ATEHEXAL® 25 / 50 / 100 Film-coated tablets

DESCRIPTION
Each **Atehexal®** 25, 50, 100 film-coated tablet contains atenolol 25mg, 50mg and 100mg respectively.

PHARMACODYNAMICS
Atenolol is a long acting β_1-selective (cardioselective) adrenoceptor blocking drug and acts by competitively blocking the adrenergic stimulation of β-adrenoceptors within the myocardium and within vascular smooth muscle. At high doses (e.g. greater than 100mg daily), the selectivity of atenolol for β_1-adrenoceptors usually diminishes, resulting in competitive blocking of β_1- and β_2-adrenoceptors. Atenolol has no intrinsic sympathomimetic activity (ISA) or membrane stabilizing properties.

It has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure).

The mechanism of action of atenolol in the treatment of hypertension is not clear. Some of the theories include suggestions that the decrease in blood pressure is due to a decrease in cardiac output, the suppression of renin release, some degree of interference with central sympathetic outflow, and possibly prevention of neurotransmitter release and presynaptic receptors.

Atenolol is effective for at least 24 hours after a single oral dose. The drug facilitates compliance by its acceptability to patients and simplicity of dosing. The narrow dose range and early patient response ensure that the effect of the drug in individual patients is quickly demonstrated. Atenolol is compatible with diuretics, other hypotensive agents and antianginal agents. Since it acts preferentially on β_1-receptors in the heart, atenolol may, with care, be used successfully in the treatment of patients with respiratory disease, who cannot tolerate non-selective β-blockers.

PHARMACOKINETICS
Absorption
About 50% of an oral dose of atenolol is absorbed. Peak plasma concentrations occur in 2 to 4 hours. The atenolol blood levels are consistent and subject to little variability. Food decreases bioavailability of atenolol by 20%.

Distribution
It crosses the placenta and is distributed into breast milk where concentrations higher than those in maternal plasma have been achieved. Atenolol penetrates tissues poorly due to its low lipid solubility. Only small amounts are reported to cross the blood-brain barrier, and plasma-protein binding is minimal (approximately 3%).

Metabolism
Atenolol undergoes little or no hepatic. More than 90% of that absorbed reaches the systemic circulation unaltered.

Excretion
The plasma half-life is about 6 to 7 hours but this can be significantly increased in patients with renal insufficiency since the kidney is the major route of elimination.

The majority of a dose is excreted unchanged in the urine; 40% to 50% of an oral dose is excreted unchanged in the urine, with excretion being independent of urinary pH. Approximately 50% of an oral dose is excreted unchanged in the faeces. Atenolol is dialyzable.

INDICATIONS
Atehexal® is indicated in the treatment of :
i) Hypertension
ii) Angina pectoris
iii) Cardiac arrhythmias
iv) Myocardial infarction. Early and late intervention

CONTRAINDICATIONS
Atenolol, as with other beta-blockers, should not be used in patients with any of the following:
- known hypersensitivity to atenolol or any component of the product
- bradycardia (<45bpm)
- cardiogenic shock
- second or third degree heart block
- uncontrolled heart failure
- hypotension
- metabolic acidosis
- severe peripheral arterial circulatory disturbances
- sick sinus syndrome
- untreated phaeochromocytoma

SIDE EFFECTS/ ADVERSE REACTIONS
The frequency of possible side effects listed below are defined as: Very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥1/1.000, <1/100), rare (≥1/10.000, <1/1.000), very rare (< 1/10.000), not known (frequency cannot be estimated from the available data).

Blood and lymphatic system disorders
Rare: purpura, thrombocytopenia

Psychiatric disorders
Uncommon: sleep disturbances
Rare: mood changes, nightmares, confusion, psychoses and hallucinations

Nervous system disorders
Rare: dizziness, headache, paresthesia

Eye disorders
Rare: dry eyes, visual disturbances

Cardiac disorders
Common: bradycardia
Rare: heart failure deterioration, precipitation of heart block

Vascular disorders
Common: cold extremities
Rare: postural hypotension which may be associated with syncope, intermittent claudication may be increased if already present, in susceptible patients Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders
Rare: bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints

Gastrointestinal disorder
Common: gastrointestinal disturbances
Rare: dry mouth
Not known: constipation

Hepatobiliary disorders
Uncommon: elevations of transaminase levels
Rare: hepatic toxicity including intrahepatic cholestasis

Skin and subcutaneous tissue disorders
Rare: alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes
Not known: hypersensitivity reactions, including angioedema and urticarial

Reproductive system and breast disorders
Rare: impotence

General disorders and administration site conditions
Common: fatigue

Investigations
Very rare: An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear

PRECAUTIONS / WARNINGS
Abrupt withdrawal of atenolol in coronary artery disease, may exacerbate angina pectoris or cause myocardial infarction or ventricular arrhythmias. The dosage should be withdrawn gradually over a period of 7-14 days, to facilitate a reduction in beta-blocker dosage. Patients should be followed during withdrawal, especially those with ischaemic heart disease.

When a patient is scheduled for surgery, and a decision is made to discontinue beta-blocker therapy, this should be done at least 24 hours prior to the procedure. The risk-benefit assessment of stopping beta-blockade should be made for each patient. If treatment is continued, an anaesthetic with little negative inotropic activity should be selected to minimise the risk of myocardial depression.

The patient may be protected against vagal reactions by intravenous administration of atropine.

Although contraindicated in uncontrolled heart failure *(see Contraindication)*, may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

May increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Atenolol is a $beta_1$-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.

Although contraindicated in severe peripheral arterial circulatory disturbances *(see Contraindication)*, may also aggravate less severe peripheral arterial circulatory disturbances.

Caution must be exercised if it is given to patients with first degree heart block.

Possibility of masked symptoms of hypoglycaemia, in particular, tachycardia.

May mask the signs of thyrotoxicosis (eg, tachycardia). Abrupt withdrawal may precipitate thyroid storm.

Will reduce heart rate, as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate and the pulse rate drops to less than 50-55 bpm at rest, the dose should be reduced.

May cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. These patients may be more reactive to rechallenge during therapy but may not respond to usual doses of adrenaline. May cause a hypersensitivity reaction including angioedema and urticaria.

The safety and efficacy of atenolol in children have not been established.

Should be used with caution in the elderly, starting with a lesser dose.

Dosage should be reduced in patients with a creatinine clearance of below 35ml/min/1.7m^2.

Atenolol should be avoided in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use. Where such reasons exist, atenolol may be used with caution. Occasionally, some increase in airways resistance may occur in asthmatic patients, however, and this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline.

Withdrawal of concomitant clonidine therapy; atenolol may increase risk of rebound hypertension; atenolol should be discontinued several days before clonidine is withdrawn.

As with other beta-blockers, in patients with a phaeochromocytoma, an alpha-blocker should be given concomitantly.

Effect on ability to drive or operate machinery
Use is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However it should be taken into account that occasionally dizziness or fatigue may occur.

PREGNANCY AND LACTATION
Atenolol crosses the placental barrier and appears in the cord blood. No studies have been performed on the use of atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of atenolol to pregnant women in the management of mild to moderate hypertension has been associated with intra-uterine growth retardation. Caution should be exercised when atenolol is administered during pregnancy or to a woman who is breast-feeding.

The use of atenolol in women who are, or may become, pregnant requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters, since beta-blockers, in general, have been associated with a decrease in placental perfusion which may result in intra-uterine deaths, immature and premature deliveries.

Lactation
There is significant accumulation of atenolol in breast milk. Neonates born to mothers who are receiving atenolol at parturition or breast-feeding may be at risk of hypoglycaemia and bradycardia.

Caution should be exercised when atenolol is administered during pregnancy or to a woman who is breast-feeding.

DRUG INTERACTIONS
Combined use of beta-blockers and calcium channel blockers with negative inotropic effects, e.g. verapamil and diltiazem, can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sinoatrial or atrioventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridines, e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Digitalis glycosides, in association with beta-blockers, may increase atrioventricular conduction time. Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have a potentiating effect on atrial-conduction time and induce negative inotropic effect.

Concomitant use of sympathomimetic agents, e.g. adrenaline (epinephrine), may counteract the effect of beta-blockers.

Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs. Symptoms of hypoglycaemia, particularly tachycardia, may be masked (see *Warning and Precautions*).

Concomitant use of prostaglandin synthetase-inhibiting drugs, e.g. ibuprofen and indometacin, may decrease the hypotensive effects of beta-blockers.

Caution must be exercised when using anaesthetic agents with atenolol. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

Concomitant use of baclofen may increase the antihypertensive effect making dose adjustments necessary.

RECOMMENDED DOSAGE
Dosage of **Atehexal®** tablets must be individualized according to patient's response and tolerance.

The dose must always be adjusted to individual requirements of the patients, with the lowest possible starting dosage so that heart failure, bradycardia and bronchial symptoms are noticed timely.

Adults

Hypertension
Once daily. Most patients respond to 100 mg daily given orally as a single dose. Some patients, however, will respond to 50 mg given as a single daily dose. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining **Atehexal®** with other antihypertensive agents. For example, co-administration of **Atehexal®** with a diuretic, provides a highly effective and convenient antihypertensive therapy.

Angina
Most patients with angina pectoris will respond to 100 mg given orally once or 50 mg given twice daily. It is unlikely that additional benefit will be gained by increasing the dose.

Cardiac Arrhythmias
Initially controlled intravenously. Having controlled the arrhythmias with intravenous atenolol, a suitable oral maintenance dosage is 50-100 mg daily, given as a single dose.

Myocardial Infarction
In suitable patients, initially controlled intravenously, followed by atenolol 50 mg orally about 15 minutes later, provided no untoward effects have occurred from the intravenous dose. This should be followed by a further 50 mg orally 12 hours after the intravenous dose and then 12 hours later by 100 mg orally, once daily. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, atenolol should be discontinued. Late intervention after acute myocardial infarction: For patients who present some days after suffering an acute myocardial infarction an oral dose of atenolol (100 mg daily) is recommended for long-term prophylaxis of myocardial infarction.

Elderly
Dosage requirements may be reduced, especially in patients with impaired renal function.

Children
There is no paediatric experience with atenolol and for this reason it is not recommended for use in children.

Renal Failure
Since atenolol is excreted via the kidneys the dosage should be reduced in cases of severe impairment of renal function. No significant accumulation of atenolol occurs in patients who have a creatinine clearance greater than 35 ml/min/1.73 m^2 (normal range is 100 - 150 ml/min/1.73m^2). For patients with a creatinine clearance of 15 - 35 ml/min/1.73m^2 (equivalent to serum creatinine of 300 - 600micromole/litre) the oral dose should be 50 mg daily. For patients with a creatinine clearance of <15 ml/min/1.73m^2 (equivalent to serum creatinine of >600 micromole/litre) the oral dose should be 25 mg daily or 50 mg on alternate days.

Patients on haemodialysis should be given 50 mg orally after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

There is no need to modify the dosage of **Atehexal®** in liver disease.

MODE OF ADMINISTRATION
For oral administration.

SYMPTOMS AND TREATMENTS OF OVERDOSE
The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision; treatment in an intensive care ward; the use of gastric lavage; activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract; the use of plasma or plasma substitutes to treat hypotension and shock. The possible uses of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be countered with atropine 1 – 2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1–10 mg/hour depending on response.

If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased.

if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

PACKING / PACK SIZES
Blister pack of 10 tablets per strip. Box of 30, 50 and 100 film-coated tablets.

STORAGE CONDITIONS, USER INSTRUCTION & PHARMACEUTICAL PRECAUTIONS
Store in a cool, dry place below 30°C.
Protect from heat, light and moisture.
Keep out of reach of children.
Jauhi daripada kanak-kanak.

SHELF LIFE: Please refer to the outer box label.

Manufactured by:
Salutas Pharma GmbH
Otto-von-Guericke-Allee 1,
39179 Barleben, Germany

For:
HEXAL AG
Industriestraβe 25
D-83607 Holzkirchen
Germany.

Date of Revision: 1 June 2017