SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

{(Invented) name} 5mg /75mg Capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 5 mg Bisoprolol fumarate and 75 mg Acetylsalicylic acid.
Excipient(s) with known effect: Lecithin (Soya)
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard

White capsule printed 5/75, size 1

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

Posology

Capsules for oral administration.

One capsule to be taken daily

Special populations

Older people: No dosage adjustment is normally required, but 5 mg of bisoprolol per day may be adequate in some patients.

Renal or hepatic impairment

Due to the acetylsalicylic acid component, **{(Invented) name}** capsules are contraindicated in patients with severe hepatic or renal insufficiency (see section 4.3). Caution should be exercised in patients with mild or moderate hepatic or renal insufficiency (see section 4.4 and 5.2).

Paediatric population: the safety and efficacy of bisoprolol in children and adolescents has not been established. Therefore, **{(Invented) name}** capsules should not be used in children or adolescents.

Duration of therapy:

Treatment with bisoprolol is generally a long-term therapy.

The treatment with bisoprolol must not be stopped abruptly since this might lead to a transitory worsening of condition. Especially in patients with ischemic heart disease, treatment must not be discontinued suddenly. Gradual reduction of daily dose is recommended.

4.3 Contraindications

This medicine is contraindicated in patients with:

- hypersensitivity to bisoprolol
- hypersensitivity to salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint and certain patients who may suffer from bronchospasm, rhinitis and urticaria) and to any of the excipients
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- sinoatrial block
- sick sinus syndrome
- second or third degree AV block (without pacemaker)
- symptomatic bradycardia
- symptomatic hypotension
- 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
- gastric symptoms or patients who have suffered from stomach ache when previously using this medicine
- peptic ulceration or history of peptic ulceration and/or/gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages
- severe hepatic or renal insufficiency
- haemorrhagic diathesis or coagulation disorders such as haemophilia and hypoprothrombinaemia and where there is concurrent anti-coagulant therapy
- glucose-6-phosphatedehydrogenase deficiency (G6Pd deficiency)
- methotrexate used at doses > 15mg/week (see section 4.5)
- peanut or soya allergies
- gout
- breastfeeding
- doses > 100mg/day during third trimester of pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

Bisoprolol

Bisoprolol must be used with caution in:

- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) can be masked
- strict fasting
- ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment 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

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

Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (e.g. bisoprolol) after carefully balancing 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 beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocking agent therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

In bronchial asthma or other chronic obstructive pulmonary disease, 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 $beta_2$-stimulants may have to be increased.

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.

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

Acetylsalicylic acid

Concomitant treatment with anticoagulants (coumarin derivatives, heparin) and other drugs that alter haemostasis (e.g. antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended and should generally be avoided. If concurrent use cannot be avoided, frequent monitoring of the International Normalised Ratio (INR) is indicated and patients should be cautioned to watch for signs of bleeding, especially in the gastrointestinal tract.

Acetylsalicylic acid may promote bronchospasm and asthma attacks or other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

Patients with a history of peptic ulcer disease and/or gastrointestinal haemorrhages should avoid using acetylsalicylic acid (which can cause gastric mucosal irritation and bleeding). If bleeding signs and symptoms continue due to the acetylsalicylic acid component, the physician may discontinue this product.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin-reuptake inhibitors and deferasirox (see section 4.5).

Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid (see section 4.8). **{(Invented) name}** capsules should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including acetylsalicylic acid, especially gastrointestinal bleeding and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly.

Caution should be exercised in patients with hepatic insufficiency (as acetylsalicylic acid is metabolised mainly via the liver, see section 5.2) and in patients with renal failure. Liver tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion or who are undergoing concomitant treatment with uricosuric agents (e.g. benzbromarone, probenecid, sulphinpyrazone) may experience gout attacks (see section 4.5).

Acetylsalicylic acid must be used with care in cases of very severe menstrual bleeding.

It is preferable to stop use of acetylsalicylic acid before a surgical procedure (including tooth extraction) because of the risk of a prolonged bleeding time or an aggravation of the bleeding. The length of the interruption of the treatment should be determined on a case-by-case basis, but will usually be one week.

There is a possible association with acetylsalicylic acid and Reye's Syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason acetylsalicylic acid should not be given to children under 16 years unless specifically indicated.

This medicine contains soya lecithin and is contraindicated in patients who have peanut or soya allergies.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Bisoprolol

Combinations not recommended

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

Centrally-acting antihypertensive drugs (e.g. clonidine methyldopa, moxonidine, rilmenidine): concomitant use of centrally-acting antihypertensive drugs may further decrease the central sympathetic tonus and may thus lead to reduction of heart rate and cardiac output and to vasodilation. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase the 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 such as felodipine and amlodipine: Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

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

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

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

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).

Cardiac glycosides (e.g.digoxin) : 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.

<u>Combinations to be considered</u>

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-metabolising enzymes. Normally no dosage adjustment is necessary.

Ergotamine derivatives: exacerbation of peripheral circulatory disturbances.

Acetylsalicylic acid

The use of several platelet aggregation inhibitors, i.e. acetylsalicylic acid, NSAIDs, ticlopidine, clopidogrel, tirofiban, eptifibatide, increases the risk of bleeding, likewise their combination with heparin and its derivatives (hirudine, fondaparinux), oral anticoagulants and thrombolytics. Clinical and biological parameters of haemostasis should be regularly monitored.

Contraindicated combinations

Methotrexate (used at doses > 15 mg/week): the combined drugs, methotrexate and acetylsalicylic acid, increase haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate with this medicine is contraindicated (see section 4.3).

Not recommended associations

Uricosurics agents (benzbromarone, probenecid, and sulphinpyrazone): reduced effect of uric acid excretion by competition of renal tubular uric acid elimination. Therefore, the concomitant use of this medicine with uricosurics agents is not recommended (see section 4.4).

Combinations requiring precautions for use

NSAIDS may decrease the antihypertensive effects of diuretics and other antihypersensitive agents. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency.

Diuretics: risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

Aspirin antagonises the diuretic effect of spironolactone.

Corticosteroids: the concomitant administration of steroids may enhance the risk of GI bleeding or ulceration.

Methotrexate used at doses lower than 15 mg/week: the combined drugs, methotrexate and acetylsalicylic acid, increased haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring in the presence of even mildly impaired renal function, as well as in older people.

Heparin used at curative dosage or in older patients: when acetylsalicylic acid is coadministered with heparin at curative dosage or in older patients, there is an increased risk of bleeding. Close monitoring of the INR, aPTT and/or bleeding time should be performed in the case of concomitant administration of both drugs.

Cardiac glycosides (e.g. digoxin): NSAIDs (including acetylsalicylic acid) may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Lithium : acetylsalicylic acid impairs the renal elimination of lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of lithium is recommended when initiating and terminating treatment with bisoprolol and acetylsalicylic acid. Dose adjustment may be necessary.

Carbonic anhydrase inhibitors (acetazolamide): may result in severe acidosis and increased central nervous system toxicity.

Ciclosporin, tacrolimus: concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effects of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

Valproate: acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Phenytoin: salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

Ibuprofen: experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding the extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see Section 5.1).

Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose acetylsalicylic acid for cardioprotection.

<u>Combinations to be taken into account</u>

Other anticoagulants (coumarin derivatives, heparin at preventive dosage), other platelet antiaggregants and other thrombolytics, and selective serotonin inhibitors (SSRIs, such as sertraline or paroxetine): increased risk of bleeding.

NSAIDs: increased risk of bleeding and of damage on gastrointestinal mucosa and enhancement of prolonging bleeding time.

Antacids: antacids can increase the renal excretion of acetylsalicylic acid by alkalinising the urine.

Principle incompatibilities are iron salts, carbonates and alkali hydroxides.

Alcohol: increased risk of gastrointestinal bleeding

Antidiabetics, e.g. sulphonylureas: acetylsalicylic acid may increase the hypoglycaemic effect.

Metoclopramide: potentiates the effect of acetylsalicylic acid

4.6 Fertility, pregnancy and breast-feeding

{(Invented) name} capsules are not recommended during pregnancy unless clearly necessary

Pregnancy

There are no data from the use of **{(Invented) name}** capsules in pregnant women

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/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 foetus 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 foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Acetylsalicylic acid: Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy all prostaglandin synthesis inhibitors may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)

- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis

Additionally, at the end of pregnancy, prostaglandin synthesis inhibitors may expose both the mother and neonate to:

- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
- Inhibition of uterine contractions resulting in delayed or prolonged labour

Consequently, acetylsalicylic acid at doses of 100mg/day and higher is contraindicated during the third trimester of pregnancy.

Breastfeeding

It is not known whether bisoprolol is excreted in human milk. Salicylates and their metabolites are excreted in small amounts in human milk. Therefore, breastfeeding is not recommended during administration of this product.

Fertility

There is no data on the possible effects of this medicine on male or female fertility.

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

Tabulated summary of adverse reactions

Adverse reactions are classified according to frequency and System Organ Class.

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)

Bisoprolol

The following data results from bisoprolol:

Investigations:

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

Cardiac disorders:

Uncommon: bradycardia

worsening of pre-existing heart failure

AV-stimulus disturbances

Ear and labyrinth disorders:

Rare: hearing disorders

Eye disorders:

Rare: reduced tear flow (to be considered if the patient uses lenses)

Very rare: conjunctivitis

Gastrointestinal disorders:

Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation

General disorders:

Common: fatigue*

Uncommon: asthenia

Hepatobiliary disorders:

Rare: hepatitis

Nervous system disorders:

Common: dizziness*, headache*

Rare: 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 (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: muscle weakness, muscle cramps

Vascular disorders:

Common: feeling of coldness or numbness in the extremities

Uncommon: hypotension

Psychiatric disorders

Uncommon: sleep disturbances, depression

Rare: nightmares, hallucinations

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

Acetylsalicylic acid

The undesirable effects are often dose-dependent and are due to the pharmacological effect of acetylsalicylic acid (see section 5.1). Most undesirable effects are usually associated with the gastrointestinal tract. Patients with known allergies or asthma are at increased risk of hypersensitivity reactions. Cross hypersensitivity to other NSAIDs may develop.

Blood and the lymphatic disorders:

Common: increased bleeding tendencies

Uncommon: blood in urine

Rare: haemorrhagic syndrome (nosebleeds, bleeding gums, bloody vomiting and blood loss via the faeces, etc.), thrombocytopenia, agranulocytosis, aplastic anaemia.

Not known: cases of bleeding with prolonged bleeding time such as epistaxis, gingival bleeding and heavier menstruation. Symptoms may persist for a period of 4 – 8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures.

Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses)

Endocrine disorders:

Very rare: hypoglycaemia

Metabolism and nutrition disorders:

Not known : hyperuricaemia

Nervous system disorders:

Rare: intracranial haemorrhage, dizziness

Not known: vertigo, headache

Respiratory, thoracic and mediastinal

Uncommon: rhinitis, dyspnoea

Rare: bronchospasm, asthma attacks

Ear and labyrinth disorders:

Not known: reduced hearing ability, tinnitus

Vascular disorders

Rare: haemorrhagic vasculitis

Reproductive system and mammary disorders

Rare: menorrhagia

Gastrointestinal disorders:

Common: gastritis, dyspepsia, mild to moderate blood loss in the gastrointestinal tract. With long-term or repeated use this blood loss can lead to anaemia

Rare: severe gastrointestinal haemorrhage, nausea, vomiting

Not known: gastric or duodenal ulcers and perforation, diarrhoea

Hepato-biliary disorders:

Very rare: liver impairment

Skin and subcutaneous tissue disorders:

Uncommon: urticaria

Rare: Steven-Johnsons syndrome, Lyell's syndrome, purpura, erythema nodosum, erythema multiforme

Renal and urinary disorders:

Not known: acute renal insufficiency, especially in patients with existing renal insufficiency, heart decompensation, nephrotic syndrome or concomitant treatment with diuretics. Salt and water retention

Immune system disorders:

Rare: hypersensitivity reactions, angio-oedema, allergic oedema, anaphylactic reactions including shock

Very rare: aggravation of allergic symptoms of food allergy

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **www.XXX.XX.XX.**

4.9 Overdose

Bisoprolol

The most common signs expected with overdosage 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 and patients with heart failure are probably very sensitive.

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.

Acetylsalicylic acid

Overdosage is unlikely due to the low level of acetylsalicylic acid in this product. However intoxication (accidental overdose) in very young children or therapeutic overdose in older people may present as follows: The following are associated with moderate intoxication: dizziness, headache, tinnitus, confusion, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate, hyperventilation and gastrointestinal symptoms (nausea, vomiting and gastric pain).

With severe intoxication, serious disturbances of the acid-base equilibrium occur. Initial hyperventilation leads to respiratory alkalosis. Subsequently a respiratory acidosis occurs as a result of a suppressive effect on the respiratory centre. A metabolic acidosis also arises due to the presence of salicylate. Acidosis may increase salicylate transfer across the blood brain barrier. Given that children, infants and toddlers are often only seen at a late stage of intoxication, they will usually have already reached the acidosis stage. The following can also arise: hyperthermia and perspiration, leading to dehydration, restlessness, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system can lead to coma, cardiovascular collapse and respiratory arrest. The lethal dose of acetylsalicylic acid is 25-30 gram. Plasma salicylate concentrations above 300 mg/l (1.67 mmol/l) suggest intoxication.

If a toxic dose has been ingested then admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting; if this fails, gastric lavage is indicated. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalising of the urine (250 mmol $NaHCO_3$ for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: beta blocking agents; bisoprolol combination; ATC code: C07FX04

Bisoprolol is a potent, highly β_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 β_1-receptors reduces heart action and thus reduces oxygen demand. Hence bisoprolol is effective in eliminating or reducing the symptoms.

Acetylsalicylic acid inhibits the platelet activation: blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatosic lesions. The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%.

Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after treatment interruption.

Acetylsalicylic acid extends bleeding time on average by approximately 50 to 100%, but individual variations can be observed.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

The European Medicines Agency has waived the obligation to submit the results of studies with **{(Invented) name}** capsules in all subsets of the paediatric population in essential (primary) hypertension, secondary hypertension, angina pectoris. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Bisoprolol

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

Bisoprolol is eliminated from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency. The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied.

The kinetics of bisoprolol are linear and independent of age.

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

Acetylsalicylic acid

Absorption

Maximum plasma concentration (C_{max}) is reached after about 50 minutes (t_{max}). The principal site of absorption is the proximal small intestine. A significant portion of the dosage, however, is already hydrolysed to salicylic acid in the intestinal wall during the absorption process.

The degree of hydrolysis is contingent on the rate of absorption.

Simultaneous ingestion of food delays the absorption of acetylsalicylic acid (lower plasma concentrations) but does not reduce it.

Distribution

The volume of distribution of acetylsalicylic acid is ca. 0.16 l/kg of body weight. The salicylic acid, which is the first conversion product made from acetylsalicylic acid, is bound to plasma protein, largely albumin, by more than 90%. Salicylic acid slowly diffuses into the synovial fluid. It passes the placenta and passes into breast milk.

Biotransformation

Acetylsalicylate is primarily converted into salicylic acid through hydrolysis.

The half-life of acetylsalicylic acid is short: ca. 15 – 20 minutes.

Salicylic acid is subsequently converted into glycine and glucuronic acid conjugates, and traces of gentisic acid. At higher therapeutic dosage rates the conversion capacity of salicylic acid is exceeded with the pharmacokinetics becoming non-linear.

This results in protraction of the apparent elimination half-life of salicylic acid from a few hours to around a twenty-four hour period.

Elimination

Elimination largely occurs through the kidneys. The tubular reabsorption of acetylsalicylic acid is pH-contingent. Through the alkalisation of the urine, the portion of unaltered acetylsalicylic acid in the urine may increase from ca. 10% up to ca. 80%.

5.3 Preclinical safety data

Bisoprolol

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/foetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses, but was not teratogenic.

Acetylsalicylic acid

In rat studies, foetotoxicity and teratogenic effects were observed with acetylsalicylic acid at maternotoxic doses. Clinical relevance is unknown as the doses used in non-clinical studies are much higher (7 times at least) than the maximal recommended doses in targeted cardiovascular indications.

No carcinogenic effects were observed in mice and rat studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspirin tablet:
Maize Starch
Cellulose, microcrystalline
Stearic acid

Film Coating:
Polyvinyl alcohol hydrolysed
Titanium dioxide (E171)
Talc
Lecithin (Soya) (E322)
Xanthan gum

Bisoprolol powder:
Cellulose, microcrystalline
Magnesium stearate

Capsule:
Gelatin
Titanium dioxide (E171)

Ink containing:
Shellac, Iron oxide black (E172), propylene glycol, ammonium hydroxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Polychlorotrifluoroethylene /PVC blister with aluminium /PVC foil.
Pack sizes: 7, 10, 14, 20, 28, 30, 50, 56, 84, 98 and 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

[To be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT