benefit-Risk Assessment

Module 6: Steps taken after initial procedure ................................................................. Not applicable
## Module 1

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Bisoprolol and Aspirin 5mg/75mg and 10/75mg Capsules</th>
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<tr>
<td>Type of Application</td>
<td>Generic, Article 10(b) Fixed combination applications</td>
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<td>Active Substance</td>
<td>Acetylsalicylic acid and Bisoprolol fumarate</td>
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<td>Form</td>
<td>Capsules</td>
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<tr>
<td>Strength</td>
<td>5mg/75mg and 10mg/75mg</td>
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<td>MA Holder</td>
<td>ASA Pharma PLC</td>
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Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol and Aspirin 5mg /75mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

<table>
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<tr>
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<td>Acetylsalicylic acid Ph. Eur.</td>
<td>75mg</td>
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<tr>
<td>Bisoprolol fumarate Ph. Eur.</td>
<td>5mg</td>
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For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Capsule, hard
White capsule printed ASABIS 5/75

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of hypertension in patients previously stabilised on the individual components.
Treatment of angina pectoris in patients previously stabilised on the individual components.

4.2 Posology and method of administration
Capsules for oral administration.
One capsule to be taken daily

There is no experience of the use of Bisoprolol and Acetylsalicylic acid capsules in children.

Special populations (Bisoprolol)

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

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

4.3 Contraindications
Bisoprolol and Acetylsalicylic acid capsules are contraindicated in patients with
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock,
- sinoarterial block,
- second or third degree AV block, (without pacemaker)
- marked bradycardia (heart rate less than 60 beats per minute, prior to start of therapy),
- hypotension (systolic blood pressure < 100mmHg)
- severe bronchial asthma, or severe chronic obstructive pulmonary disease
- severe forms of peripheral arterial occlusive disease and Raynaud's syndrome
- untreated phaeochromocytoma (see section 4.4)
- Metabolic acidosis
- Bisoprolol and Acetylsalicylic acid capsules should not be given to patients with a hypersensitivity to bisoprolol or Acetylsalicylic acid, to non-steroidal anti-inflammatory drugs or to any of the excipients.
- They should not be administered in cases of hypoprothrombinaemia, haemophilia or active peptic ulceration.

4.4 Special warnings and precautions for use

Use with care in patients with a prolonged PR conduction interval, poor cardiac reserve, and peripheral circulatory disturbances such as Raynauds phenomenon.

Treatment should not be withdrawn abruptly.

Bisoprolol and Acetylsalicylic acid capsules should be used with caution in patients with chronic obstructive Airways disease or a family history of asthma.

In asthmatic patients some increase in Airways resistance may be occur and this may be regarded as a signal to discontinue therapy.

Bronchospasm can usually be reversed by commonly used bronchodilators such as salbutamol.

In patients with controlled congestive cardiac failure therapy should be discontinued if signs of decompensation occur.

Use with caution in diabetic patients, diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked.

Prior to anaesthesia the anaesthetist should be informed if the patient is taking bisoprolol 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. In cases of severe ischaemic heart disease the risk benefit of continuing therapy should be evaluated.

Care should be taken when using cyclopropane or trichloroethylene.

Bisoprolol and Acetylsalicylic acid capsules should not be administered to children. They should be used with caution in patients with a history of peptic ulceration or coagulation abnormalities. They may induce gastrointestinal haemorrhage.

Prinzmetal's angina

Peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy)

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

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

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

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

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

Athletes: Athletes should note that this product contains an active substance which may cause a positive reaction in doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Bisoprolol may potentiate the effect of other antihypertensive drugs administered concurrently.

Concomitant therapy with neurone blocking agents such as guanethidine, reserpine, α methyldopa and clonidine may result in an exaggerated hypotensive response. In particular if clonidine treatment is to be discontinued this should not be done until bisoprolol treatment has been discontinued for several days.

Bisoprolol and Acetylsalicylic acid capsules should be used with care when myocardial depressants, inhibitors of AV conduction such as verapamil and diltiazem type class I antidysrhythmic agents such as disopyramide, quinidine or alpha adrenoceptor agonists such as noradrenaline are concurrently used. Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.
Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.

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.

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

The concomitant use of rifampicin can reduce the elimination half-life of bisoprolol.

The effect of insulin or oral hypoglycaemic agents may be potentiated when used with Bisoprolol and Acetylsalicylic acid capsules. 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).

Moxisylyte: Possibly causes severe postural hypotension.

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.

Salicylates may enhance the effects of anti-coagulants, inhibit the uricosuric effect of probenecid and may affect the activity of non-steroidal anti-inflammatory drugs.

Alcohol and corticosteroids may enhance the effects of Acetylsalicylic acid on the gastrointestinal tract. Acetylsalicylic acid may enhance the effects of coumarin anticoagulants and oral hypoglycaemics of the sulphonylurea type. The toxicity of methotrexate may be enhanced by concomitant use of Acetylsalicylic acid.

4.6 Pregnancy and lactation

Bisoprolol and Acetylsalicylic acid capsules should not be used during pregnancy unless clearly necessary

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn (see section 5.3). 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 should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental blood flow and 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.

Acetylsalicylic acid may prolong labour and contribute to maternal and neonatal bleeding, and should be avoided at term.

Lactation

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

Acetylsalicylic acid is secreted into breast milk in low concentration and should therefore be avoided during lactation because of the possible risk of Reye's Syndrome and the fact that high doses could potentially impair platelet function.
4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive or use machines have been performed. In a study of coronary heart disease patients, bisoprolol did not impair driving performance. However, due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at the start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects
Bisoprolol is well tolerated and its side effects are generally attributed to its pharmacological action.

The following definitions apply to the frequency terminology used hereafter:
Very common (1/10)
Common (1/100, < 1/10)
Uncommon (1/1,000, < 1/100)
Rare (1/10,000, < 1/1,000)
Very rare (< 1/10,000)

The following data results from post-marketing experience with bisoprolol:

Cardiac disorders:

Ear and labyrinth disorders:
Rare: hearing impairment.

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

Gastrointestinal disorders:
Common: Nausea, vomiting, diarrhoea, constipation.

General disorders:
Uncommon: Muscular weakness and cramps.

Hepatobiliary disorders:
Rare: increased liver enzymes (ALAT, ASAT), hepatitis.

Metabolism and nutrition disorders:
Rare: Increased triglycerides.

Nervous system disorders:
Common: Tiredness*, exhaustion*, dizziness*, headache*.
Uncommon: Sleep disturbances, depression.
Rare: Nightmares, hallucinations, syncope

Reproductive system and breast disorders:
Rare: Potency disorders.

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

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

Vascular disorders:
Common: Feeling of coldness or numbness in the extremities.
Uncommon: orthostatic hypotension.
*These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1-2 weeks.

Acetylsalicylic acid
Dyspepsia, nausea and vomiting
Less commonly irritation of the gastrointestinal mucosa may lead to erosion, ulceration and gastrointestinal bleeding. Hypersensitivity reactions including urticaria, rhinitis, angioneurotic oedema and severe bronchospasm

4.9 Overdose
The most common signs expected with overdose of a ß-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000 mg) with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol.

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

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

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

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

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

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, ß2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Overdosage of Acetylsalicylic acid produces dizziness, tinnitus, sweating, nausea and vomiting, confusion and hyperventilation. Gross overdose may lead to CNS depressions and coma. Uncommon features of salicylate poisoning include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.

Treatment of overdose consists of gastric lavage and forced alkaline diuresis. Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations>700mg/L (5.1mmol/L), or lower concentrations associated with severe clinical or metabolic features.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

ATC code: C07AB57 Bisoprolol combination

Bisoprolol is a potent, highly ß₁-selective adrenoreceptor blocking agent. The mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin activity. In patients with angina, the blockade of ß₁-receptors reduces heart action and thus reduces oxygen demand. Hence bisoprolol is effective in eliminating or reducing the symptoms.

Acetylsalicylic acid has an antithrombotic action, which is mediated through inhibition of platelet activity. Acetylsalicylic acid also inhibits platelet aggregation by irreversible acetylation of platelet cyclooxygenase.
5.2 Pharmacokinetic properties
Bisoprolol is absorbed almost completely from the gastrointestinal tract. With a very small first pass effect in the liver, bioavailability is approximately 90%. The drug is cleared equally by the liver and kidney. The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage. About 95% of the drug substance is excreted through the kidney, half of this is as unchanged bisoprolol. There are no active metabolites in man.

Absorption of non ionised Acetylsalicylic acid occurs in the stomach and upper intestine. Hydrolysis to salicylic acid occurs rapidly in the intestine and in the circulation. Appreciable plasma concentrations are found in less than 30 minutes. After a single dose, a peak value is reached in about 2 hours and then gradually declines. Salicylates are extensively bound to plasma proteins (50-90%); Acetylsalicylic acid to a lesser degree. Acetylsalicylic acid and salicylates are rapidly distributed to all body tissues. They appear in milk and cross the placenta.

Salicylate is mainly eliminated by hepatic metabolism the metabolites including salicylic acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid and gentisuric acid. As a result of zero order kinetics, plasma steady state salicylate concentrations increase disproportionately with dose. Salicylate is also excreted unchanged in the urine to an extent which depends on the dosage and urinary pH. Renal excretion involves glomerular filtration, active renal tubular secretion and passive tubular reabsorption.

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Maize Starch,
Cellulose, microcrystalline Magnesium stearate,
Stearic acid

Coating:
Polyvinyl alcohol hydrolysed
Titanium dioxide (E171)
Talc
Lecithin (Soya)
Xanthan gum

(Capsule)
Gelatin
Edible ink containing:
Shellac, Iron oxide black (E172), propylene glycol, ammonium hydroxide.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C

6.5 Nature and contents of container
Aclar /PVC blister with aluminium /PVC foil.
Pack sizes: 7, 10, 14, 20, 28, 30, 50, 56, 84, 98, 100 capsules

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
ASA Pharma PLC
6 Northbrook Road, Dublin 6, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 32226/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/11/2010

10 DATE OF REVISION OF THE TEXT
02/11/2010
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol and Aspirin 10mg /75mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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<th>Bisoprolol and Aspirin 10mg/75mg capsules</th>
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<tr>
<td>Acetylsalicylic acid Ph. Eur.</td>
<td>75mg</td>
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<tr>
<td>Bisoprolol fumarate Ph. Eur.</td>
<td>10mg</td>
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For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Capsule, hard

White capsule printed ASABIS 10/75

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of hypertension in patients previously stabilised on the individual components.

Treatment of angina pectoris in patients previously stabilised on the individual components.

4.2 Posology and method of administration
Capsules for oral administration.
One capsule to be taken daily

There is no experience of the use of Bisoprolol and Acetylsalicylic acid capsules in children.

Special populations (Bisoprolol)

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

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.

4.3 Contraindications
Bisoprolol and Acetylsalicylic acid capsules are contraindicated in patients with
acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
cardiogenic shock,
sinoarterial block,
second or third degree AV block, (without pacemaker)
marked bradycardia (heart rate less than 60 beats per minute, prior to start of therapy),
hypotension (systolic blood pressure < 100mmHg)
severe bronchial asthma, or severe chronic obstructive pulmonary disease
severe forms of peripheral arterial occlusive disease and Raynaud's syndrome
untreated phaeochromocytoma (see section 4.4)
Metabolic acidosis
Bisoprolol and Acetylsalicylic acid capsules should not be given to patients with a hypersensitivity to
bisoprolol or Acetylsalicylic acid, to non-steroidal anti-inflammatory drugs or to any of the excipients.
They should not be administered in cases of hypoprothrombinaemia, haemophilia or active peptic ulceration.
4.4 Special warnings and precautions for use

Use with care in patients with a prolonged PR conduction interval, poor cardiac reserve, and peripheral circulatory disturbances such as Raynaud's phenomenon.

Treatment should not be withdrawn abruptly.

Bisoprolol and Acetylsalicylic acid capsules should be used with caution in patients with chronic obstructive airways disease or a family history of asthma.

In asthmatic patients some increase in airways resistance may be occur and this may be regarded as a signal to discontinue therapy.

Bronchospasm can usually be reversed by commonly used bronchodilators such as salbutamol.

In patients with controlled congestive cardiac failure therapy should be discontinued if signs of decompensation occur.

Use with caution in diabetic patients, diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked.

Prior to anaesthesia the anaesthetist should be informed if the patient is taking bisoprolol 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. In cases of severe ischaemic heart disease the risk benefit of continuing therapy should be evaluated.

Care should be taken when using cyclopropane or trichloroethylene.

Bisoprolol and Acetylsalicylic acid capsules should not be administered to children. They should be used with caution in patients with a history of peptic ulceration or coagulation abnormalities. They may induce gastrointestinal haemorrhage.

Prinzmetal's angina
Peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy)
Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type or with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

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

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

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

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

Athletes: Athletes should note that this product contains an active substance which may cause a positive reaction in doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Bisoprolol may potentiate the effect of other antihypertensive drugs administered concurrently.
Concomitant therapy with neurone blocking agents such as guanethidine, reserpine, α methyldopa and clonidine may result in an exaggerated hypotensive response. In particular if clonidine treatment is to be discontinued this should not be done until bisoprolol treatment has been discontinued for several days.

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

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

The concomitant use of rifampicin can reduce the elimination half-life of bisoprolol.

The effect of insulin or oral hypoglycaemic agents may be potentiated when used with Bisoprolol and Acetylsalicylic acid capsules. 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).

Moxisylyte: Possibly causes severe postural hypotension.

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.

Salicylates may enhance the effects of anti-coagulants, inhibit the uricosuric effect of probenecid and may affect the activity of non steroidal anti-inflammatory drugs. Alcohol and corticosteroids may enhance the effects of Acetylsalicylic acid on the gastrointestinal tract. Acetylsalicylic acid may enhance the effects of coumarin anticoagulants and oral hypoglycaemics of the sulphonylurea type. The toxicity of methotrexate may be enhanced by concomitant use of Acetylsalicylic acid.

4.6 **Pregnancy and lactation**

Bisoprolol and Acetylsalicylic acid capsules should not be used during pregnancy unless clearly necessary

**Pregnancy**

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn (see section 5.3). 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 should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental blood flow and 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. Acetylsalicylic acid may prolong labour and contribute to maternal and neonatal bleeding, and should be avoided at term.

**Lactation**

It is not known whether this drug is excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol. Acetylsalicylic acid is secreted into breast milk in low concentration and should therefore be avoided during lactation because of the possible risk of Reye's Syndrome and the fact that high doses could potentially impair platelet function.

4.7 **Effects on ability to drive and use machines**

No studies on the effects on the ability to drive or use machines have been performed. In a study of coronary heart disease patients, bisoprolol did not impair driving performance. However, due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at the start of treatment and upon change of medication as well as in conjunction with alcohol.
4.8 Undesirable effects
Bisoprolol is well tolerated and its side effects are generally attributed to its pharmacological action.

The following definitions apply to the frequency terminology used hereafter:
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Common (1/100, < 1/10)
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Rare (1/10,000, < 1/1,000)
Very rare (< 1/10,000)

The following data results from post-marketing experience with bisoprolol:

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Rare: hearing impairment.

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Rare: reduced tear flow (to be considered if the patient uses lenses).
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Gastrointestinal disorders:
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General disorders:
Uncommon: Muscular weakness and cramps.

Hepatobiliary disorders:
Rare: increased liver enzymes (ALAT, ASAT), hepatitis.

Metabolism and nutrition disorders:
Rare: Increased triglycerides.

Nervous system disorders:
Common: Tiredness*, exhaustion*, dizziness*, headache*.
Uncommon: Sleep disturbances, depression.
Rare: Nightmares, hallucinations, syncope

Reproductive system and breast disorders:
Rare: Potency disorders.

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

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

Vascular disorders:
Common: Feeling of coldness or numbness in the extremities.
Uncommon: orthostatic hypotension.
*These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1-2 weeks.

Acetylsalicylic acid
Dyspepsia, nausea and vomiting
Less commonly irritation of the gastrointestinal mucosa may lead to erosion, ulceration and gastrointestinal bleeding. Hypersensitivity reactions including urticaria, rhinitis, angioneurotic oedema and severe bronchospasm.
4.9 Overdose

The most common signs expected with overdosage of a β-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000 mg) with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol.

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

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

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

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

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

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, β2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Overdosage of Acetylsalicylic acid produces dizziness, tinnitus, sweating, nausea and vomiting, confusion and hyperventilation. Gross overdosage may lead to CNS depressions and coma. Uncommon features of salicylate poisoning include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema. Treatment of overdose consists of gastric lavage and forced alkaline diuresis. Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations>700mg/L (5.1mmol/L), or lower concentrations associated with severe clinical or metabolic features.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Atc code: C07AB57 Bisoprolol combination

Bisoprolol is a potent, highly β1-selective adrenoreceptor blocking agent. The mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin activity. In patients with angina, the blockade of β1-receptors reduces heart action and thus reduces oxygen demand. Hence bisoprolol is effective in eliminating or reducing the symptoms.

Acetylsalicylic acid has an antithrombotic action, which is mediated through inhibition of platelet activity. Acetylsalicylic acid also inhibits platelet aggregation by irreversible acetylation of platelet cyclooxygenase.

5.2 Pharmacokinetic properties

Bisoprolol is absorbed almost completely from the gastrointestinal tract. With a very small first pass effect in the liver, bioavailability is approximately 90%. The drug is cleared equally by the liver and kidney. The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage. About 95% of the drug substance is excreted through the kidney, half of this is as unchanged bisoprolol. There are no active metabolites in man.

Absorption of non ionised Acetylsalicylic acid occurs in the stomach and upper intestine. Hydrolysis to salicylic acid occurs rapidly in the intestine and in the circulation. Appreciable plasma concentrations are found in less than 30 minutes. After a single dose, a peak value is reached in about 2 hours and then gradually declines. Salicylates are extensively bound to plasma proteins (50-90%); Acetylsalicylic acid
to a lesser degree. Acetylsalicylic acid and salicylates are rapidly distributed to all body tissues. They appear in milk and cross the placenta. Salicylate is mainly eliminated by hepatic metabolism the metabolites including salicylic acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid and gentisuric acid. As a result of zero order kinetics, plasma steady state salicylate concentrations increase disproportionately with dose. Salicylate is also excreted unchanged in the urine to an extent which depends on the dosage and urinary pH. Renal excretion involves glomerular filtration, active renal tubular secretion and passive tubular reabsorption.

5.3 Preclinical safety data
Non clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential. 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
Maize Starch, Cellulose, microcrystalline Magnesium stearate, Stearic acid

Coating:
Polyvinyl alcohol hydrolysed
Titanium dioxide (E171)
Talc
Lecithin (Soya)
Xanthan gum

(Capsule)
Gelatin
Edible ink containing:
Shellac, Iron oxide black (E172), propylene glycol, ammonium hydroxide.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C

6.5 Nature and contents of container
Aclar /PVC blister with aluminium /PVC foil.
Pack sizes: 7, 10, 14, 20, 28, 30, 50, 56, 84, 98, 100 capsules
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
ASA Pharma PLC
6 Northbrook Road, Dublin 6, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 32226/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/11/2010
10  DATE OF REVISION OF THE TEXT
02/11/2010
Module 3

1.3.1 Patient Information Leaflet

Text Version of Package Leaflet

PATIENT INFORMATION LEAFLET

{{Invented name}} 5mg/75 mg, 5mg/100 mg, 10mg/75 mg and 10mg/100 mg
Bisoprolol Fumarate and Acetylsalicylic acid

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

In this leaflet:
1. {{Invented name}} capsules are and what they are used for
2. Before you take {{Invented name}} capsules
3. How to take {{Invented name}} capsules
4. Possible side effects
5. How to store {{Invented name}} capsules
6. Further information

1. What {{Invented name}} capsules are and what they are used for

{{Invented name}} capsules contain two active ingredients, bisoprolol and acetylsalicylic acid. Bisoprolol belongs to a group of drugs called beta blockers. It interferes with messages sent through the nerves and has the effect of reducing blood pressure. Acetylsalicylic acid is a pain killer which also has the effect of preventing the development of blood clots. Acetylsalicylic acid is also known as Aspirin.

{{Invented name}} capsules are used in the treatment of high blood pressure in patients at risk of heart disease who were previously treated with the individual ingredients.

2. Before you take {{Invented name}} capsules

You should not take {{Invented name}} capsules if you:

Know that you are allergic to bisoprolol or acetylsalicylic acid or any of the other ingredients in this medicine (see 'Further Information' for the list of ingredients):
• know you are allergic to any other non-steroidal anti-inflammatory drugs (NSAIDs)
• have severe heart failure or cardiac shock causing breathlessness and circulation collapse
• have a slow heart rate (less than 50 beats per minute). Ask your doctor if you are unsure
• have very low blood pressure (which may make you dizzy when you stand up)
• suffer from asthma or wheezing
• know you are suffering from haemophilia or hypoprothrombinaemia (rare conditions affecting the blood)
• If you suffer from a condition where there is a change in the acid/base balance of the body (metabolic acidosis)
• If you suffer from severe blood circulation problems in the fingers, toes, arms and legs, like Raynaud’s phenomenon.
• have a stomach or bowel ulcer (peptic ulcer)

Make sure your doctor knows if you suffer from any of the above.

Before you are given {{Invented name}} capsules, your doctor will take special care if any of the following situations apply to you:
any problems with your heart, pulse rate or circulation
- difficulty with breathing or a history of asthma in your family
- you suffer from diabetes
- you are due to have an anaesthetic – let the anaesthetist know you are taking Bisoprolol and Acetylsalicylic acid
- you have a past history of peptic ulcer or blood clotting problems
- you suffer (or have suffered) from a recurrent skin disorder involving a scaling, dry skin rash (psoriasis).
- you have a tumour of the adrenal medulla (phaeochromocytoma); this medicine may only be used in combination with certain medicinal products (the so-called alpha-blockers)
- you suffer from a thyroid problem, as this medicine may hide the symptoms of an overactive thyroid

Make sure your doctor is aware of these situations.

Athletes should note that this product contains an active substance which may cause a positive reaction in doping tests.

Taking other medicines

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines as the effects of these and/or ((Invented) name) capsules may change. This includes medicines obtained without a prescription.

In particular, tell your doctor if you are taking any of the following:

- other medicines used to treat high blood pressure including those that work by blocking nerve impulses, i.e. guanethidine, reserpine, methyldopa and clonidine
- medicines which affect the heart rate such as diltiazem, verapamil, disopyramide, noradrenaline and amiodarone
- rifampicin for tuberculosis
- medication for diabetes including insulin and tablets
- anticoagulants for thinning the blood, e.g. warfarin
- probenecid used in the treatment of gout
- other non-steroidal anti-inflammatory drugs, e.g. ibuprofen, naproxen
- antimalarial medicine i.e. mefloquine
- medicines used to treat severe depression such as the so-called MAO-A inhibitors (modobemide).

Pregnancy and breast feeding

Please let the doctor know if you are pregnant, think you might be pregnant, are planning to become pregnant or are breast-feeding. ((Invented) name) capsules should not be used during pregnancy unless absolutely necessary, as the possible risks to the baby are not known. Your doctor will be able to advise you.

It is unknown if this medicine 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 medicine.

Driving and using machines

((Invented) name) capsule should not usually affect your ability to drive or use machines. If they make you feel tired or dizzy wait until the symptoms have worn off before driving or using machines.

3. How to take ((Invented) name) capsules

((Invented) name) capsules should be swallowed whole with water.

The normal dose for adults is one daily taken at about the same time each day. Your doctor will decide on the most suitable dose for you.

((Invented) name) capsules are not suitable for children

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

Patients with a severely reduced kidney & liver function The maximum dose is 10 mg per day.

If you take more ((Invented) name) capsules than you should
If you have accidentally taken more than the prescribed dose, tell your doctor/pharmacist immediately. Take any remaining tablets or this leaflet with you so the medical staff know exactly what you have taken. The likely signs of an overdose are a sudden drop in pulse rate and/or blood pressure which may make you feel dizzy, light-headed, confused, sick or even be sick, cause buzzing in the ears and breathlessness.

**If you miss a dose of ([Invented] name) capsules**

If you forget a capsule, take it if you remember within 12 hours. If more than 12 hours have passed wait until your next dose. Do not take a double dose to catch up.

If you have any further questions on the use of this product ask your doctor or pharmacist.

**If you stop taking ([Invented] name) capsules**

Treatment with Bisoprolol and Acetylsalicylic acid capsules must not be stopped abruptly as your condition may get worse, or your blood pressure may start to rise again. Instead, the capsules must be reduced gradually over one or two weeks as advised by your doctor. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. **Possible side effects**

Like all medicines ([Invented] name) capsules can sometimes cause side-effects, although not everybody gets them.

All medicines can cause allergic reactions although serious allergic reactions are very rare. Any sudden wheeze, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body) should be reported to your doctor immediately.

The following terms are used to describe how often side effects have been reported:

| Very common: affects more than 1 user in 10 |
| Common: affects 1 to 10 users in 100 |
| Uncommon: affects 1 to 10 users in 1,000 |
| Rare: affects 1 to 10 users in 10,000 |
| Very rare: affects less than 1 user in 10,000 |
| Not known: frequency cannot be estimated from the available data |

**Common side effects affecting fewer than 1 person in 10, but more than 1 person in 100 include:**
- Fatigue, exhaustion, dizziness or headache (these side effects occur especially at the beginning of the treatment and are generally mild in nature and often disappear within 1-2 weeks)
- Cold hands and/or feet, numbness of hands and/or feet, exacerbation of the pain in the legs and impingement (intermittent claudication, Raynaud's Phenomenon)
- Nausea, vomiting, diarrhoea, abdominal pain or constipation.

**Uncommon side effects affecting fewer than 1 person in 100, but more than 1 person in 1,000 include:**
- Reduced heart rate, exacerbation of existing rhythm disorders such as AV-block, exacerbation of a reduced action of the heart (heart failure)
- Blood pressure reduction, for instance due to standing up quickly from a sitting or supine position, sometimes involving dizziness (orthostatic hypotension)
- Severe depression
- Shortness of breath due to narrowing of the airways in patients with asthma or disorders of the airways
- Muscle weakness and muscle cramps, joint problems
- Sleep disorders.

**Rare side effects affecting fewer than 1 person in 1,000, but more than 1 person in 10,000 include:**
- Hypersensitivity reactions such as itching, redness, skin rash and swelling (face, hands, feet); you
should contact your Doctor immediately if you suspect that you are having a severe allergic reaction

- Increase in liver enzymes
- Low blood glucose level (hypoglycemia) involving feelings of hunger, sweating, dizziness, palpitations
- Increase in a type of fat found in the blood (triglycerides)
- Male impotence
- Inflammation of the liver (hepatitis) involving a yellow discolouration of the skin or eyes (jaundice)
- Inflammation of the nasal mucous membrane characterised by a blocked up nose, sneezing (allergic rhinitis)
- Dry eyes (can be very troublesome when you are wearing contact lenses)
- Nightmares, observations of things that are not present (hallucinations)
- Hearing disorders.

Very rare side effects affecting fewer than 1 person in 10,000 include:

- Worsening of a recurrent skin disorder involving scaling, dry skin rash (psoriasis)
- Hair loss
- Inflammation of the eye or eyelid (conjunctivitis).

Please tell your doctor as soon as possible if any of these have occurred.

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.

5. How to store (Invented name) capsules

Keep out of the reach and sight of children.

Do not store above 25°C. It should not be used after the expiry date that is shown on the carton. The expiry date refers to the last day of that month.

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 substances are bisoprolol and acetylsalicylic acid.

The other ingredients are maize starch, cellulose microcrystalline, magnesium stearate, stearic acid, polyvinyl alcohol hydrolysed, titanium dioxide (E171), talc, lecithin (soya), xanthan gum, gelatin, Shellac glaze 45%, iron oxide black (E172 propylene glycol, ammonium hydroxide.

What (Invented name) capsules look like and contents of pack

The capsules come in four strengths: 5 and 75 mg, 5 and 100 mg, 10 and 75 mg, 10 and 100 mg of bisoprolol and acetylsalicylic acid respectively.

All capsules are white with the strength printed on them.

The capsules are supplied in packs of 7, 10, 14, 20, 28, 30, 50, 64, 98, 100 capsules

Not all pack sizes may be marketed

Marketing authorization holder:
ASA Pharma PLC, 6 Northbrook Road, Dublin 6, Ireland

Manufacturer:
Pharmaceutical Works Polpharma S.A 19, Pelplinska St., 83-200 Starogard, Gdanski, Poland

This leaflet was last approved in:
Module 4
Labelling

PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

Carton

1. NAME OF THE MEDICINAL PRODUCT

<Product> 10mg/75mg Capsules
Bisoprolol fumarate/Acetylsalicylic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each Capsule contains 10 mg of Bisoprolol Fumarate and 75 mg Acetylsalicylic Acid

3. LIST OF EXCIPIENTS
Not applicable

4. PHARMACEUTICAL FORM AND CONTENTS
Capsule, hard
7 capsules
10 capsules
14 capsules
20 capsules
28 capsules
30 capsules
50 capsules
56 capsules
84 capsules
98 capsules
100 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION
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 of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY
Not applicable

8. EXPIRY DATE
Exp. mmm-yyyy

9. SPECIAL STORAGE CONDITIONS
Do not store above 25°C
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER
To be completed nationally

12. MARKETING AUTHORIZATION NUMBER(S)
To be completed nationally

13. BATCH NUMBER
Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY
To be completed nationally

15. INSTRUCTIONS ON USE
Not applicable

16. INFORMATION IN BRAILLE
To be completed nationally

BLISTER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT
<Product name> 10mg/75mg Capsules—Here
Bisoprolol fumarate/Acetylsalicylic acid

2. NAME OF THE MARKETING AUTHORIZATION HOLDER
<To be completed nationally>

3. EXPIRY DATE
Exp:

4. BATCH NUMBER
Batch:

5. OTHER
Not applicable
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Bisoprolol and Aspirin 5mg/75mg and 10mg/75mg Capsules in the treatment of hypertension and angina pectoris in patients previously stabilised on the individual components, could be approved.

With UK as the RMS in these Decentralised Procedures(UK/H/3451/01-02/DC), ASA Pharma PLC applied for the Marketing Authorisations for Bisoprolol and Aspirin 5mg/75mg and 10mg/75mg Capsules in Bulgaria, Czech Republic, Estonia, Hungary, Lithuania, Latvia, Poland, Romania and Slovak Republic.

Bisoprolol is a potent, highly $\beta_1$-selective adrenoreceptor blocking agent. The mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin activity. In patients with angina, the blockade of $\beta_1$-receptors reduces heart action and thus reduces oxygen demand. Hence bisoprolol is effective in eliminating or reducing the symptoms. Acetylsalicylic acid has an antithrombotic action, which is mediated through inhibition of platelet activity. Acetylsalicylic acid also inhibits platelet aggregation by irreversible acetylation of platelet cyclooxygenase.

No new preclinical or clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of the originator products that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly 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, of 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 suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant respective licence for the above products at the end of procedure (Day 210 – 20th October 2010). After a subsequent national phase, the UK granted a licence for these products on 2nd November 2010 (PL 32226/0009-10).
# ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Bisoprolol and Aspirin 5mg/75mg and 10mg/75mg Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Acetylsalicylic acid and Bisoprolol fumarate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>C07 AB57 – Bisoprolol, combinations</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Capsules</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/3451/01-02/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States</td>
<td>Bulgaria, Czech Republic, Estonia, Hungary, Lithuania, Latvia, Poland, Romania and Slovak Republic</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 32226/0009-10</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>ASA Pharma Plc</td>
</tr>
<tr>
<td></td>
<td>6, Northbrook Rd, Dublin 6, Ireland</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Acetylsalicylic acid (Aspirin)
Chemical Name: 2-acetobenzoic acid
Structure:

\[
\text{O} \begin{array}{c}
\text{H} \\
\text{C} \\
\text{H} \\
\text{C}
\end{array}
\]

Molecular Formula: C_{9}H_{8}O_{4}
Molecular Weight: 180.2g/mol

Appearance and solubility: white crystalline powder with a melting point of 143°C. It is slightly soluble in water, freely soluble in alcohol and soluble in ether.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

INN: Bisoprolol fumarate
Chemical name: 1-[4-[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol(E)-2-butenedioate (2:1) (salt).
Structure:

Molecular Formula: C_{18}H_{31}NO_{4}•\frac{1}{2}C_{4}H_{4}O_{4}
Molecular Weight: 766.98

Appearance and solubility: It is a white crystalline powder which is approximately equally hydrophilic and lipophilic, and is readily soluble in water, methanol, ethanol, and chloroform.

Synthesis of the drug substance from the designated starting material 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.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of Analysis for all working standards have been provided.
Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of the pharmaceutical excipients maize starch, cellulose, microcrystalline, magnesium stearate, stearic acid, Opadry AMB OY-B-28920 (polyvinyl alcohol, titanium dioxide (E171), talc, lecithin (soya), xanthan gum), gelatine (shellac, iron oxide black (E172), propylene glycol and ammonium hydroxide).

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of Opadry AMB OY-B-28920 and gelatine which comply with in-house specifications.

It has been confirmed that the excipients used are free of TSE/BSE and the corresponding certificates issued by each supplier were suitably provided. This is acceptable.

**Pharmaceutical Development**

The aim of Pharmaceutical Development was to produce a stable presentation of aspirin and bisoprolol in a single dosage form in order that therapy is simplified for patients stabilised on the individual drugs at each dosage.

Comparative impurity and dissolution profiles have been presented for test and reference products.

**Manufacture**

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

**Finished product specification**

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

**Container-Closure System**

The capsules are packed in Aclar/polyvinylchloride blister with aluminium/polyvinylchloride foil. Pack sizes are 7, 10, 14, 20, 28, 30, 50, 56, 84, 98 and 100 capsules.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.
Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with a storage condition ‘Do not store above 25 °C’ is set, and this is acceptable.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SPC, 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. 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 it contains.

The Marketing Authorisation Holder has committed to providing the label and leaflet mock-ups prior to marketing the product.

Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

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

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY
The pharmacological, pharmacokinetic and toxicological properties of acetylsalicylic acid and bisoprolol fumarate are well-known.

No new preclinical data have been supplied with these applications and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of the environmental risk assessment.

There are no objections to the approval of these products from a pre-clinical point of view.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of the application, the applicant has submitted two bioequivalence (BE) Studies under fasting conditions.
- The first study measured Bisoprolol and Salicylic Acid (metabolite) in 26 subjects.
- The Second study measured Acetylsalicylic Acid (Aspirin) in 36 subjects.

The differences in design between the two studies are the analyte measured, the number of subjects and frequency of blood samplings.

**Study 1**
This was an open, single dose, two-treatment, two-period, two sequence, randomised, crossover study Comparing Bisoprolol/Aspirin 10/75 mg Capsules (ASA Pharma, Ireland) to Emcor 10 mg Film-coated Tablets (Merck Ltd., UK) and Hjertemagnyl 75 mg Film-coated Tablets (Nycomed, Denmark) in 26 Healthy Volunteers under Fasting Conditions.

Blood sampling was performed pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 34.00 and 48.00 hours after dosing. The wash out period between phases was 7 days.

**Results**
The pharmacokinetic data from the Bioequivalence Study of Bisoprolol/Aspirin 10/75 mg capsules under Fasting Conditions Comparison Test versus Reference are summarised below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GEOMETRIC LEAST SQUARE MEANS (CV %)</th>
<th>RATIO</th>
<th>90% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ln-transformed)</td>
<td>Test</td>
<td>Reference</td>
<td>T/R (%)</td>
</tr>
<tr>
<td>AUC_{0-t} (ng h/mL)</td>
<td>507.17 (3.10)</td>
<td>479.48 (2.81)</td>
<td>105.77</td>
</tr>
<tr>
<td>AUC_{0-\infty} (ng h/mL)</td>
<td>519.87 (3.08)</td>
<td>492.64 (2.82)</td>
<td>105.53</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>36.49 (5.57)</td>
<td>35.07 (5.05)</td>
<td>104.04</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for $C_{max}$ and AUC were within the pre-defined limits. Bioequivalence has been shown for the test formulation (Bisoprolol/Aspirin 10/75 mg capsules) and the reference formulations (Emcor 10 mg Film-coated Tablets and Hjertemagnyl 75 mg Film-coated Tablets) for the active metabolite bisoprolol.

**Summary of mean pharmacokinetic data for Salicylic Acid (n=26)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GEOMETRIC LEAST SQUARE MEANS (CV %)</th>
<th>RATIO</th>
<th>90% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ln-transformed)</td>
<td>Test</td>
<td>Reference</td>
<td>T/R (%)</td>
</tr>
<tr>
<td>AUC_{0-t} (µg h/mL)</td>
<td>15.16 (9.49)</td>
<td>15.58 (8.83)</td>
<td>97.30</td>
</tr>
<tr>
<td>AUC_{0-\infty} (µg h/mL)</td>
<td>15.62 (9.33)</td>
<td>16.05 (8.68)</td>
<td>97.31</td>
</tr>
<tr>
<td>C_{max} (µg/mL)</td>
<td>4.18 (17.35)</td>
<td>4.38 (14.57)</td>
<td>95.43</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for $C_{max}$ and AUC were within the pre-defined limits. Bioequivalence has been shown for the test formulation (Bisoprolol/Aspirin 10/75 mg capsules) and the reference formulations (Emcor 10 mg Film-coated Tablets and Hjertemagnyl 75 mg Film-coated Tablets) for the active salicylic acid.
capsules) and the reference formulations (Emcor 10 mg Film-coated Tablets and Hjertemagnyl 75 mg Film-coated Tablets) for the active metabolite salicylic acid.

**Study 2**
This was an open, single dose, two-treatment, two-period, two sequence, randomised, crossover study Comparing Bisoprolol/Aspirin 10/75 mg Capsules (ASA Pharma, Ireland) to Emcor 10 mg Film-coated Tablets (Merck Ltd., UK) and Hjertemagnyl 75 mg Film-coated Tablets (Nycomed, Denmark) in 36 Healthy Volunteers under Fasting Conditions.

Blood samples for the determination of ASA were taken prior to dosing and at 4, 8, 12, 16, 20, 25, 30, 35, 40, 45, 50, 60, 75, 90, and 120 minutes after dosing. The wash out period between phases was 7 days.

**Results**
The pharmacokinetic data from the Bioequivalence Study of Bisoprolol/Aspirin 10/75 mg capsules under Fasting Conditions Comparison Test versus Reference are summarised below:

<table>
<thead>
<tr>
<th>Parameter (ln-transformed)</th>
<th>n</th>
<th>GEOMETRIC LEAST SQUARE MEANS (CV %)</th>
<th>RATIO</th>
<th>90% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Test</td>
<td>Reference</td>
<td>T/R (%)</td>
</tr>
<tr>
<td><strong>AUC_{0-\infty} (µg h/mL)</strong></td>
<td>36</td>
<td>0.93 (442.05)</td>
<td>0.87 (166.59)</td>
<td>105.77</td>
</tr>
<tr>
<td><strong>AUC_{0-\infty} (µg h/mL)</strong></td>
<td>33</td>
<td>1.08 (337.21)</td>
<td>0.94 (352.48)</td>
<td>114.78</td>
</tr>
<tr>
<td><strong>C_{max} (µg/mL)</strong></td>
<td>36</td>
<td>1.17 (340.41)</td>
<td>1.12 (201.49)</td>
<td>103.96</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for the test/reference mean ratio of the pharmacokinetic variables AUC_{0-\infty} (as primary characteristic of the extent of absorption of aspirin) and C_{max} also fall within the conventional bioequivalence range of 80% to 125%, indicating that the test capsule and reference tablets can be considered bioequivalent with respect to Aspirin (even though the active metabolite was measured only in the first study, but not the second).

The above bioequivalence studies confirmed that the test formulation, Bisoprolol/Aspirin 10mg/75mg Capsules is bioequivalent to respective reference products, Emcor 10mg Tablets and the Hjertmagnyl 75mg Tablets, containing 10mg Bisoprolol and 75mg Aspirin respectively.

**Pharmacodynamics**
The pharmacodynamic characteristics of acetylsalicylic acid and bisoprolol fumarate have been well-studied in the past. There would be no particular concerns for generic medicinal products.

**Clinical Efficacy**
No new data have been submitted and none are required for applications of this type.

**Clinical Safety**
No new data have been submitted and none are required for applications of this type.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference products.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Forms
The MAA forms are medically satisfactory.

Clinical Conclusion
There are no objections to the approval of these products from a clinical point of view.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Bisoprolol and Aspirin 5mg/75mg and 10mg/75mg Capsules 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.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Bisoprolol and Aspirin 10mg/75mg Capsules and the mono component reference products administered separately.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of the reference products.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with acetylsalicylic acid and bisoprolol fumarate is considered to have demonstrated the therapeutic value of the compound. The risk benefit 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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