SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atenolol Denk 50

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: atenolol
Each film-coated tablet contains 50 mg atenolol.

Excipients with known effect:
Each film-coated tablet contains 5 mg lactose monohydrate and less than 1 mmol sodium (23 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White, oblong film-coated tablet with both-sided score, without imprint.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Cardiovascular function disorders (hyperkinetic heart syndrome, hypertensive dysregulation)

Chronic stable angina pectoris or unstable angina pectoris (in the presence of concomitant tachycardia or hypertension)

Supraventricular arrhythmias
- additional therapeutic measure in thyrotoxicosis-associated sinus tachycardia
- paroxysmal supraventricular tachycardia
- atrial fibrillation and atrial flutter (when response to high-dose therapy with cardiac glycosides is inadequate)

Ventricular arrhythmias such as
- ventricular extrasystoles if these are the result of increased sympathetic activity (physical exercise, induction phase of anaesthesia, halothane anaesthesia and administration of exogenous sympatho-mimetics)
- ventricular tachycardias and ventricular fibrillation (prophylactic treatment only, especially when the ventricular arrhythmias are the result of elevated sympathetic activity)

Hypertension

4.2. Posology and method of administration

Posology
The dosage should be established for each patient individually based on the success of the treatment. The following dosing guidelines apply:

Cardiovascular function disorders (hyperkinetic heart syndrome, hypertensive dysregulation)
25 mg atenolol once daily (equivalent to ½ film-coated tablet of Atenolol Denk 50)

Chronic stable angina pectoris or unstable angina pectoris
50 mg-100 mg atenolol once daily (equivalent to 1-2 film-coated tablets of Atenolol Denk 50). A further increase in dose will probably not provide any increase in efficacy.

Hypertension
Induction of treatment with 50 mg atenolol once daily (equivalent to 1 film-coated tablet of Atenolol Denk 50). If necessary, the daily dose may be increased after one week to 100 mg atenolol (equivalent to 2 film-coated tablets of Atenolol Denk 50). The full effect is obtained after one to two weeks. Blood pressure may be further reduced by combining Atenolol Denk with other antihypertensive agents.

Supraventricular and ventricular arrhythmias
50 mg once or twice daily or 100 mg atenolol once daily (equivalent to 1-2 film-coated tablets of Atenolol Denk 50 or 2 film-coated tablets of Atenolol Denk 50).

Impaired renal function
In patients with impaired renal function the dose of atenolol must be adapted to renal clearance since atenolol is excreted via the kidneys:
If creatinine clearance is reduced to levels of 10-30 mL/min (serum creatinine > 1.2 and < 5 mg/dL) a dose reduction to half the standard dose and at levels < 10 mL/min (serum creatinine > 5 mg/dL) a dose reduction to one quarter is recommended.

Elderly patients
A reduction in dose may be considered, particularly in patients with impaired renal function.

Children
Since there is no experience with the use of atenolol in children, this medicinal product should not be used in children.

Method of administration
The film-coated tablets must be swallowed whole with sufficient liquid before meals. If treatment with Atenolol Denk 50 is to be interrupted or discontinued after prolonged use, it should in principle be tapered off slowly because sudden discontinuation may result in cardiac ischaemia with exacerbation of angina pectoris or in myocardial infarction or exacerbation of hypertension.

4.3. Contraindications

Atenolol must not be used in the following cases:
- hypersensitivity to the active substance, other beta-receptor blockers or to any of the excipients listed in section 6.1,
- manifest heart failure,
- shock,
- second or third degree AV block,
- sick sinus syndrome,
- sinaoatrial block,
- bradycardia (resting pulse rate less than 50 beats per minute before the beginning of treatment),
- hypotension (systolic pressure less than 90 mmHg),
- acidosis,
- bronchial hyperreactivity (e.g. in bronchial asthma),

– late stages of peripheral perfusion disorders,
– coadministration of monoaminoxidase (MAO) inhibitors (except MAO-B inhibitors).

Intravenous administration of calcium antagonists of the verapamil or diltiazem type or other anti-arrhythmics (such as disopyramide) is contraindicated in patients treated with atenolol (except in intensive care).

4.4. Special warnings and precautions for use

Particularly careful medical monitoring is required in the case of
– first degree AV block,
– diabetics with widely fluctuating blood glucose levels (because of possible severe hypoglycaemic states; hypoglycaemic tachycardia may become modified),
– prolonged strict fasting and heavy physical exercise (because of possible severe hypoglycaemic states),
– patients with pheochromocytoma (adrenal medullary tumour; preparative treatment with alpha-receptor blockers required),
– patients with impaired renal function (see section 4.2).

In patients with a personal or family history of psoriasis and in patients with Prinzmetal's angina beta-receptor blockers should be prescribed only after careful benefit-risk assessment, since in some cases this may increase the number and frequency of anginal attacks.

Beta receptor blockers may increase the sensitivity to allergens and the severity of anaphylactic reactions. The indication must therefore be strictly established in patients with a history of severe hypersensitivity reactions and in patients undergoing desensitisation therapy (caution, excessive anaphylactic reactions).

Minor peripheral perfusion disorders may be exacerbated by the use of beta-receptor blockers.

Beta-receptor blockers may mask the signs of thyrotoxicosis. The administration of beta-receptor blockers reduces the heart rate. In the rare event that a patient develops clinical symptoms due to a slow heart rate, the dose may be reduced.

Beta-receptor blockers should not be discontinued abruptly if the patient is suffering from ischaemic heart disease.

Beta-receptor blockers may increase airway resistance in asthmatics. Caution should therefore be exercised with their use. If there is an increase in airway resistance, atenolol should be discontinued and bronchodilator therapy (e.g. with salbutamol) administered.

The use of atenolol may return positive results in antidoping tests.

This medicine contains lactose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

The following interactions have been described subsequent to concomitant use of atenolol and
- Antihypertensives, diuretics, vasodilators, tricyclic antidepressants, barbiturates, phenothiazines: exacerbated hypotensive effect of atenolol.
- Antiarrhythmics: exacerbated cardiac depressant effects of atenolol.
- Calcium antagonists of the verapamil or diltiazem type: hypotension, bradycardia or other cardiac arrhythmias and heart failure (careful patient monitoring). These calcium antagonists may only be administered no less than 48 hours after the withdrawal of atenolol.

- Class I antiarrhythmics (e.g. disopyramide) and amiodarone: the effect on atrioventricular conduction time may be exacerbated and a negative inotropic effect induced.
- Calcium antagonists of the nifedipine type: exacerbated hypotension and in individual cases the onset of heart failure in patients with latent impaired cardiac performance are possible.
- Cardiac glycosides, reserpine, alpha-methyldopa, guanfacine, clonidine: bradycardia, delayed cardiac conduction.
- Following the sudden withdrawal of clonidine in concomitant use with atenolol, blood pressure can increase excessively. Clonidine may therefore be discontinued only if administration of atenolol has ended several days previously. Clonidine may then gradually be reduced (see summary of product characteristics for clonidine). Do not start treatment with atenolol until several days after the discontinuation of clonidine.
- Oral antidiabetics, insulin: exacerbated hypoglycaemic effect of atenolol. Warning signs of hypoglycaemia, particularly tachycardia and tremor, are masked or attenuated. Regular blood glucose monitoring is therefore required.
- Norepinephrine, epinephrine: may counteract the hypotensive effect of beta-receptor blockers, excessive blood pressure increase possible.
- Indomethacin, ibuprofen: hypotensive effect of atenolol may be reduced.
- Narcotics, anaesthetics: increased fall in blood pressure, addition of the negative inotropic effect (the anaesthetist should be informed about treatment with atenolol: the anaesthetic of choice should be as little negatively inotropic as possible. Concomitant use of beta-receptor blockers and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension. Anaesthetics with a depressant effect on the heart should be avoided).
- Peripheral muscle relaxants (e.g., suxamethonium halogenide, tubocurarine): enhanced and prolonged muscle relaxant effect of atenolol (the anaesthetist should be informed about treatment with atenolol).

4.6. Fertility, pregnancy and lactation

Atenolol may be used during pregnancy only after careful consideration of the benefit-risk ratio. Particularly careful medical monitoring is required during lactation.

Pregnancy

Atenolol crosses the placenta and reaches approximately the same concentrations in umbilical blood as in maternal blood.

There is no experience with the use of atenolol in the first trimester of pregnancy, therefore possible foetal injury cannot be excluded. Animal studies revealed no evidence of teratogenic effects of atenolol, but embryotoxic effects were observed (see section 5.3).

Atenolol has been used under strict medical supervision following antihypertensive treatment in the third trimester. In this case, treatment of mild to moderate hypertension was associated with intrauterine growth inhibition.

When treatment was given near to term, the possibility of bradycardia, hypoglycaemia and respiratory depression (neonatal asphyxia) in neonates was described, as well as cases of beta-blockade. For this reason atenolol should be discontinued 24-48 hours before delivery.

Breast-feeding

Atenolol accumulates in breast milk, where it reaches levels several times those in maternal serum. Although the quantity of active substance absorbed with the milk does not constitute any risk to infants, they should be examined for signs of beta blockade.

For neonates of mothers treated with atenolol at birth or while breast-feeding, there may be an increased risk of hypoglycaemia and bradycardia. Atenolol should be used with caution during pregnancy or in breast-feeding women.

4.7. Effects on ability to drive and use machines

Treatment with these medicinal products requires regular medical monitoring. Different reactions in individuals may alter reactivity to such an extent that the ability to drive a vehicle, operate machinery or work without a safe support may be impaired. This applies in particular at the beginning of treatment, following an increase in dosage, following a change of brand and in combination with alcohol.

4.8. Undesirable effects

The frequencies of adverse reactions are ranked according to the following convention:
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)
Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders:
Rare: purpura, thrombocytopenia

Immune system disorders:
Very rare: enhanced allergic reactions not responding to the usual doses of adrenaline, increase in ANA titre (clinical significance not yet elucidated)

Endocrine disorders:
Uncommon: latent diabetes, exacerbation of manifest diabetes

Nervous system disorders:
Common: dizziness, sweating
Uncommon: increased dream activity, insomnia
Rare: hallucinations, psychoses, confusion, drowsiness, paraesthesia, headache, depressive moods, nightmares
Frequency not known: central nervous system disorders

Eye disorders:
Uncommon: conjunctivitis
Rare: visual disturbances, reduced lacrimation (wearers of contact lenses should note)

Cardiac disorders:
Common: bradycardia
Rare: exacerbation of heart failure, atrioventricular conduction disorders
Very rare: exacerbated attacks in patients with angina pectoris

Vascular disorders:
Common: cold extremities
Rare: hypotension with orthostatic dysregulation or syncope, exacerbation of symptoms in patients with peripheral perfusion disorders (including patients with intermittent claudication) or with spasms of the digital arteries (Raynaud's syndrome)

Respiratory, thoracic and mediastinal disorders:
Rare: dyspnoea resulting from possible increase in airway resistance in patients with a tendency to bronchospastic reactions (particularly in obstructive airway disorders)

Gastrointestinal disorders:
Common: gastrointestinal disorders (nausea, vomiting, constipation, diarrhoea)
Rare: dry mouth

Hepatobiliary disorders:
Uncommon: elevated transaminase levels
Rare: liver injury including intrahepatic cholestasis

Skin and subcutaneous tissue disorders:
Rare: allergic skin reactions (redness, pruritus, exanthemas), alopecia, induction or exacerbation of psoriasis vulgaris, psoriasiform exanthemas

Musculoskeletal and connective tissue disorders
Uncommon: muscle weakness, muscle spasm
Not known: lupus-like-syndrome

Reproductive system and breast disorders:
Rare: disorders of libido and potency

General disorders:
Common: tiredness

Special remarks
Since during treatment with other beta-receptor blockers a deterioration of renal function has been observed in very rare cases of patients with severe renal impairment, appropriate monitoring of renal function is required during the use of atenolol.

Since severe liver injury may develop during treatment with other beta-receptor blockers, liver function should be monitored at regular intervals during therapy with atenolol.

Central nervous system disorders may occur in particular at the beginning of treatment.

Following prolonged strict fasting or heavy physical exercise, hypoglycaemic states may occur during concomitant therapy with atenolol. Warning signs of hypoglycaemia (particularly tachycardia and tremor) may be masked.

Disorders of fat metabolism may occur during therapy with atenolol. While total cholesterol remains mostly normal, a reduction in HDL cholesterol and increase in plasma triglycerides levels have been observed.

In patients with hyperthyroidism, the clinical signs of thyrotoxicosis (e.g., tachycardia, tremor) may be masked during treatment with atenolol.

Reporting suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

Symptoms
Depending on the degree of intoxication, the clinical presentation is characterised essentially by cardiovascular and central nervous symptoms. Overdose may result in severe hypotension, bradycardia progressing as far as cardiac arrest, heart failure, and cardiogenic shock. In addition, respiratory problems, bronchospasm, vomiting, impaired consciousness, and occasionally also generalised seizures may occur.

Management
Following an overdose or a life-threatening reduction in heart rate and/or blood pressure, treatment with atenolol must be discontinued.

The vital parameters must be monitored and, where necessary, corrected in an intensive care setting. General management to reduce absorption should include gastric lavage, administration of activated charcoal, and a laxative. In cases of shock and hypotension, plasma or other suitable infusions may be administered.

Severe bradycardia may be treated as follows:
Atropine: intravenous bolus of 0.5-2.0 mg
Glucagon: initially 1-10 mg intravenously followed by a continuous infusion of 2-2.5 mg per hour.

If the effect is inadequate, sympathomimetics (dopamine, dobutamine, isoprenaline, orciprenaline and epinephrine) may be administered depending on body weight and effect.

In case of hypotension and heart failure dobutamine (intravenous infusion of 2.5-10 μg/kg/min) may also be used because of its positive inotropic effect.

In refractory bradycardia, temporary cardiac pacing should be instituted.

In case of bronchospasm, beta-2 sympathomimetics aerosols may be administered (or intravenously if the effect is inadequate) or aminophylline IV.

Slow intravenous administration of diazepam is recommended in generalised seizures.

Atenolol is dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: beta blocking agents
ATC code: C07AB03

Atenolol is a hydrophilic beta-receptor blocker with relative beta-1 selectivity ("cardioselectivity") without intrinsic sympathomimetic activity (ISA) and without a membrane-stabilising effect. Beta-1 selectivity decreases with increasing dose.

The substance reduces cardiac rate and contractility (negative inotropic effect), AV conduction rate and plasma renin activity depending on the amount of sympathetic tone. Atenolol may increase smooth muscle tone by inhibiting beta-2 receptors.

5.2. Pharmacokinetic properties

Following oral administration about 50% of the atenolol is absorbed by the gastrointestinal tract. As atenolol does not undergo first-pass metabolism, systemic availability is also about 50%. Peak plasma levels are reached after 2-4 hours. Plasma protein binding is about 3%; the relative volume of distribution is 0.7 L/kg. Due to its low lipid solubility atenolol crosses the blood-brain barrier to only a limited extent.

Atenolol is metabolised to a rather limited extent. No active metabolites of clinical relevance are formed.
About 90% of systemically available atenolol is eliminated unchanged within 48 hours via the kidneys. The elimination half-life of atenolol in patients with normal renal function is 6-10 hours. In patients with end-stage renal disease the elimination half-life may slow to 140 hours.

5.3. Preclinical safety data

Acute toxicity
See section 4.9.

Chronic toxicity
Rats and dogs receiving various atenolol dosages over a prolonged period (3-12 months) exhibited no significant biochemical, morphological or haematological changes. Increased heart and spleen weight was observed at very high doses.

Mutagenic and carcinogenic potential
Atenolol has not undergone extensive mutagenicity testing. *In-vitro* and *in-vivo* tests to date have been clearly negative.
Long-terms studies in rats and mice revealed no evidence of carcinogenic potential for atenolol.

Reproductive toxicity
The embryotoxic potential of atenolol has been studied in two animal species (rat and rabbit). Foetal resorptions occurred at doses below the maternal toxic range. Malformations have not been observed. An adverse effect on fertility has not been established.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose, lactose monohydrate, povidone K29/32, talc, croscarmellose sodium, magnesium stearate [vegetable], maize starch, pregelatinised starch (maize), hypromellose, titanium dioxide, macrogol 6000.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store below 30°C.
Store in the original packaging in order to protect from light.

6.5. Nature and contents of container

Aluminium/aluminium blisters.
Pack size: 100 film-coated tablets

6.6. Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

8. MARKETING AUTHORISATION NUMBER IN ETHIOPIA

04908/07193/REN/2019
07994/07459/VAR/2021

9. DATE OF FIRST AUTHORISATION IN ETHIOPIA

24.10.1989

10. DATE OF REVISION OF THE TEXT

Jan 13, 2020

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription