BETAWIN TABLET

DESCRIPTION:

BETAWIN TABLET 50MG: A 9mm, round, white tablet with markings 'd' on both sides.
BETAWIN TABLET 100MG: A 11mm, round scored tablet, white in colour.

COMPOSITION:

BETAWIN TABLET 50 MG: Each tablet contains Metoprolol Tartrate 50 mg.
BETAWIN TABLET 100 MG: Each tablet contains Metoprolol Tartrate 100 mg.

PHARMACODYNAMICS:

Pharmacotherapeutic group: Beta-receptor blocker, selective
ATC code: C07A B02

Metoprolol is a beta1-selective receptor blocker, i.e. metoprolol affects the beta1-receptors of the heart in lower doses than needed to affect beta2-receptors in peripheral vessels and bronchi. At increasing doses the beta1-selectivity may decrease.
Metoprolol has no beta-stimulating effect and has little membrane-stimulating effect. Beta-receptor blockers have negative inotropic and chronotropic effect.
Metoprolol therapy reduces the effect of catecholamines in association with physical and psychic strain and gives lower heart rate, cardiac output and blood pressure. In stress situations with an increased release of adrenaline from the adrenal glands, metoprolol does not prevent the normal physiological vascular dilation. In therapeutic doses, metoprolol has less contractile effect on the bronchial muscles than non-selective beta-blockers. This property enables treatment of patients with bronchial asthma or other pronounced obstructive lung diseases with metoprolol in combination with beta2-receptor stimulants. Metoprolol influences insulin release and carbohydrate metabolism to less extent than non-selective beta-blockers and therefore it can also be given to patients with diabetes mellitus. The cardiovascular reaction in hypoglycaemia, e.g. tachycardia, is less influenced by metoprolol and the return of blood sugar level to normal is faster than for non-selective beta-receptor blockers.
In hypertension, Betawin lowers the blood pressure significantly for more than 24 hours both in lying and standing positions as well as during exercise. In treatment with metoprolol an increase in the peripheral vascular resistance is observed initially. In long-term treatment, however, the obtained lowering in blood pressure may be due to reduced peripheral vascular resistance and unchanged cardiac output. In males with moderate/severe hypertension, metoprolol reduces the risk of cardiovascular death. There is no electrolyte imbalance.
In tachyarrhythmias the effect of increased sympatholytic activity is blocked and this gives a lower heart rate primarily by reduced automatisation in the pacemaker cells, but also through a prolonged supraventricular conduction time.
Betawin has shown fast and effective amelioration of symptoms in thyrotoxicosis. Increased T3-values may be decreased with high dose metoprolol. T4 are not affected.
Metoprolol reduces the risk of reinfarction and cardiac death, especially sudden death after myocardial infarction.

PHARMACOKINETICS:

The bioavailability of Betawin is 40-50%. Maximal beta-blockade is reached after 1-2 hours. After per oral once-daily dosage of 100 mg the effect on the heart rate is still pronounced after 12 hours. Metoprolol is metabolised in the liver mainly by CYP2D6. Three main metabolites have been identified, though none has a beta-blocking effect of clinical importance. The half-life in plasma is 3-5 hours. Metoprolol is excreted to approximately 5% in unchanged form via the kidneys, the remaining dose as metabolites.

INDICATION:

Hypertension: to reduce blood pressure and to reduce the risk of cardiovascular and coronary mortality (including sudden death), and morbidity.
Angina pectoris.
Disturbances of cardiac rhythm including especially supraventricular tachycardia.
Confirmed or suspected myocardial infarction - prevention of cardiac death and reinfarction.
Functional heart disorders with palpitations.
Migraine prophylaxis.
Hyperthyroidism.

RECOMMENDED DOSAGE:

Dosage should be adjusted individually to avoid bradycardia. The tablets should be taken on an empty stomach. Concomitant intake of food increases the bioavailability of metoprolol with 40 %. The following is valid as guidelines:
Hypertension: 100-200 mg daily divided on one or two occasions. The tablets should be taken in the morning if once-daily dosage. In patients not responding to 200 mg, the dose could be combined with other antihypertensive agents, preferably diuretics and calcium antagonists of the dihydropyridine type, or increased.
Angina pectoris: 100-200 mg daily divided on two occasions. If needed, the dose can be combined with nitrates or increased.
Cardiac arrhythmias: 100-200 mg daily divided on two occasions. If needed, other antiarrhythmic agents may be added.
Prophylactic therapy after myocardial infarction: As maintenance dosage, 100 mg morning and evening.
Functional heart disorders with palpitations: 100 mg once daily, given as a single dose in the morning. If needed, the dose can be increased to 200 mg.
Migraine prophylaxis: 100-200 mg daily divided on two occasions.
Hyperthyroidism: The recommended dosage is 150-200 mg daily, divided in 3-4 doses. If needed, the dose can be increased.
Impaired renal function: The elimination rate is insignificantly affected by renal function, and dose adjustment is not needed in patients with impaired renal function.
Impaired hepatic function: Usually Betawin is given in the same dose to patients suffering from liver cirrhosis as to patients with normal liver function. Only, when there are signs of serious impairment of liver function (e.g. shunt-operated patients) a dose reduction should be considered.
Elderly: Dose adjustment is not needed.
Children: There is limited experience with Betawin treatment in children.

ROUTE OF ADMINISTRATION:

Oral

CONTRAINDICATIONS:

1. Cardiogenic shock.
2. Sick-sinus syndrome (provided there is no permanent pacemaker).
3. AV-block of second and third degree.
4. Patients with unstable, decompensated heart failure (pulmonary oedema, hypoperfusion or hypotension), and patients with continuous or intermittent inotropic therapy acting through beta-receptor agonism.
5. Symptomatic bradycardia or hypotension. Metoprolol should not be given to patients with suspected acute myocardial infarction as long as the heart rate is <45 beats/min, the P-Q interval is >0.24 sec or the systolic blood pressure is <100 mm Hg.
6. Serious peripheral vascular disease with gangrene threat.
7. Hypersensitivity to the active substance or to any of the excipients of this product.

WARNINGS & PRECAUTIONS:

Intravenous administration of verapamil should not be given to patients treated with beta-blockers.
Metoprolol may aggravate the symptoms of peripheral arterial circulatory disorders e.g. intermittent claudication. Severely impaired renal function. Serious acute conditions with metabolic acidosis. Combination treatment with digitalis.
Betawin should not be given to patients with latent or manifested heart insufficiency without concomitant treatment. In patients with Prinzmetal's angina the frequency and the extent of angina attacks may increase due to alpha-receptor mediated contraction of the coronary vessels. For this reason non-selective beta-blockers must not be used in these patients. Beta1-selective receptor blockers should be used with caution.
In bronchial asthma or other chronic obstructive lung diseases, adequate bronchodilating therapy should be given concomitantly. The dose of beta2-stimulants may need to be increased.
During treatment with metoprolol the risk for interfering with carbohydrate metabolism or masking hypoglycaemia is less than with non-selective beta-blockers.
Very rarely, a pre-existing AV conduction disorder of moderate degree may become aggravated (possibly leading to AV block).
Treatment with beta-blockers may aggravate the treatment of an anaphylactic reaction. Adrenaline treatment in normal dose does not always give the expected therapeutic effect. If Betawin is given to a patient with phaeochromocytoma, treatment with an alpha-blocker should be considered.
Withdrawal of Betawin should, when possible, be done gradually over 2 weeks. The dose should be reduced gradually until a final dose of 25 mg is reached (half a 50 mg tablet). During this period especially patients with known ischemic heart disease should be kept under close surveillance. The risk for coronary events, including sudden death, may increase during withdrawal of beta-blockers.
Prior to surgery the anaesthetist should be informed that the patient is receiving Betawin. It is not recommended to stop beta-blocker treatment in patients undergoing surgery. Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.
The tablet contains lactose. Patients with any of the following rare hereditary conditions should not use this medicine: galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

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INTERACTION WITH OTHER MEDICAMENTS:

Metoprolol is a CYP2D6-substrate. Drugs that inhibit CYP2D6 can have an effect on the plasma concentration of metoprolol. Examples of drugs that inhibit CYP2D6 are quinidine, terbinafine, paroxetine, fluoxetine, sertraline, celecoxib, propafenon and difenhydramine. When treatment with these drugs are initiated the dose of Betawin might have to be reduced for patients treated with Betawin.

The following combinations with Betawin should be avoided:

Barbituric acid derivatives: Barbiturates (investigated for pentobarbital) induce the metabolism of metoprolol by enzyme induction.

Propafenone: Upon administration of propafenone to four patients on metoprolol therapy, the plasma concentrations of metoprolol increased 2-5 fold and two patients experienced side-effects typical of metoprolol. The interaction was confirmed in eight healthy volunteers. The interaction is probably explained by the fact that propafenone, similarly to quinidine, inhibits the metabolism of metaprolol via cytochrome P450 2D6. The combination is probably difficult to handle since propafenone also has beta-receptor blocking properties.

Verapamil: In combination with beta-receptor blocking drugs (described for atenolol, propranolol and pindolol) verapamil may cause bradycardia and fall in blood pressure. Verapamil and beta-blockers have additive inhibitory effects on AV-conduction and sinus node function.

The following combinations with Betawin may require modified drug dosage:

Amiodarone: A case report suggests that patients treated with amiodarone may develop pronounced sinus bradycardia when treated simultaneously with metoprolol. Amiodarone has extremely long half-life (around 50 days), which implies that interactions can occur for a long time after withdrawal of the drug.

Antiarrythmics, class I: Class I-antiarrythmics and beta-receptor blocking drugs have additive negative inotropic effects which may result in serious haemodynamic side effects in patients with impaired left ventricular function. The combination should also be avoided in "sick sinus syndrome" and pathological AV-conduction. The interaction is best documented for disopyramide.

Non-steroidal anti-inflammatory/antirheumatic drugs: NSAID-antiphlogistics have been shown to counteract the antihypertensive effect of beta-receptor blocking drugs. Primarily, indomethacin has been studied. This interaction probably does not occur with sulindac. A negative interaction study on diclofenac has been performed.

Diphenhydramin: Diphenhydramin decreases (2.5 times) clearance of metoprolol to alpha-hydroximetoprolol via CYP 2D6 in fast hydroxylating persons. The effects of metoprolol are enhanced. Diphenhydramin may probably inhibit the metabolism of other CYP 2D6 substrates.

Digitalis glycosides: Digitalis glycosides in association with beta-blockers, may increase atrioventricular conduction time and may induce bradycardia.

Diltiazem: Diltiazem and beta-receptor blockers have additive inhibitory effects on the AV-conduction and sinus node function. Pronounced bradycardia has been observed (case reports) during combination treatment with diltiazem.

Epinephrine: There are about ten reports on patients treated with non-selective beta-receptor blockers (including pindolol and propranolol) that developed pronounced hypertension and bradycardia after administration of epinephrine (adrenaline). These clinical observations have been confirmed in studies in healthy volunteers. It has also been suggested that epinephrine in local anaesthetics may provoke these reactions upon intravasal administration. The risk is probably less with cardioselective beta-receptor blockers.

Phenylpropanolamine: Phenylpropanolamine (norephedrine) in single doses of 50 mg may increase the diastolic blood pressure to pathological values in healthy volunteers. Propranolol generally counteracts the rise in blood pressure induced by phenylpropanolamine. However, beta-receptor blockers may provoke paradoxical hypertensive reactions in patients who take high doses of phenylpropanolamine. Hypertensive crises during treatment with only phenylpropanolamine have been described in a couple of cases.

Quinidine: Quinidine inhibits the metabolism of metoprolol in so-called rapid hydroxylators (more than 90% in Sweden) with markedly elevated plasma levels and enhanced beta-blockade as a result. A corresponding interaction might occur with other beta-blockers metabolised by the same enzyme (cytochrome P450 2D6).

Clonidine: The hypertensive reaction when clonidine is suddenly withdrawn may be potentiated by beta-blockers. If concomitant treatment with clonidine is to be discontinued, the beta-blocker medication should be withdrawn several days before clonidine.

Rifampicin: Rifampicin may induce the metabolism of metoprolol resulting in decreased plasma levels.

Patients receiving concomitant treatment with other beta-blockers (i.e. eye drops) or MAO-inhibitors should be kept under close surveillance. In patients receiving beta-receptor blocker therapy, inhalation anaesthetics enhance the cardio-depressant effect. The dosages of oral antidiabetics may have to be readjusted in patients receiving beta-blockers. The plasma concentration of metoprolol can increase when cimetidine or hydralazine are administered simultaneously.

USE IN PREGNANCY & LACTATION:

Use in pregnancy: Betawin should not be given during pregnancy and lactation unless its use is considered essential. In general, beta-blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion and early labour. It is therefore suggested that appropriate maternofetal monitoring be performed in pregnant women treated with metoprolol.

Beta-receptor blockers may cause bradycardia, in the foetus and in the newborn infant. This should be considered if these drugs are prescribed in the last trimester and in association with delivery.

Betawin should gradually be withdrawn 48-72 hours before planned childbirth. If this is not possible the newborn infant should be supervised during 48-72 hours postpartum for signs and symptoms of beta blockade (e.g. heart and lung complications).

Use during lactation: Metoprolol is concentrated in human breast milk in a quantity that corresponds to approximately three times the quantity found in the plasma of the mother. The risk for harmful reactions with respect to the breast-feeding child seems to be low at therapeutic doses of the medicine. The breast-feeding child should however be observed regarding signs of beta blockade.

SIDE EFFECTS:

Adverse reactions occur in approximately 10% of the patients and they are usually dose-related.

Heart

Common: Bradycardia, palpitations

Less common: Chest pain, transient aggravation of heart failure, cardiogenic shock in patients with acute myocardial infarction.

Rare: Prolonged AV-conduction time, cardiac arrhythmias.

Blood and lymphatic system

Rare: Thrombocytopenia.

Central and peripheral nervous system

Common: Dizziness, headache.

Less common: Paraesthesia.

Eyes

Rare: Visual disturbances, dry and/or irritated eyes.

Frequency unknown: Conjunctivitis.

Ear and balance organ

Rare: Tinnitus.

Respiratory

Common: Shortness of breath when physically active.

Less common: Bronchospasm in patients with bronchial asthma or asthmatic problems.

Frequency unknown: Rhinitis.

Gastrointestinal

Common: Abdominal pain, nausea, vomiting, diarrhea, constipation.

Rare: Taste changes.

Frequency unknown: Dry mouth.

Skin and subcutaneous tissue

Less common: Hypersensitivity reactions in the skin.

Rare: Aggravated psoriasis, photosensitivity reactions, hyperhidrosis, hair loss.

Musculoskeletal system and connective tissue

Frequency unknown: Muscle cramps, arthralgia.

Vascular

Common: Peripheral coldness in extremities.

Rare: Syncope.

Frequency unknown: Gangrene in patients with severe peripheral vascular disorders.

General symptoms and/or symptoms at administration site

Very common: Fatigue.

Less common: Oedema, weight gain.

Liver and biliary tracts

Rare: Elevated transaminases.

Frequency unknown: Hepatitis.

Reproductive organs and mammary glands

Rare: Reversible libido dysfunction.

Psychiatric disorders

Less common: Depression, nightmares, sleeping disturbance.

Rare: Memory impairment, confusion, hallucinations, nervousness, anxiety.

Frequency unknown: Impaired concentration ability.

Effect on ability to drive and use machines

As dizziness and fatigue may occur in Betawin treatment, this should be considered when strict attention is required, e.g. when driving or operating machines.

SYMPTOMS AND TREATMENT OF OVERDOSE:

Toxicity

7.5 g to an adult caused lethal intoxication. 100 mg to a 5-year old gave no symptoms after gastric lavage. 450 mg to a 12-year old and 1.4 g to an adult gave moderate intoxication, 2.5 g to an adult caused serious intoxication, and 7.5 g to an adult gave very serious intoxication.

Symptoms

Cardiovascular symptoms are most important, but in some cases, especially in children and young individuals, CNS symptoms and respiratory depression may dominate. Bradycardia, AV-block I-III, QT-prolongation (exceptional cases), asystole, fall in blood pressure, poor peripheral perfusion, cardiac insufficiency, cardiogenic shock. Respiratory depression, apnoea. Others: Fatigue, confusion, unconsciousness, fine tremor, cramps, perspiration, paraesthesiae, bronchospasm, nausea, vomiting, possibly oesophageal spasm, hypoglycaemia (especially in children) or hyperglycaemia, hyperkalaemia. Effect on the kidneys. Transient myasthenic syndrome. Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates may aggravate the patient's condition. The first signs of overdosing may be seen 20 minutes to 2 hours after ingestion.

Management

Care should be provided at a unit that can offer suitable support measures, monitoring and supervision.

If justified, gastric lavage and/or activated charcoal can be used.

Atropine, adrenoceptor stimulant or pacemaker for treatment of bradycardia and conduction disorders.

Intubation and mechanical ventilation should be done with very broad indication. Pacemaker is option. With circulatory arrest in connection with overdose, resuscitation measures for several hours may be warranted.

Hypotension, acute myocardial infarction and shock to be treated with appropriate volume expansion, administration of glucagon (followed by intravenous infusion of glucagon if necessary), intravenous administration of an adrenoceptor stimulant, such as dobutamine, with the addition of α1 receptor agonists upon vasodilation. Intravenous use of Ca^{2+} may also be considered.

Bronchospasm can usually be reversed by bronchodilators.

STORAGE CONDITIONS:

Store below 30˚C. Protect from light. Keep out of reach of children. *Jauhkan daripada kanak-kanak.*

Consume within 6 months after opening the pouch.

SHELF LIFE:

Please refer to outer package.

PACK SIZE:

Blister pack of 10 x 10's and 50 x 10's tablets.

PRODUCT REGISTRATION HOLDER & MANUFACTURER:

DUOPHARMA (M) SDN BHD
Lot 2599, Jalan Seruling 59 Kawasan 3,
Taman Klang Jaya, 41200 Klang, Selangor, MALAYSIA.

15000

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