Concor®
Bisoprolol fumarate

Selective beta blocking agents

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Concor 1.25 mg	Each film-coated tablet contains 1.25 mg Bisoprolol fumarate.
Concor 2.5 mg	Each film-coated tablet contains 2.5 mg Bisoprolol fumarate.
Concor 5 mg	Each film-coated tablet contains 5 mg Bisoprolol fumarate.
Concor 10 mg	Each film-coated tablet contains 10 mg Bisoprolol fumarate.

2. PHARMACEUTICAL FORM

Film-coated tablets.

Concor 1.25 mg	White, round, biconvex film-coated tablets, plain on both sides.
Concor 2.5 mg	White, hearth-shaped, biconvex film-coated tablets, scored on both sides.
Concor 5 mg	Yellowish-white, heart-shaped, biconvex film-coated tablets, scored on both sides.
Concor 10 mg	Pale orange - light orange, heart-shaped, biconvex film-coated tablets, scored on both sides.

3. CLINICAL PARTICULARS

3.1 Indications

Concor 1.25 mg, Concor 2.5 mg, Concor 5 mg, and Concor 10 mg

Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

Concor 5 mg and Concor 10 mg

- Treatment of hypertension
- Treatment of coronary heart disease (angina pectoris)

3.2 Posology and Method of Administration

Posology

Treatment of hypertension or angina pectoris

Adults: For both indications the dosage is 5 mg Bisoprolol fumarate once daily. If necessary, the dose may be increased to 10 mg Bisoprolol fumarate once daily.

The maximum recommended dose is 20 mg once daily.

In all cases the dosage is adjusted individually, in particular according to the pulse rate and therapeutic success.

Treatment of stable chronic heart failure

The patients should have stable chronic heart failure without acute failure during the past six weeks and a mainly unchanged basic therapy during the past two weeks. They should be treated at optimal dose with

an optimal dose with an ACE inhibitor (or other vasodilator in case of intolerance to ACE inhibitors) and a diuretic, and optionally cardiac glycosides, prior to the administration of Bisoprolol.

Titration phase
The treatment of stable chronic heart failure with bisoprolol is initiated according to the following titration scheme, individual adaptation may be necessary depending on how well the patient tolerates each dose, i.e. the dose is to be increased only, if the previous dose is well tolerated.

- 1.25 mg Bisoprolol fumarate once daily for 1week; if well tolerated increase to
- 2.5 mg Bisoprolol fumarate once daily for a further week; if well tolerated increase to
- 3.75 mg Bisoprolol fumarate once daily for a further week; if well tolerated increase to
- 5 mg Bisoprolol fumarate once daily for the 4 following weeks; if well tolerated increase to
- 7.5 mg Bisoprolol fumarate once daily for the 4 following weeks; if well tolerated increase to
- 10 mg Bisoprolol fumarate once daily for the maintenance therapy.

Close monitoring of vital signs (blood pressure, heart rate) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first day after initiating the therapy.

The maximum recommended dose is 10 mg Bisoprolol fumarate once daily.

Treatment modification
If the maximum recommended dose is not well tolerated gradual dose reduction may be considered.

In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation.

The reintroduction and/or uptitration of bisoprolol should always be considered when the patient becomes stable again.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patients condition.

Treatment with bisoprolol is generally a long-term therapy.

Renal or liver impairment
Treatment of hypertension or angina pectoris: In patients with liver or kidney function disorders of mild to moderate severity, no dosage adjustment is normally required. In patients with severe renal impairment (creatinine clearance <20 mL/min) and in patients with severe liver function disorders it is recommended that a daily dose of 10 mg Bisoprolol fumarate is not exceeded.

Treatment of stable chronic heart failure: There is no information regarding pharmacokinetics of Bisoprolol in patients with chronic heart failure and with impaired liver or renal function. Uptitration of the dose in these populations should therefore be made with additional caution.

Elderly
No dosage adjustment is required.

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

Administration
Tablets are taken in the morning with or without food. They are swallowed with some liquid and not to be chewed.

3.3 Contraindications
Bisoprolol is contraindicated in patients with:
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- second or third degree AV block
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma
- severe forms of peripheral arterial occlusive disease or Raynaud's syndrome
- untreated phaeochromocytoma (*see section 3.4 Special Warnings and Special Precautions for Use*)
- metabolic acidosis
- hypersensitivity to Bisoprolol or to any of the excipients (*see section 5.1 List of Excipients*)

3.4 Special Warnings and Special Precautions for Use
The treatment of stable chronic heart failure with Bisoprolol has to be initiated with a special titration phase.

Especially in patients with ischaemic heart disease the cessation of therapy with Bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition.

The initiation and cessation of treatment with bisoprolol necessitates regular monitoring.

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

There is no therapeutic experience of bisoprolol treatment of heart failure in patients with the following diseases and conditions:
- insulin dependent diabetes mellitus (type I)
- severely impaired renal function,
- severely impaired liver function,
- restrictive cardiomyopathy,
- congenital heart diseases
- haemodynamically significant organic valvular disease.
- myocardial infarction within 3 months.

Bisoprolol must be used with caution in:
- bronchospasm (bronchial asthma, obstructive airways diseases)
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked
- strict fasting,
- ongoing desensitisation therapy. 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 angina; Cases of coronary vasospasm have been observed. Despite its high beta$_1$-

selectivity, angina attacks cannot be completely excluded when Bisoprolol is administered to patients with Prinzmetal's angina.

- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy,
- general anaesthesia
  In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhytmias 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 bradyarrhytmias, 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.

Combination of Bisoprolol with calcium antagonist of the Verapamil or Diltiazem type, with Class I antiarrhytmic drugs and with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 3.5 Interaction with other medicinal products and other forms of interaction.

Although cardioselective (beta$_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, Bisoprolol may be used with caution. In patients with obstructive airways diseases the treatment with Bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta$_2$-stimulants may have to be increased.

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 thyreotoxicosis may be masked.

3.5 Interaction with Other Medicinal Products and Other Forms of Interaction
Combinations not recommended
Treatment of stable chronic heart failure
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.

All indications
Calcium antagonists of the Verapamil type and to a lesser extent of the Diltiazem type: Negative influence on contractility, atrio-ventricular conduction and blood pressure. Intravenous administration of Verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

Centrally acting blood pressure-lowering medicines (such as Clonidine, Methyldopa, Moxonodine, Rilmenidine): Concomitant use of centrally acting antihypertensive drug may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardic output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of rebound hypertension.

Combinations to be used with caution

Treatment of hypertension or coronary heart disease (angina pectoris)

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.

All indications

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

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

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

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

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

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension.

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

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

Beta-Sympathomimetics (e.g. Isoprenaline, Dobutamine): combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that active both beta-and alpha-adrenoceptors (e.g. Noradrenaline, Adrenaline): Combination with Bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effect of these agents leading to blood pressure increase and exacerbated intermittent claudiation. Such interactions are considered to be more likely with nonselective beta-blockers

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

Combinations to be considered

Mefloquine: increased risk of bradycardia.

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

3.6 Pregnancy and Lactation

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g.

hypoglycaemia and bradycardia) may occur in the fetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary beta1-selective adrenoceptor blockers are preferable.

Bisoprolol should not be used during pregnancy unless clearly necessary. If treatment with Bisoprolol is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breast-feeding
It is not known whether this drug is excreted in human milk. Therefore, breastfeeding is not recommended during administration of Bisoprolol.

3.7 Effects on Ability to Drive and Use Machines
In a study with 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 start of treatment and upon change of medication as well as in conjunction with alcohol.

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

Cardiac disorders

Very common:	bradycardia (in patients with chronic heart failure)
Common:	worsening of heart failure (in patients with chronic heart failure)
Uncommon:	AV-conduction disturbances; worsening of pre-existing heart failure (in patients with hypertension or angina pectoris); bradycardia (in patients with hypertension or angina pectoris)

Investigations

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

Nervous system disorders

Common:	dizziness*, headache*
Rare:	syncope

Eye disorders

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

Ear and labyrinth disorders

Rare:	hearing disorders

Respiratory, thoracic and mediastinal disorders

Uncommon:	bronchospasm in patients with bronchial asthma or a history of obstructive airways disease

Rare: allergic rhinitis

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

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

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

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

General disorders
Common: asthenia (in patients with chronic heart failure), fatigue*
Uncommon: asthenia (in patients with hypertention of angina pectoris)

Hepatobilary disorders
Rare: hepatitis

Reproductive system and breast disorders
Rare: erectile dysfunction

Psychiatric disorders
Uncommon: depression, sleep disorder
Rare: nightmare, hallucination

* applies only to Hypertension or angina pectoris:
These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1-2 weeks.

3.9 Overdose
Symptoms
With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general the most common signs expected with overdosage of a beta-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 in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension; all patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive. Therefore it is mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme given in section 3.2 Posology and Method of Administration.

Management
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 pharmacologic actions and recommendations for other beta-bockers, the following general measures

should be considered when clinically warranted.

Bradycardia: Administer intravenous atropine. If 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, $beta_2$-sympathomimetic drugs and/or Aminophylline.

Hypoglycaemia: administer i.v. glucose.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic Properties

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

Mechanism of action

Bisoprolol is a highly $beta_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the $beta_2$-receptors concerned with metabolic regulation. Therefore, Bisoprolol is generally not to be expected to influence the airway resistance and $beta_2$- mediated metabolic effects. Its $beta_1$-selectivity extends beyond the therapeutic dose range.

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

Clinical efficacy and safety

In total 2647 patients with chronic heart failure were included in the CIBIS II trial. 83% (n = 2202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction <35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of Bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the Bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1010 patients aged ≥65 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction ≤35%, who had not been treated previously with ACE inhibitors, beta-blockers, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either Bisoprolol or Enalapril.

There was a trend toward higher frequency of chronic heart failure worsening when Bisoprolol was used as the initial 6 months treatment. Non inferiority of Bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at study end (32.4% in the Bisoprolol-first group vs. 33.1 % in the Enalapril-first group, per-protocol population). The study shows that Bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate disease.

Bisoprolol is also used for the treatment of hypertension and angina.

4.2 Pharmacokinetic Properties

Absorption

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration.

Distribution

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.

Metabolism and elimination

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

Linearity

The kinetics of Bisoprolol are linear and independent of age.

Special population

Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with mild to moderate 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. In patients with chronic heart failure (NYHA stage III) the plasma levels of Bisoprolol are higher and 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.

4.3 Preclinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity/mutagenicity or carcinogenicity. Like other beta-blockers, Bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Concor 1.25 mg: Calcium hydrogen phosphate anhydrous, Corn starch, Pregelatinized maize starch, Colloidal silicon dioxide, Microcrystalline cellulose pH 101, Crosspovidone, Magnesium stearate, Hydroxypropyl methyl cellulose 2910, Polyethylene Glycol 400, Dimeticon 100, Titanium Dioxide, Talc fine powder, Purified water.

Concor 2.5 mg: Calcium hydrogen phosphate anhydrous, Corn starch, Colloidal silicon dioxide, Microcrystalline cellulose pH 101, Crospovidone, Magnesium stearate, Hydroxypropyl methyl cellulose 615, Polyethylene Glycol 400, Titanium dioxide, Dimeticon 100, Purified water.

Concor 5 mg: Calcium hydrogen phosphate anhydrous, Corn starch, Colloidal silicon dioxide, Microcrystalline cellulose pH 101, Crospovidone, Magnesium stearate, Hydroxyproyl methyl cellulose 615, Polyethylene Glycol 400, Titanium dioxide, Dimeticon 100, Iron Oxide Yellow (CI No. 77492), Purified water.

Concor 10 mg: Calcium hydrogen phosphate anhydrous, Corn starch, Colloidal silicon dioxide, Microcrystalline cellulose pH 101, Crospovidone, Magnesium stearate, Hypermelose 2910, Macrogol 400, Dimeticon 100, Iron oxide yellow, Iron oxide red, Titanium dioxide, Purified water.

5.2 Shelf-life
The expiry date is indicated on the packaging.

5.3 Storage Condition
Store below 30°C.

6. MANUFACTURER(S)
Manufactured by PT Merck Tbk, Jakarta, Indonesia
Under licence from Merck Healthcare KGaA, Darmstadt, Germany

7. MARKETING AUTHORISATION HOLDER
Registered by PT Merck Tbk, Jakarta, Indonesia

8. PACKAGE QUANTITIES AND MARKETING AUTHORISATION NUMBER(S)

Concor 1.25 mg	Box, 5 blisters @ 10 film-coated tablets	Reg. No. DKL1015803817C1
Concor 2.5 mg	Box, 10 blisters @ 10 film-coated tablets	Reg. No. DKL0215803817B1
Concor 5 mg	Box, 10 blisters @ 10 film-coated tablets	Reg. No. DKL9115803817A1
Concor 10 mg	Box, 3 blisters @ 10 film-coated tablets	Reg. No. DKL9115803817B1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Concor 1.25 mg
Date of first authorisation: 05 April 2010
Date of latest renewal: xxxxxxxx

Concor 2.5 mg
Date of first authorisation: 23 November 2009
Date of latest renewal: 07 June 2020

Concor 5 mg
Date of first authorisation: 24 October 2002
Date of latest renewal: 07 December 2023

Concor 10 mg
Date of first authorisation: 12 April 1991
Date of latest renewal: 04 July 2022

10. CLASSIFICATION OF MEDICINE
Medicinal product subject to medical prescription. Obat Keras.

DISETUJUI OLEH BPOM : 29/10/2024 ID : EREG10014912400098

HARUS DENGAN RESEP DOKTER

11. DATE OF REVISION OF THE TEXT

SmPC based on CCDS version 12.0 (27-Jan-2020)
Date of BPOM approval for the update: xxxxxxxx

INFORMASI UNTUK PASIEN

Concor®
Bisoprolol fumarate

Baca petunjuk ini dengan seksama sebelum mulai minum obat ini karena mengandung informasi penting untuk Anda.
- Simpan lembar petunjuk ini, Anda mungkin akan memerlukannya kembali.
- Jika Anda mempunyai pertanyaan, harap menghubungi dokter atau apoteker.
- Obat ini diresepkan untuk Anda, jangan diberikan kepada orang lain karena dapat membahayakan orang tersebut meskipun terdapat gejala yang sama pada orang tersebut.
- Jika ada efek samping yang serius atau Anda menemukan efek samping yang tidak terdapat pada petunjuk ini, harap hubungi dokter atau apoteker.

Petunjuk ini terdiri dari informasi sebagai berikut:

1 Apa yang dimaksud dengan Concor dan apa kegunaannya

Zat aktif dalam Concor adalah Bisoprolol. Bisoprolol termasuk dalam kelompok obat yang disebut beta-blocker. Obat ini bekerja dengan mempengaruhi respon tubuh terhadap beberapa rangsangan saraf, terutama di jantung. Akibatnya, Bisoprolol memperlambat denyut jantung dan membuat jantung lebih efisien memompa darah ke seluruh tubuh.

Gagal jantung terjadi ketika otot jantung lemah dan tidak mampu memompa cukup darah untuk memasok kebutuhan tubuh. Concor digunakan untuk mengobati gagal jantung kronis yang stabil. Concor digunakan dalam kombinasi dengan obat lain yang cocok untuk kondisi tersebut (seperti ACE-inhibitor, diuretik, dan glikosida jantung).

Concor juga digunakan untuk mengobati tekanan darah tinggi dan mengobati penyakit jantung koroner (angina pektoris).

2 Apa yang perlu Anda ketahui sebelum Anda minum Concor

Jangan minum Concor

Jangan minum Concor jika Anda mengalami salah satu dari kondisi berikut:
- alergi (hipersensitivitas) terhadap Bisoprolol atau salah satu bahan lainnya (lihat bagian 6 Apa kandungan Concor)
- asma berat
- masalah berat pada sirkulasi darah di tungkai Anda (seperti sindroma Raynaud), yang mungkin menyebabkan jari tangan dan jari kaki seperti tergelitik atau berubah pucat atau biru
- feokromositoma yang tidak diobati, yaitu tumor langka pada kelenjar anak ginjal (adrenal)
- asidosis metabolik, yaitu suatu kondisi ketika terdapat terlalu banyak asam dalam darah

Jangan minum Concor jika Anda memiliki salah satu masalah jantung berikut:
- gagal jantung akut
- memburuknya gagal jantung yang membutuhkan suntikan obat ke pembuluh darah, yang meningkatkan kekuatan kontraksi jantung
- denyut jantung yang lambat
- tekanan darah rendah
- kondisi jantung tertentu yang menyebabkan detak jantung sangat lambat atau detak jantung tidak teratur
- syok kardiogenik, yang merupakan kondisi jantung serius akut yang menyebabkan tekanan darah rendah dan kegagalan sirkulasi darah.

Peringatan dan tindakan pencegahan
Jika Anda memiliki salah satu dari kondisi berikut beritahukan dokter sebelum Anda minum Concor; dokter mungkin akan memberikan perawatan khusus (misalnya memberikan pengobatan tambahan atau melakukan pemeriksaan lebih sering):
- diabetes
- puasa yang ketat
- penyakit jantung tertentu seperti gangguan irama jantung, atau nyeri dada yang parah saat istirahat (angina Prinzmetal)
- gangguan ginjal atau hati
- masalah sirkulasi darah agak parah di tungkai
- penyakit paru-paru kronis atau asma agak parah
- riwayat ruam kulit bersisik (psoriasis)
- tumor kelenjar adrenal (feokromositoma)
- gangguan tiroid.

Selain itu, beritahukan dokter jika Anda akan mendapat:
- terapi desensitisasi (misalnya untuk pencegahan alergi serbuk bunga (*hay fever*)), karena Concor mungkin akan membuat Anda mengalami reaksi alergi, atau reaksi tersebut mungkin menjadi lebih parah
- anestesi (misalnya untuk operasi), karena Concor dapat mempengaruhi bagaimana tubuh Anda bereaksi terhadap kondisi sedasi.

Jika Anda memiliki penyakit paru-paru kronis atau asma agak parah segera informasikan ke dokter jika Anda mulai mengalami kesulitan dalam bernapas, batuk, sesak setelah berolahraga, dan sebagainya ketika menggunakan Concor.

Anak-anak dan remaja
Concor tidak dianjurkan untuk digunakan pada anak-anak atau remaja.

Obat lain dan Concor
Beritahu dokter atau apoteker jika Anda minum, baru-baru ini minum, atau kemungkinan akan minum obat lain.

Jangan minum obat berikut dengan Concor tanpa saran khusus dari dokter Anda:
- obat tertentu yang digunakan untuk mengobati denyut jantung yang tidak normal dan tidak teratur (Kelas I obat antiaritmia seperti Quinidine, Disopyramide, Lidocaine, Phenytoin; Flecainide, Propafenone)
- obat tertentu yang digunakan untuk mengobati tekanan darah tinggi, angina pectoris atau detak jantung tidak teratur (antagonis kalsium seperti Verapamil dan Diltiazem)
- obat tertentu yang digunakan untuk mengobati tekanan darah tinggi seperti Clonidine, Methyldopa, Moxonodine, Rilmenidine. Namun, **jangan berhenti minum obat tersebut** sebelum berkonsultasi terlebih dahulu dengan dokter Anda.

Diskusikan dengan dokter terlebih dahulu sebelum minum obat berikut ini bersamaan dengan Concor; dokter mungkin perlu memeriksa kondisi Anda lebih sering:
- obat tertentu yang digunakan untuk mengobati tekanan darah tinggi atau angina pectoris (antagonis kalsium tipe-dihidropiridin seperti Felodipin dan Amlodipine)
- obat tertentu yang digunakan untuk mengobati denyut jantung yang tidak teratur atau tidak normal (obat antiaritmia Kelas III seperti Amiodarone)
- beta-bloker yang digunakan secara lokal (seperti tetes mata Timolol untuk pengobatan glaukoma).
- obat tertentu yang digunakan misalnya untuk mengobati penyakit Alzheimer atau glaukoma (parasimpatomimetik seperti Tacrine atau Carbachol) atau obat yang digunakan untuk mengobati masalah jantung akut (simpatomimetik seperti Isoprenaline dan Dobutamine)
- obat antidiabetes termasuk insulin.
- obat anestesi (misalnya selama operasi)
- digitalis, digunakan untuk mengobati gagal jantung
- obat anti-inflamasi non-steroid (OAINS) yang digunakan untuk mengobati radang sendi, nyeri atau peradangan (misalnya Ibuprofen atau Diklofenac)
- obat apapun, yang dapat menurunkan tekanan darah baik itu berupa efek yang diinginkan atau efek samping seperti antihipertensi, obat tertentu untuk depresi (antidepresan trisiklik seperti Imipramine atau Amitriptyline), obat tertentu yang digunakan untuk mengobati epilepsi atau selama anestesi (barbiturates seperti Phenobarbital), atau obat tertentu untuk mengobati gangguan mental yang ditandai dengan hilangnya kontak dengan kenyataan (phenothiazines seperti Levomepromazine)
- Mefloquine, digunakan untuk pencegahan atau pengobatan malaria
- obat depresi yang disebut monoamine oxidase inhibitor (kecuali MAO-B inhibitor) seperti Moclobemide.

Kehamilan dan menyusui

Kehamilan

Terdapat risiko bahwa penggunaan Concor selama kehamilan dapat membahayakan janin. Jika Anda sedang hamil atau berencana untuk hamil, beritahukan dokter. Dokter akan memutuskan apakah Anda dapat minum Concor selama masa kehamilan.

Menyusui

Tidak diketahui apakah Bisoprolol masuk ke dalam ASI. Oleh karena itu, pemberian ASI tidak direkomendasikan selama pengobatan dengan Concor.

Mengemudi dan menjalankan mesin

Kemampuan Anda untuk mengemudi atau menjalankan mesin mungkin akan terpengaruh tergantung pada seberapa baik Anda mentolerir obat. Harap berhati-hati terutama pada awal pengobatan, ketika dosis meningkat atau obat berubah, serta dalam kombinasi dengan alkohol.

3 Bagaimana meminum Concor

Selalu minum obat ini persis seperti yang dokter anjurkan kepada Anda. Tanyakan kembali kepada dokter atau apoteker jika Anda tidak yakin.

Pengobatan dengan Concor membutuhkan pemantauan berkala oleh dokter. Hal ini diperlukan terutama di awal pengobatan, selama peningkatan dosis, dan ketika Anda menghentikan pengobatan.

Minum tablet dengan air di pagi hari, dengan atau tanpa makanan. Jangan menggerus atau mengunyah tablet.

Tablet yang memiliki garis tengah dapat dibagi menjadi dua dosis yang sama

Pengobatan dengan Concor biasanya jangka panjang.

Dewasa termasuk lansia
Pengobatan dengan Bisoprolol harus dimulai dengan dosis rendah dan meningkat secara bertahap.

Dokter akan memutuskan bagaimana meningkatkan dosis, yang biasanya akan dilakukan dengan cara berikut:
- 1.25 mg Bisoprolol sekali sehari selama satu minggu
- 2.5 mg Bisoprolol sekali sehari selama satu minggu
- 3.75 mg Bisoprolol sekali sehari selama satu minggu
- 5 mg Bisoprolol sekali sehari selama empat minggu
- 7.5 mg Bisoprolol sekali sehari selama empat minggu
- 10 mg Bisoprolol sekali sehari untuk terapi pemeliharaan (berkesinambungan).

Dosis harian maksimum yang dianjurkan adalah Bisoprolol 10 mg.

Tergantung pada seberapa baik Anda mentolerir obat, dokter mungkin memutuskan untuk memperpanjang waktu di antara peningkatan dosis. Jika kondisi Anda semakin memburuk atau tidak dapat lagi mentolerir obat, mungkin diperlukan penurunan dosis lagi atau penghentian pengobatan. Pada beberapa pasien, dosis pemeliharaan cukup menggunakan dosis Bisoprolol di bawah 10 mg.

Dokter Anda akan memberitahu Anda apa yang harus dilakukan.

Jika Anda harus menghentikan pengobatan seluruhnya, dokter biasanya akan menyarankan Anda untuk mengurangi dosis secara bertahap, jika tidak kondisi Anda dapat menjadi lebih buruk.

Jika Anda minum tablet Concor lebih dari yang seharusnya
Jika Anda telah minum tablet Concor lebih dari yang seharusnya, segera beritahu dokter. Dokter akan memutuskan tindakan apa yang diperlukan.

Gejala overdosis dapat termasuk melambatnya denyut jantung, kesulitan bernapas yang parah, merasa pusing atau gemetar (karena gula darah menurun).

Jika Anda lupa untuk minum Concor
Jangan minum dosis sebanyak 2 kali lipat untuk mengganti dosis yang terlupakan. Minum dosis yang biasa Anda minum keesokan harinya.

Jika Anda berhenti minum Concor
Jangan pernah berhenti minum Concor kecuali atas saran dokter. Jika tidak, kondisi Anda bisa menjadi jauh lebih buruk.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan produk ini, tanyakan kepada dokter atau apoteker.

4 Efek samping yang mungkin terjadi

Seperti halnya obat lain, obat ini dapat menyebabkan efek samping, meskipun tidak semua pasien mengalaminya.

Untuk mencegah terjadinya reaksi yang serius, segera hubungi dokter jika timbul efek samping yang parah, timbul mendadak atau memburuk dengan cepat.

Efek samping yang paling serius terkait dengan fungsi jantung:
- melambatnya denyut jantung (dapat mempengaruhi lebih dari 1 dari 10 pasien)
- memburuknya gagal jantung (dapat mempengaruhi hingga 1 dari 10 pasien)
- detak jantung lambat atau tidak teratur (dapat mempengaruhi hingga 1 dalam 100 pasien)

Jika Anda merasa pusing atau lemah, atau kesulitan bernapas, segera hubungi dokter.

Efek samping lebih lanjut tercantum di bawah ini sesuai dengan seberapa sering dapat terjadi:
Efek samping yang umum terjadi (dapat mempengaruhi hingga 1 dari 10 pasien)
- kelelahan, merasa lemah, pusing, sakit kepala
- merasa dingin atau mati rasa di tangan atau kaki
- tekanan darah rendah
- masalah pada perut atau usus seperti mual, muntah, diare, atau sembelit.

Efek samping yang tidak umum terjadi (dapat mempengaruhi hingga 1 dari 100 pasien)
- gangguan tidur
- depresi
- pusing saat berdiri
- masalah pernapasan pada pasien dengan asma atau penyakit paru-paru kronis
- otot melemah, kram otot.

Efek samping yang jarang terjadi (dapat mempengaruhi hingga 1 dari 1.000 pasien)
- masalah pendengaran
- pilek alergi
- berkurangnya aliran air mata
- peradangan hati yang dapat menyebabkan kulit dan bagian putih mata menjadi berwarna kuning
- hasil tes darah tertentu untuk fungsi hati atau kadar lemak yang berbeda dari normal
- reaksi alergi seperti seperti gatal, memerah, ruam. Segera konsultasikan kepada dokter Anda jika Anda mengalami reaksi alergi yang lebih berat dengan gejala berupa pembengkakan pada wajah, leher, lidah, mulut, atau tenggorokan, atau kesulitan untuk bernapas.
- gangguan/disfungsi ereksi
- mimpi buruk, halusinasi.
- pingsan

Efek samping yang sangat jarang terjadi (bisa mempengaruhi hingga 1 dari 10.000 pasien)
- iritasi dan kemerahan mata (konjungtivitis)
- rambut rontok
- timbulnya atau memburuknya ruam kulit seperti bersisik (psoriasis); ruam seperti psoriasis.

Jika Anda mengalami efek samping apapun, bicarakan dengan dokter atau apoteker Anda. Juga termasuk kemungkinan efek samping yang tidak tercantum dalam petunjuk ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5 Bagaimana menyimpan Concor

• Simpan obat Concor jauh dari penglihatan dan jangkauan anak-anak.

- Jangan minum obat setelah tanggal kedaluwarsa berakhir, yang tertera pada kemasan setelah tulisan 'EXP'. Tanggal kedaluwarsa mengacu pada hari terakhir bulan tersebut.
- Jangan simpan Concor di atas suhu 30 °C.

Jangan membuang obat ini melalui saluran pembuangan air atau limbah rumah tangga. Tanyakan kepada apoteker bagaimana membuang obat-obatan yang tidak diperlukan. Hal ini untuk menjaga lingkungan.

6 Isi dari kemasan dan informasi lain

Apa Kandungan Concor

Zat aktif obat adalah Bisoprolol fumarate.

Concor 1.25 mg

- Satu tablet salut selaput mengandung Bisoprolol fumarate 1.25 mg.
- Bahan lainnya: Calcium hydrogen phosphate anhydrous, Corn starch, Pregelatinized maize starch, Colloidal silicon dioxide, Microcrystalline cellulose pH 101, Crosspovidone, Magnesium stearate, Hydroxypropyl methyl cellulose 2910, Polyethylene Glycol 400, Dimeticon 100, Titanium Dioxide, Talc fine powder, Purified water.

Concor 2.5 mg

- Satu tablet salut selaput mengandung Bisoprolol fumarate 2.5 mg.
- Bahan lainnya: Calcium hydrogen phosphate anhydrous, Corn starch, Colloidal silicon dioxide, Microcrystalline cellulose pH 101, Crospovidone, Magnesium stearate, Hydroxypropyl methyl cellulose 615, Polyethylene Glycol 400, Titanium dioxide, Dimeticon 100, Purified water.

Concor 5 mg

- Satu tablet salut selaput mengandung Bisoprolol fumarate 5 mg.
- Bahan lainnya: Calcium hydrogen phosphate anhydrous, Corn starch, Colloidal silicon dioxide, Microcrystalline cellulose pH 101, Crospovidone, Magnesium stearate, Hydroxyproyl methyl cellulose 615, Polyethylene Glycol 400, Titanium dioxide, Dimeticon 100, Iron Oxide Yellow (CI No. 77492), Purified water.

Concor 10 mg

- Satu tablet salut selaput mengandung Bisoprolol fumarate 10 mg.
- Bahan lainnya: Calcium hydrogen phosphate anhydrous, Corn starch, Colloidal silicon dioxide, Microcrystalline cellulose pH 101, Crospovidone, Magnesium stearate, Hypermelose 2910, Macrogol 400, Dimeticon 100, Iron oxide yellow, Iron oxide red, Titanium dioxide, Purified water.

Seperti apa Concor dan isi kemasannya

Concor 1.25 mg:	tablet salut selaput berwarna putih dan bulat, polos pada kedua sisi
Concor 2.5 mg:	tablet salut selaput berwarna putih dan berbentuk hati dengan garis tengah di kedua sisi
Concor 5 mg:	tablet salut selaput berwarna putih kekuningan dan berbentuk hati dengan garis tengah pada kedua sisi
Concor 10 mg:	tablet salut selaput berwarna oranye pucat - oranye terang dan berbentuk hati dengan garis tengah pada kedua sisi

Produsen

Diproduksi oleh PT Merck Tbk, Jakarta, Indonesia
Atas lisensi dari Merck Healthcare KGaA, Darmstadt, Germany

Pemilik Izin Edar
Didaftarkan oleh PT Merck Tbk, Jakarta, Indonesia

Kemasan dan Nomor Izin Edar

Concor 1.25 mg	Dus, 5 blister @ 10 tablet salut selaput	Reg. No. DKL1015803817C1
Concor 2.5 mg	Dus, 10 blisters @ 10 tablet salut selaput	Reg. No. DKL0215803817B1
Concor 5 mg	Dus, 10 blisters @ 10 tablet salut selaput	Reg. No. DKL9115803817A1
Concor 10 mg	Dus, 3 blisters @ 10 tablet salut selaput	Reg. No. DKL9115803817B1

HARUS DENGAN RESEP DOKTER

PIL is aligned with SmPC based on CCDS version 12.0 (27-Jan-2020)
Update Approval xxxxxx