

BETAC 20 mg Film-coated Tablets

Betaxolol Hydrochloride

COMPOSITION AND PHARMACEUTICAL FORM

Each 'Betac' 20mg tablet contains 20mg Betaxolol hydrochloride.

'Betac' 20mg tablets are film-coated tablets for oral administration.

DESCRIPTION

Film-coated, white, round, convex, scored tablet with nucleus diameter of 9.5 mm.

INDICATIONS

- Hypertension
- Prophylaxis of exertional angina episodes

DOSAGE AND ADMINISTRATION:

The usual dosage for the two therapeutic indications is one tablet of 20 mg per day, taken once daily.

Dosage in patients with renal insufficiency:

It is advisable to adjust the dosage according to the state of the renal function; for a creatinine clearance over 20 ml/min, it is not necessary to change the dosage. However, clinical monitoring is recommended at the start of the treatment until the equilibration of blood levels is reached (4 days on average).

In case of severe renal insufficiency (creatinine clearance < 20 ml/min), the initial recommended dose is 10 mg/day (taken irrespective of the frequency and timing of dialysis sessions for dialysed patients).

In patients with hepatic insufficiency, no modification of the dosage is necessary, though clinical monitoring is advised at the start of treatment.

CONTRA-INDICATIONS:

- Severe forms of asthma and chronic obstructive pulmonary disease
- Cardiac insufficiency not controlled with treatment
- Cardiogenic shock
- Second and third-degree atrioventricular blocks, without pacemakers
- Prinzmetal's angina (as monotherapy in its isolated/typical form)
- Sinus node dysfunction (including sinoatrial block)
- Bradycardia (<45-50 beats per minute)
- Severe forms of Raynaud's phenomenon and peripheral arterial disorders
- Untreated pheochromocytoma
- Hypotension
- Hypersensitivity to betaxolol

- Previous history of anaphylactic reaction
- In combination with floctafenine and sultopride (see interactions with other medicinal products and other forms of interaction)
- The use of this medicine is generally in combination with amiodarone, bepridil, diltiazem and verapamil (see interactions with other medicinal products and other forms of interaction), and while breast-feeding

WARNINGS & PRECAUTIONS:

Warnings

Lactose

Due to the presence of lactose, this medicinal product is contraindicated in the event of congenital galactosaemia, glucose/galactose malabsorption or lactase deficiency syndrome.

Precautions

Discontinuation of the treatment

Treatment should not be suddenly interrupted, particularly in patients with coronary heart disease. The dosage should be decreased progressively, over one or two weeks, while at the same time initiating, if necessary, substitution therapy to prevent worsening of the angina.

Asthma and chronic obstructive pulmonary disease

Beta-blockers may only be administered in mild forms of these conditions, using a beta-1 selective blocker at an initially low dose.

It is recommended to have pulmonary function tests performed before beginning treatment. In case of an attack while undergoing treatment, beta-mimetic bronchodilators may be used.

Cardiac insufficiency

In patients with cardiac insufficiency which is controlled with treatment, and when necessary, betaxolol should be administered at very low doses and then progressively increased under strict medical monitoring.

Bradycardia

If the heart rate decreases to less than 50-55 beats per minute at rest and the patient exhibits bradycardia-related symptoms, the dosage should be reduced.

First-degree atrio ventricular block

Given the negative dromotropic effect of beta-blockers, betaxolol should only be administered with caution to patients with first-degree atrioventricular block.

Prinzmetal's angina

Beta-blockers can increase the number and duration of angina episodes in patients with Prinzmetal's angina. The use of a beta-1 cardioselective beta-blocker is possible in mild and related forms provided that it is administered concomitantly with a vasodilator.

Peripheral arterial disorders

In patients with peripheral arterial disorders (Raynaud's disease or phenomenon, arteritis or chronic obliterating arteriopathies of the lower limbs), the use of beta-blockers can worsen these conditions. In these situations, it is advisable to use a cardio-selective beta-blocker with partial agonist potential, which shall be administered with caution.

Phaeochromocytoma

The use of beta-blockers in the treatment of hypertension due to treated pheochromocytoma requires close monitoring of arterial blood pressure.

Children

The safety and efficacy of betaxolol in children have not been established; therefore, the use of betaxolol in children is inadvisable.

Elderly patients (see Dosage and method of administration)

In elderly patients, it is imperative to strictly comply with the contraindications. Treatment should be initiated at a low dosage and closely monitored.

Renal insufficiency (see Dosage and method of administration)

In case of renal insufficiency, it is advisable to adjust the dosage according to the serum creatinine levels or the creatinine clearance.

Diabetic patients (see interactions with other medicinal products and other forms of interaction and undesirable effects)

Instruct the patient and reinforce self-monitoring of blood glucose at the start of treatment. The warning signs of hypoglycaemia may be masked, particularly tachycardia, palpitations and sweats.

Psoriasis (see Undesirable effects)

As exacerbations of the disorder have been reported with the use of beta-blockers, the indication of use should be carefully considered.

Allergic reactions

In patients with a risk of any severe anaphylactic reaction, particularly to floctafenine (see Interaction with other medicinal products and other forms of interaction), or in those receiving drug desensitisation treatments, treatment with beta-blockers may lead to an exacerbation of the reaction and resistance to its treatment with adrenaline at the usual doses.

General anaesthesia

Beta-blockers result in a reduction of reflex tachycardia and an increased risk of hypotension. Continuation of treatment with beta-blockers reduces the risk of arrhythmias, myocardial ischaemia and hypertensive episodes. It is advisable to inform the anaesthetist that the patient is being treated with beta-blockers. If the discontinuation of treatment is deemed necessary, a 48-hour interruption is considered sufficient to restore catecholamine sensitivity.

Beta-blocker treatment may not be interrupted in certain cases:

- in patients with coronary insufficiency, it is advisable to continue treatment until the intervention, given the risks involved with the sudden withdrawal of beta-blockers
- in case of emergency or the impossibility of stopping treatment, the patient should be protected from a predominant vagal reaction by sufficient premedication with atropine, repeated as necessary. The anaesthetist should use products with as little myocardial depressant effects as possible and blood loss should be compensated for. The anaphylactic risk should be taken into account.

Thyrotoxicosis

Beta-blockers may mask the cardiovascular signs.

Athletes

Athletes should take note of the fact that this product contains an active substance which may induce a positive reaction in tests performed during antidoping controls.

INTERACTIONS

Numerous medicines can induce bradycardia. These include beta-blockers, class Ia antiarrhythmics (quinidine, disopyramide), amiodarone and sotalol in the class III antiarrhythmics, diltiazem and verapamil in the class IV antiarrhythmics, and digitalis glycosides, clonidine, guanfacine, mefloquine and anticholinesterase agents indicated in the treatment of Alzheimer's disease.

Contraindicated combinations

+ Floctafenine

In case of shock or hypotension due to floctafenine, there is a reduction of the compensatory cardiovascular reactions by beta-blockers.

+ Sultopride

Automatism disorders (excessive bradycardia) due to additive bradycardiac effects. Inadvisable combination

+ Calcium antagonist (bepridil, diltiazem and verapamil)

Automatism disorders (excessive bradycardia, sinus arrest), sinoatrial and atrioventricular conduction disturbances and cardiac failure (synergistic effects). Such combination should only be carried out under close clinical and electrocardiographic monitoring, particularly in elderly patients or at the start of the treatment.

+ *Amiodarone*

Contractility, automatism and conduction disorders (suppression of compensatory sympathetic mechanisms), Combinations requiring precautions for use.

+ *Volatile halogenated anaesthetics*

Reduction of compensatory cardiovascular reactions by beta-blockers. (The beta-adrenergic inhibition may be alleviated during the intervention with beta-stimulants). As a general rule, do not discontinue beta-blocker treatment and, in any case, do not withdraw it abruptly. Inform the anaesthetist of this treatment.

+ *Medicines which may cause torsades de pointes (apart from sultopride): Class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide), Class III antiarrhythmics (amiodarone, dofetilide, ibutilide, sotalol), Some phenothiazine neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine), Benzamides (amisulpride, sulpiride, tiapride), Butyrophenones (droperidol, haloperidol) and other medicines (cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, moxifloxacin, spiramycin IV, vincamine IV).*

Concomitant use increases the risk of ventricular arrhythmias, particularly torsades de pointes (hypokalaemia is a contributing factor). Clinical and electrocardiographic monitoring is recommended.

+ *Propafenone*

Contractility, automatism and conduction disorders (suppression of compensatory sympathetic mechanisms). Clinical and electrocardiographic monitoring is recommended.

+ *Baclofen*

Increased antihypertensive effect. Blood pressure monitoring and dosage adjustment of the antihypertensive agent, if necessary.

+ *Insulin, sulfonylurea hypoglycaemic agents (see Special warning and special precaution/or use)*

All beta-blockers may mask certain symptoms of hypoglycaemia, particularly palpitations and tachycardia. The patient should be instructed to reinforce self-monitoring of blood glucose, especially at the start of treatment.

+ *Anticholinesterase agents (ambenonium, donepezil, galantamine, neostigmine, pyridostigmine, rivastigmine, tacrine)*

Risk of excessive bradycardia (additive bradycardic effects). Regular clinical monitoring is recommended.

+ *Centrally acting antihypertensive agents (clonidine, apraclonidine, alphas-methyldopa, guanfacine, moxonidine, rilmenidine)*

Significant blood pressure increase in case of sudden withdrawal of the centrally acting antihypertensive treatment. Avoid sudden withdrawal of the centrally acting antihypertensive treatment. Clinical monitoring is recommended.

+ *Lidocaine by IV route*

Increased plasma levels of lidocaine with possible increase in neurological and cardiac adverse effects (reduced hepatic clearance of lidocaine).

Clinical and electrocardiographic monitoring, and, if appropriate, monitoring of lidocaine plasma concentrations during combination therapy and after discontinuation of the beta-blocker, are recommended. Adjustment of the lidocaine dosage, if necessary.

Combinations to be taken into account:

+ *NSAIDs (systemic route), including selective COX-2 inhibitors*

Reduction of the antihypertensive effect (inhibition of vasodilating prostaglandins by the NSAIDs and sodium and water retention with the pyrazole NSAIDs).

+ *Calcium antagonists (dihydropyridine)*

Hypotension and heart failure in patients with latent or uncontrolled cardiac insufficiency. Beta-blockers may also minimise the reflex sympathetic response that occurs in the event of excessive haemodynamic changes.

+ *Imipraminic antidepressants, neuroleptics*

Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effects).

+ *Mefloquine*

Risk of bradycardia (additive bradycardiac effects)

+ *Dipyridamole (IV route)*

Increased antihypertensive effect.

+ *Alpha blockers, for urological use (alfuzosin, doxazosin, prazosin, tamsulosin, terazosin)*

Increased antihypertensive effects.

Increased risk of orthostatic hypotension.

+ *Amifostine*

Increased antihypertensive effect.

PREGNANCY AND LACTATION:

Pregnancy:

Teratogenic aspect.

Animal studies have not demonstrated any teratogenic effect. In humans, no teratogenic effect has been reported to date and the results of controlled prospective studies have not shown malformations at birth.

Neonatal aspect.

In neonates of treated mothers, the beta-blocking action persists for several days after birth. Though this residual effect may have no clinical consequences, it is nevertheless possible that cardiac failure may

occur. This would require hospitalisation in intensive care (see overdose), in which replacement fluids should be avoided (risk of acute pulmonary oedema). In addition, bradycardia, respiratory distress and hypoglycaemia have been reported, therefore careful monitoring of the neonate (cardiac rate and serum glucose during the first 3 to 5 days of life) is recommended in a specialised setting.

Lactation:

Betaxolol is excreted in breast milk. The risk of the occurrence of hypoglycaemia and bradycardia has not been evaluated therefore, as a precaution, breast-feeding is inadvisable during treatment.

EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINERIES:

The ability to drive or use machinery is not affected.

ADVERSE REACTIONS

Clinical aspects

Those most frequently reported are:

- *Asthenia*
- *Cool extremities*
- *Bradycardia, possibly severe*
- *Digestive disorders (gastralgiyas, nausea, vomiting)*
- *Impotence*
- *Insomnia*

Much more infrequent:

- Slowing of the atrioventricular or worsening of a pre-existing atrioventricular block
- Cardiac insufficiency
- A drop in blood pressure
- Bronchospasm
- Hypoglycaemia
- Raynaud's syndrome
- Aggravation of pre-existing intermittent claudication
- Various cutaneous manifestations including psoriasis-like rashes or psoriasis exacerbation (see special warnings and special precautions for use)
- Paresthesia
- Eye dryness
- Nightmares

Biological aspects

The rare occurrence of antinuclear antibodies has been observed. These are only exceptionally associated with clinical manifestations of the sort of lupus syndrome and cease with the discontinuation of treatment.

OVERDOSE:

In case of bradycardia or excessive decrease in blood pressure, the administration of the following is required:

- atropine, 1-2 mg IV
- glucagon, 1 mg, repeated if necessary
- followed by, if necessary, isoprenaline 25µg by slow injection or dobutamine 2.5 to 10 µg/kg/min.

In case of cardiac decompensation in the neonate of a mother treated with beta-blockers:

- glucagon, at a dose of 0.3 mg/kg
- hospitalisation in an intensive care unit
- isoprenaline and dobutamine. As the dosages are generally high and the treatment prolonged, specialised monitoring is required.

PHARMACOLOGY:

Pharmacodynamics

Pharmacotherapeutic group: β_1 selective adrenergic receptor blocking agent

Betaxolol is a cardioselective beta-adrenoceptor blocking agent. The drug is characterized by a long duration of action, no intrinsic sympathomimetic activity, weak membrane stabilizing activity, and low lipid solubility.

Pharmacokinetics

Absorption

Following oral administration betaxolol HCl is absorbed almost completely from the gastrointestinal tract.

The bioavailability of the drug ranges between 78% - 90%, and the administration with food has not been shown to affect the rate or extent of absorption. Also, the concomitant administration of alcohol does not affect the absorption.

Distribution

Peak serum concentrations are achieved in about 3 hours after a single oral dose (range 1.6 to 6 hours). Therapeutic drug concentration for beta-blocking activity is 0.005 to 0.05 mcg/ml. Total protein binding is between 50-60%.

Steady state plasma concentrations are achieved after 5 to 7 days with a once a day dosage schedule. Forty-two percent is bound to albumin and the remainder to alpha-1-glycoprotein. No significant change in the extent of plasma protein binding was observed in patients with renal or hepatic disease.

Also, betaxolol rapidly crosses the placenta and equilibrium (ratio approximately 1) between cord and maternal vein blood is reached in 4 to 6 hours after dosing. Volume of distribution is 4.0 to 13 l/kg.

Metabolism

Betaxolol undergoes extensive hepatic metabolism and the metabolites are inactive.

The elimination half-life of the parent compound ranges between 14 to 22 hours. The half-life is prolonged in severe renal failure.

Elimination

Approximately 15 % of a dose is recovered in the urine as unchanged drug and the remainder is metabolites. 80% of the dose is excreted in urine. Renal clearance is between 0.2 and 0.34 L/kg/hour.

Concentrations in breast milk are high, being about 3 times greater than in blood. The milk to plasma ratio ranges from 2.5 to 3.

Betaxolol hydrochloride is dialyzable by hemodialysis or peritoneal dialysis.

TOXICOLOGY

Its long-term administration in several animal species has shown that betaxolol is well tolerated and that it has a wide therapeutic safety margin. The oral LD50 is 350 to 400 mg betaxolol/kg in mice and 860 to 980 mg/kg in rats.

When betaxolol is administered to pregnant animals at doses 600 times more than the maximum recommended human dose, it increased post-implantation loss, reduced litter size and weight, and an increased incidence of skeletal and visceral abnormalities was observed. At lower doses (up to 60 times the maximum recommended human dose), no foetal abnormalities were observed.

Betaxolol did not adversely affect fertility or mating performance of male and female rats at doses up to 380 times more than the maximum recommended human dose.

No evidence of carcinogenic potential was shown when betaxolol HCl was administered in mice at doses up to 72 times more than the maximum recommended human dose. *In vivo* and *in vitro* tests revealed no mutagenic potential of the drug.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS: ‘Betac’ 20mg tablets also contain: lactose, cellulose microcrystalline, sodium starch glycolate, colloidal anhydrous silica, magnesium stearate, titanium oxide (E171), hypromellose, polyethylene glycol 400.

INCOMPATIBILITIES: None known.

SHELF LIFE: 36 months after the production date

STORAGE CONDITIONS: Store below 30°C in the original package, in order to protect from light and moisture.

PACKAGING

Boxes of 30 and 100 tablets. Tablets are packed in PVC-Al blisters of 10 tablets.

NAME & ADDRESS OF MANUFACTURER:

Medochemie (Far East) Ltd., (Solid Oral Facility), No 40 Street 6 Vietnam Singapore Industrial Park II Binh Duong Ward, Ho Chi Minh, Vietnam

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