Concor 5 Plus
Merck Serono

Composition
Medicinally active ingredients.
One film-coated tablet contains 5 mg bisoprolol fumarate (2:1) and 12.5 mg hydrochlorothiazide.

Other ingredients
Colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, corn starch, calcium hydrogen phosphate, dimethicone 100, macrogol 400, methyl hydroxypropylcellulose, colorings E171, E172.

Indications
Arterial hypertension
The combination preparation Concor 5 Plus is recommended if monotherapy is not sufficiently effective.

Contraindications
Concor 5 plus must not be used in:
- manifest heart failure
- shock
- 2nd or 3rd degree AV block
- sick sinus syndrome
- sinoatrial block
- bradycardia (resting pulse less than 50 beats/min before the start of therapy)
- acidosis
- bronchial hyperresponsiveness (e.g. bronchial asthma)
- late stages of peripheral circulatory disturbances
- concomitant administration of MAO inhibitors (exception: MAO-B inhibitors)
- severe disturbances of kidney function (renal insufficiency with oliguria or anuria; creatinine clearance less than 30 ml/min and/or serum creatinine more than 1.8 mg 100 MI)
- acute glomerulonephritis
- coma and hepatic precoma
- refractory hypokalaemia
- severe hyponatraemia

- hypercalcaemia
- gout
- hypersensitivity to hydrochlorothiazide and other thiazides, sulphonamides, and beta-blockers
- children (no therapeutic experience).

Side Effects
Central nervous disturbances, such as tiredness, depression, dizziness, confusion, headache, perspiration, nightmares or vivid dreams, sleep disturbances and hallucinations, can occur occasionally. Lack of appetite and gastrointestinal complaints (e.g. nausea, vomiting, constipation, diarrhoea, abdominal pain and cramps have been observed occasionally. Skin reactions (e.g. erythema, pruritus, photoallergic rash, urticaria) can occur occasionally. Paraesthesia and sensation of cold extremities, muscular weakness or cramp (e.g. calf cramp) and arthropathy with monoarthritis and polyarthritis can occur occasionally. Also an aggravation of complaints in patients with peripheral circulatory disturbances (including patients with Raynaud’s disease) has been observed. Therapy with Concor 5 Plus may lead occasionally to brady-cardia, atrioventricular conduction disturbances or exacerbation of heart failure with peripheral oedema and/or exertional dyspnoea, orthostatic hypotension, and rarely to a marked decrease in blood pressure, syncope and palpitation. In patients with angina pectoris an exacerbation of attacks is not to be excluded in isolated cases. Due to the possible increase in airway resistance, respiratory distress may occur in patients predisposed to bronchospastic reactions (especially with obstructive airway diseases).
Dry mouth conjunctivitis, reduced lacrimation (to be borne in mind if contact lenses are worn) and visual disturbances have been observed rarely. Therapy with Concor 5 Plus leads rarely to increased serum lipids (cholesterol, triglycerides). Latent diabetes mellitus may become manifest, an already manifest diabetes mellitus may deteriorate. After prolonged peri-
sensitivity to allergens and the severity of anaphylactic reactions. Therefore, in patients with a history of severe hypersensitivity reactions and in patients undergoing desensitisation therapy this may result in excessive anaphylactic reactions.

The therapy should be discontinued in:
- refractory disturbances of the electrolyte balance
- orthostatic regulatory disturbances
- hypersensitivity reactions
- pronounced gastrointestinal complaints
- central nervous disorders
- pancreatitis
- changes in blood count (anaemia, leucopenia, thrombocytopenia)
- acute cholecystitis
- occurrence of vasculitis
- deterioration of existing myopia
- serum creatinine concentration more than 1.8 mg/100 ml or creatinine clearance <30 ml/min.

Warnings and Precautions
Patients with any of the following should be monitored closely:
- 1st degree AV block
- manifest or latent diabetes mellitus (severe hypoglycaemic conditions possible; regular monitoring of blood glucose)
- prolonged periods of strict fasting and heavy physical strain (possibility of severe hypoglycaemic conditions)
- patients with phaeochromocytoma (tumour of the adrenal medulla) (Concor 5 Plus should not be administered until after alpha-blockade)
- hypovolaemia
- cerebral sclerosis
- coronary sclerosis
- impaired kidney function of mild degree and co-existing impairment of liver function (dose adjustment)
- Prinzmetal's angina.

In patients with psoriasis in their personal or family history medication containing beta-blockers should only be prescribed if the risk benefit has been carefully evaluated. Beta-blockers can increase the
sensitivity to allergens and severity of anaphylactic reactions. Therefore, Concor 5 plus should only be prescribed if considered essential in patients with a history of severe hypersensitivity reactions and in patients undergoing desensitisation therapy (beware of excessive anaphylactic reactions).

**Warnings**

In renal insufficiency (glomerular filtrate less than 30 ml/min and/or serum creatinine more than 1.8 mg/100 ml) Concor 5 Plus is ineffective and, since the glomerular filtration rate is further reduced, even harmful.

**Pregnancy and lactation period:**

Concor 5 Plus must not be used during pregnancy due to suspected thrombocytopenia in the neonate. Use during the lactation period is contraindicated since the active substance hydrochlorothiazide can inhibit milk production. If use during this period is essential, breast-feeding should be avoided.

*Note on pregnancy and lactation period*

The use of diuretics in pregnancy - with the exception of special indications (heart disease, heart failure)- is not suited to reduce the blood pressure because it counteracts the volume expansion normal in this condition.

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

The treatment of hypertension with this drug necessitates regular medical monitoring. The ability to drive a vehicle or to operate machinery may be impaired as a result of reactions to the drug varying from individual to individual. This is especially the case at the start of treatment and with change of medication as well as in conjunction with alcohol.

**Drug Interactions**

Attention is to be paid to the following interactions between Concor 5 plus and other drugs:

During treatment with Concor 5 Plus and with concomitant administration of ACE inhibitors (e.g. captopril, enalapril) there is the risk of an excessive decrease in blood pressure at the start of therapy. The concomitant administration of Concor 5 Plus and insulin or oral antidiabetics may potentiate or prolong or else attenuate their effect. The warning signs of hypoglycaemia - especially tachycardia and tremor - are masked or diminished. Regular monitoring of blood glucose levels is therefore necessary. Salicylates and other nonsteroidal anti-inflammatory drugs (e.g. indomethacin) may attenuate the antihypertensive and diuretic effect of Concor 5 Plus. In high-dose salicylate administration the toxic effect of salicylates on the central nervous system may be potentiated. In patients developing hypovolaemia during Concor 5 Plus therapy the concomitant administration of nonsteroidal anti-inflammatory drugs can trigger acute renal failure. The antihypertensive effect of Concor 5 Plus may be potentiated by other anti hypertensive drugs, barbiturates, phenothiazines, tricyclic antidepressants, vasodilators, or alcohol. The concomitant administration of Concor 5 Plus and calcium antagonists of the nifedipine type may lead to an excessive decrease in blood pressure, and in individual cases to the development of heart failure. An addition of the cardiodepressant effects of Concor 5 Plus and antiarrhythmics is possible.

In concurrent use of Concor 5 Plus and calcium antagonists of the verapamil or diltiazem type or other antiarrhythmics (such as disopyramide) patients should be closely monitored since hypotension, bradycardia or other cardiac arrhythmias may occur.

*Note*

The intravenous administration of calcium antagonists of the verapamil and diltiazem type or other antiarrhythmics (such as disopyramide) in patients undergoing treatment with Concor 5 Plus is contraindicated (exception: intensive care medicine). The concomitant administration of Concor 5 Plus, reserpine, alpha-methyldopa, guanfacine or clonidine may lead to an excessive decrease in heart rate or to delayed cardiac conduction. The abrupt withdrawal of clonidine in concurrent use of Concor 5 Plus may lead to an excessive increase in blood pressure. Therefore, clonidine must not be discontinued unless the use of Concor 5 Plus was stopped some days previously. This maybe then followed by the
step-wise withdrawal of clonidine. The concurrent use of Concor 5 Plus and noradrenaline, adrenaline or other sympathomimetic substances (such as in cough preparations, nose and eye drops) may lead to increased blood pressure. Monoaminoxidase (MAO) inhibitors should not be taken simultaneously with Concor 5 Plus due to the possibility of excessive hypertension. The effect of uric-acid-lowering agents may be attenuated in concomitant administration of Concor 5 plus. In concurrent therapy with cardiac glycosides it should be borne in mind that in hypokalaemia and/or hypomagnesemia developing during treatment with Concor 5 Plus the myocardium shows increased sensitivity to cardiac glycosides, thus leading to a potentiation of their effects and adverse reactions. The concomitant administration of ergotamine derivatives (e.g. in ergotamine-containing migraine agents) and Concor 5 Plus may exacerbate peripheral circulatory disturbances. The concurrent use of Concor 5 Plus and glucocorticoids ACTH, carbenoxolone, amphotericin B, frusemide or laxatives may result in elevated potassium losses. The concomitant administration of Cancer 5 plus and lithium potentiates the cardiotoxic and neurotoxic effect of lithium through a reduction of lithium excretion. The concurrent use of Concor 5 Plus and narcotics may result in an excessive decrease in blood pressure. An addition of their negative inotropic effects is possible. The effect of curare type muscle relaxants may be potentiated or prolonged by Concor 5 Plus. Should it not be possible to withdraw Concor 5 Plus prior to surgery under general anaesthesia or prior to use of curare-type muscle relaxants, the anaesthetist should be informed that the patient is being treated with Concor 5 Plus. In concomitant administration of cytostatics (e.g. cyclophosphamide, fluorouracil, methotrexate) increased bone marrow toxicity is to be expected. Concor 5 Plus may reduce the excretion of lidocaine. The concomitant administration of cholestyramine or colestipol reduces the absorption of the hydrochlorothiazide component of Concor 5 Plus. In concurrent use of methyldopa haemolysis due to the formation of antibodies to hydrochlorothiazide has been described in isolated cases. During long-term therapy with Concor 5 Plus the serum electrolytes (especially potassium, sodium, calcium), creatinine and urea, serum lipids (cholesterol and triglycerides), uric acid and blood glucose should be monitored regularly. During treatment with Concor 5 Plus patients should ensure an adequate supply of fluid and food rich in potassium (e.g. bananas, vegetables, nuts) to compensate for the increased loss of potassium. The potassium losses may be reduced or prevented by concomitant therapy with potassium-sparing diuretics.

**Dosage and Administration**

The treatment of high blood pressure should principally be started with low doses of a single active substance and then increased gradually. The fixed combination of Concor 5 Plus consisting of bisoprolol and hydrochlorothiazide should be administered only if the blood pressure could not be normalised by the individual active substances or else excessive adverse reactions had occurred at high doses, and the dosage of the individual active substances as present in the Concor 5 plus combination has proven to be appropriate.

The following apply as guidelines:

**Arterial hypertension:**

Normally 1×1 film coated tablet of Concor 5 Plus (equivalent to 5 mg bisoprolol and 12.5 mg hydrochlorothiazide) daily. If the blood pressure is only inadequately reduced the dose may be increased to 1×2 film-coated tablets of Concor 5 Plus (equivalent to 10 mg bisoprolol and 25 mg hydrochlorothiazide) once daily. In co-existing impairment of kidney or liver function the elimination of the HCT component of Concor 5 Plus is reduced, so that preference may have to be given to the lower dose form.

**Mode and duration of administration**

The film-coated tablets are to be swallowed whole with the breakfast with some liquid. There is no limit to the duration of administration. It depends upon the nature and severity of the disease. After long-
term therapy - particularly in the presence of ischaemic heart disease - Concor 5 Plus should be discontinued gradually (i.e. over 7-10 days), since an abrupt withdrawal may lead to an acute deterioration of the patient's condition.

Notes
During long term-therapy with Concor 5 Plus, the serum electrolytes (especially potassium, sodium, calcium), creatinine and urea, the serum lipids (cholesterol and triglycerides), uric acid as well as blood glucose should be monitored regularly. During treatment with Concor 5 Plus patients should ensure an adequate supply of fluid and food rich in potassium (e.g. bananas, vegetables, nuts) to compensate for the increased loss of potassium. The potassium losses may be reduced or prevented by concomitant therapy with potassium-sparing diuretics. The drug is not to be used after the expiry date. Drugs should be kept out of the reach of children!